the Patch Tester

Contact Dermatitis | Haptens | Patch Testing

Edition #9
December 2021

THE AMERICAN ALLERGIES ISSUE

”The Patch Tester” is a quarterly e-magazine from Chemotechnique to the Patch Testers of the world.

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CONTENTS

PURPOSE

The Patch Tester is an e-mag developed by Chemotechnique to serve as an information resource for all Patch Testers and other Dermatologists around the world; not just in Sweden, or Europe, or America, but wherever the English language can be read and understood. This ninth issue comprises fifty-eight pages with various different topics and features. Ultimately, we plan for The Patch Tester to become the forum for all of us to communicate and cooperate, in all directions.

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ACKNOWLEDGEMENTS

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American Contact Dermatitis Society Core Allergen Series

In an article by

Peter Schalock and colleagues, published
in Dermatitis, Volume 31, issue 5, September/October 2020, pp 279-282

The American Contact Dermatitis Society Core Allergen Series was introduced in 2013 and updated in 2017. Changes in the recommended allergens are again necessary, taking into account data from the American Contact Dermatitis Society’s Contact Allergen Management Program (CAMP) Top 100 Allergens from 2018.

For the updated series, they removed methyldibromoglutaronitrile and added 11 new haptens:

1. Lyral
2. Limonene
3. Linalool
4. Carmine
5. Benzyl salicylate
6. Disperse yellow 3
7. Jasmine
8. Peppermint
9. Pramoxine
10. Shellac
11. Lauryl polyglucose (glucosides).

These additional allergens should increase the yield of relevant positive reactions for their patients.

In 2013, the American Contact Dermatitis Society (ACDS) published a core allergen series with 80 haptens. The goal of this series was to assist in logically expanding patch-testing allergen series

beyond the TRUE Test (TT) (SmartPractice, Phoenix, AZ) standard allergens, which is currently with 35 allergens and 1 negative control.

This was followed by an update in 2017, which reflected the updated TT panels, as well as adding/removing relevant allergens in the extended series panels; thus resulting in an 80-test panel.

After 8 years of use and 2 iterations, the ACDS again feel that updating the ACDS Core Allergen Series is necessary.

To evaluate the allergens on the 2017 ACDS Core Allergen Series, it was compared with the top 100 allergens in the ACDS Contact Allergy Management Program (CAMP) data for the year 2018. The CAMP database allows entry of a patient's set of individual sensitivities and produces a list of personal care products that are free of those haptens. This database was examined for the year of 2018, and the top 100 most prevalent haptens were summarised and published. Nine haptens not included in the 2017 series that the group felt to be important were identified and added to the 2020 Core Allergen Series.

Limited series patch tests with 36 haptens, such as the TT, correctly identify just 66% of clinically relevant reactions that would be identified using the North American Contact Dermatitis Group (NACDG) screening series (of 80 tests). Simply put, an extensive patch test reduces overall health care costs and improves the quality of life for many dermatitis patients.

Thus, the goal of the ACDS Core Allergen Series is to give patch testers a logical and graded tool to increase the number of haptens tested, as well as provide a helpful and scalable baseline series for those opting to use customisable patch-test screens. This should increase the yield of useful positive tests for our patients.

This new series was reviewed and approved by the ACDS Executive Committee.

For 2020, panels 4 to 8 have minimal changes. The group did not feel that the removal of haptens from the 2017 80 hapten series, other than methyldibromoglutaronitrile (MDGN), was necessary. Increasing the testing concentration of formaldehyde from 1% to 2% is recommended. This should increase reaction yields and not increase irritant reactions. Nine important allergens identified in the CAMP Top 100, as well as 2 additional common potential haptens, were added to the series (disperse yellow 3 and pramoxine).

A more extensive baseline series with relevant allergens is both a cost-effective and diagnostically effective manner to cure ACD patients. In this pursuit, the authors have chosen to expand the ACDS series to include a ninth hapten panel.

The goal is to recommend useful and appropriate patch-testing series to allow complete evaluation of our suspected ACD patients. Using the ACDS Core Allergen Series will allow the clinician to logically extend the patch-test screening to incorporate common, rare, and emerging allergens beyond those identified by the TT.

Updated panels 1 through 9 of the American Core Series are presented in Table 1.

Editor's Note
Due to the specific situation in USA with the regulatory status of T.R.U.E. Test (SmartPractice of USA) and of other individual patch test haptens, as well as the financial reimbursement structures in USA, the AC-1000 Series and the NAC-80 Series include the 35 haptens of T.R.U.E. Test as the

TABLE 1 - American Core Series AC-1000

Panel I
(1) Nickel sulfate 2.5% pet.
(2) Lanolin alcohol (Amerchol 101) 50% pet.
(3) Neomycin 20% pet.
(4) Potassium dichromate 0.25% pet.
(5) DMDM hydantoin 1% pet.
(6) Fragrance mix I 8% pet.
(7) Colophony 20% pet.
(8) Paraben mix 12% pet.
(9) Methylisothiazolinone 0.2% aq.
(10) Balsam of Peru (Myroxylon pereirae) 25% pet.

Panel II
(11) Ethylenediamine dihydrochloride 1% pet.
(12) Cobalt chloride 1% pet.
(13) p-tert-Butylphenol formaldehyde resin 1% pet.
(14) Epoxy resin 1% pet.
(15) Carba mix 3% pet.
(16) Black rubber mix 0.6% pet.
(17) Methylchloroisothiazolinone/methylisothiazolinone 100 ppm. aq.
(18) Quaternium 15 2% pet.
(19) Hydroxyperoxides of Linalool 0.5% pet.
(20) p-Phenylenediamine 1% pet.

Panel III
(21) Formaldehyde 2% aq.
(22) Mercapto mix 1% pet.
(23) 2-Bromo-2-nitropropane-1,3-diol 0.5% pet.
(24) Thiuram mix 1% pet.
(25) Diazolidinyl urea 1% pet.
(26) Benzocaine 5% pet.
(27) Tixocortol-21-pivalate 1% pet.
(28) Gold sodium thiosulfate 2% pet.
(29) Imidazolidinyl urea 2% pet.
(30) Budesonide 0.1% pet.

Panel IV
(31) Hydrocortisone-17-butyrate 1% pet.
(32) Mercaptobenzothiazole 1% pet.
(33) Bacitracin 20% pet.
(34) Fragrance mix II 14% pet.
(35) Disperse blue 106/124 mix 1.0% pet.
(36) Lidocaine 15% pet.
(37) Propylene glycol 30% aq.
(38) Iodopropynyl butylcarbamate 0.1% pet.
(39) Polymyxin B sulfate 3% pet.
(40) Cocamidopropyl betaine 1% aq.

Panel V
(41) Mixed dialkyl thioureas 1% pet.
(42) Dimethylaminopropylamine 1% aq.
(43) Hydroxyethyl methacrylate 2% pet.
(44) Oleamidopropyl dimethylamine 0.1% aq.
(45) Decyl glucoside 5% pet.
(46) Methyl methacrylate 2% pet.
(47) Lavender absolute 2% pet.
(48) Cinnamic aldehyde 1% pet.
(49) d/l-α-Tocopherol 100%.
(50) Ethyl acrylate 0.1% pet.

Panel VI
(51) Tea tree oil 5% pet.
(52) Chlorhexidine digluconate 0.5% aq.
(53) Propolis 10% pet.
(54) Chloroxylenol (PCMX) 1% pet.
(55) 2-Hydroxy-4-methoxybenzophenone (benzophenone-3) 10% pet.
(56) Tosylamide formaldehyde resin 10% pet.
(57) Sesquiterpene lactone mix 0.1% pet.
(58) Cocamide DEA (Coconut diethanolamide) 0.5% pet.
(59) Hydroxyperoxides of limonene 0.2% pet.
(60) Benzalkonium chloride 0.1% pet

Panel VII
(61) 2-Hydroxy-4-methoxybenzophenone-5-sulfonic acid (benzophenone-4) 2% pet.
(62) Sodium benzoate 5% pet.
(63) Sorbic acid 2% pet.
(64) Ylang-ylang 2% pet.
(65) Compositae mix II 5% pet.
(66) Ethyleneurea melamine-formaldehyde 5% pet.
(67) Sorbitan sesquioleate 20% pet.
(68) n,n-Diphenylguanidine 1% pet.
(69) Lyral 5% pet.
(70) Ethylhexylglycerin 5% pet.

Panel VIII
(71) Triamcinolone 1% pet.
(72) Clobetasol-17-propionate 1% pet.
(73) Amidoamine 0.1% aq.
(74) Ethyl cyanoacrylate 10% pet.
(75) Phenoxyethanol 1% pet.
(76) Disperse orange 3 1% pet.
(77) Benzoic acid 5% pet.
(78) 2, 6-ditert-butyl-4-cresol (BHT) 2% pet.
(79) 2-Ethylhexyl-4-methoxycinnamate 10.0 pet.
(80) Benzyl alcohol 10% soft

Panel IX
(81) Cetyl steryl alcohol 20% pet.
(82) Carmine 2.5% pet.
(83) Benzyl salicylate 10% pet.
(84) Disperse yellow 3 1% pet.
(85) Jasmine 2% pet.
(86) Peppermint 2.0% pet.
(87) Pramoxine hydrochloride 2% pet.
(88) Shellac 20% alcohol†
(89) Lauryl polyglucose (glucosides) 3.0% pet.
(90) p-chloro-m-cresol (PCMC) 1% pet.

6 What's new in Patch Testing

first tests listed in their respective series. Operators in USA may choose to substitute these 35 individually dispensed haptens in this series with the corresponding 35 haptens of T.R.U.E. Test.

Removal of MDBGN
A new change to the 2020 ACDS series is the removal of MDGN. This allergen was removed from products in the European Union in 2005 for leave-on products and in 2008 for wash-off products and was restricted for non-cosmetic use in 2010. The NACDG, in their last iteration of their standard series findings (2015–2016 data), had Euxyl K400 in the top 20 relevant allergens. This allergen is a mix of MDGN/phenoxyethanol, which confounds the analysis regarding which is the actual hapten. The majority of positives in this data set were reported as possible, past or unknown relevance, not probable, or definite. The CAMP database lists only 237 products (4%) potentially with MDGN of 5,551 total products. Although these data show that MDGN is still present in a few products and some patients still have patch-test reactions, the ACDS Core Allergen Committee's clinical experience supports that, although MDGN continues to show positive reactions in some, it is not usually a clinically relevant allergen at this time. Phenoxyethanol remains a screening allergen on the Core Allergen Series.

Fragrances
Thorough screening for fragrance allergy is high yield and necessary. New additions to the 2020 series include 5 fragrances - Limonene, Linalool, Lyral, peppermint, and jasmine. It is estimated that 3.5% to 4.5% of the adult population and 20% of the patch-tested population, may be allergic to 1 or more fragrances. Limonene, Linalool, and Lyral are fragrance ingredients that are commonly seen in personal care products, processed foods and beverages, and perfumes. These 3 allergens seem to be of significant relevance for many patch-tested patients. Testing should be performed with the hydroxyperoxide (oxidised variant) of Linalool and Limonene. These compounds increase relevant patch-testing yield compared with the unoxidised fragrance. Hydroxyperoxides of Linalool is available at 0.5% and 1% concentrations, and hydroxyperoxides of Limonene at 0.3% and 0.2%. At the higher concentration, there is risk of questionable/irritant reactions for both Linalool and Limonene. The authors recommend testing at 0.5% and 0.2%, respectively, in this series. Jasmine and peppermint are also within the realm of fragrances, as well as flavourings in some consumable items. Although reactions to jasmine and peppermint are less common than some other fragrances, it is important to include them in routine screening.

Carmine
Carmine is a natural red dye used in cosmetics and foods, derived from the *Dactylopius coccus* insect. The female insects are harvested and processed, yielding bright red pigment. The use of carmine is increasing because of use-restrictions on the synthetic red dyes, which may be carcinogenic. Until recently, ACD to carmine was believed to be rare. The NACDG added carmine to its screening tray in 2011, finding a 3.1% positive reaction rate. The positives tended to be mild, and caution was recommended when reading because of the red dye leading to potential false-positive results with macular erythema.

Pramoxine
Pramoxine is a topical desensitising agent used in many over-the-counter "anti-itch" and topical desensitisation creams / lotions. Contact dermatitis to the ester and amide group anaesthetics (i.e., benzocaine or lidocaine) is well known, but pramoxine reactions are less common because of its novel chemical structure. As of 2014, there were 6 reported cases of pramoxine contact allergy. The NACDG is currently testing pramoxine routinely, and these data will be published after the next 2-year study period is completed. In addition to type IV reactions, a single report of Type I anaphylactic reaction on abraded skin was reported. Pramoxine use in topical over-the-counter medicaments is common, and this group feels that it is increasing, thus warranting addition of this hapten to the series.


Disperse Orange is used in the textile industry

Shellac
Shellac is a resin derived from the *Laccifer lacca i*nsect, which is indigenous to Thailand and India. Once processed, it forms a hard lacquer, which has diverse uses in cosmetics, such as eyeliner, mascara, lipstick, lip sealants, and hair dyes and sprays. It is also used as an edible food glaze and in furniture finishing applications. Reaction rates have varied from 1.6/1.7% (NACDG data 2009–2012) to 10.5% in a recent Mayo Clinic series. Some have considered this allergen, which is tested in 20% alcohol to be non-irritant, although the rates seen in the study of Veverka et al were only 0.8%.

Alkyl Glucosides
The alkyl glucosides are commonly-found, natural, plant-derived surfactants that won the honour of being the ACDS Contact Allergen of the Year for 2017. One important component, lauryl glucosides, was added to the 2020 series. Overall, use of glucosides is common, being found in 10% of the products listed in the Contact Allergen Management Program database. The previous series included decyl glucosides, the fifth most prevalent surfactant in CAMP. Lauryl glucoside was the eighth most commonly used surfactant. Bai et al examined 65 laundering products in the United States, finding glucosides in the top 10 most common allergenic chemicals identified in everyday laundry products. Testing for individual components of the glucoside group may increase detection of this important group of haptens.

Disperse Yellow 3
The addition of disperse yellow 3 expands the screening for disperse textile dyes in this series. Disperse yellow 3 was recently found to have a 1.1% rate of reaction in textile dye allergic patients. This allergen was not present on the CAMP 100 list but is a common exposure in synthetic clothing and is felt to be potentially relevant for patients.

8 What's new at Chemotechnique?

Carmine

Carmine is a widely used "natural" food additive that has been reported to provoke both an immediate hypersensitivity and a delayed systemic response with cutaneous expression.

Cochineal, formally known as *Dactylopius coccus* (of the order Hemipteran), is an insect that has had significant global impact over the last 6 centuries. The etymology of cochineal dates back to the Greeks and Romans, where use signified a transparent red tint produced by an insect (not modern cochineal) as "kokkos," meaning berry. Kokkos was later referred to by the Latin word "coccinus," providing the basis for the Spanish word, "cochinilla." Not until the late 16th century did the French version of the word "cochenille" lead to the modernised term, cochineal. In time, cochineal was adopted in reference to the insect *Dactylopius*.

This native Mexican and South American insect is the source of the natural dye carmine. To survive, cochineals maintain a symbiotic relationship with the prickly pear cactus, a plant whose pads serve as the final haven for the static, female cochineal - the gender of the insect that is ultimately responsible for the source of the brilliant dye.

The use of dyes to colour man-made objects and art has occurred for thousands of years. Textiles, tools, pottery, and rock art have all played an integral role in documenting the history of man. These artifacts bring to life what used to be; carmine, therefore, has literally left its stain on human history. First used by Mexican and Peruvian natives, cochineal became a regularly-used pigment in their production of textiles, which are dated back to 2000 B.C. The dye was an essential part of the society of the Aztecs, Zapotecs, and Mixtecs. Although carmine was a popular regional product, it did not become an international product until invasion of areas of Latin America by the Spanish. The Spanish invaded the region occupied by the Aztecs and promptly raided the region in search of precious goods. The Spanish quickly discovered the precious dye and promptly began importing it. With the demand and value of the cochineal dye competing with silver and gold imports, it is no surprise that this brilliant colour held high regard with respect to social and religious status. Carmine bolstered mass global interest in cochineal until it fell out of favour in lieu of cheaper, synthetic alternatives.

Concerns over dye-based carcinogenicity led to modern re-emergence of carmine with regulations on its use. In Brussels, on June 30, 1994, the European Parliament and Council of the European Union declared that all permitted colours under the "E" number system must be properly reported in the food and retail industries; carmine is E120.

Currently, carmine is not regulated by the European Union; however, producers of consumer products are discouraged from its use by the European Food Safety Authority (EFSA). In the EFSA Panel on Food Additives and Nutrient Sources Added to Food, the EFSA determined that acceptable daily intake for carmine is 5 mg/kg per day. In contrast, the US Food and Drug Administration has required reporting use of carmine in food and cosmetic products since 2009.

Chemotechnique Hapten Carmine

Due to the increasing recognition of carmine as a sensitising substance causing allergic contact dermatitis, Chemotechnique has now made available this substance as a commercially available hapten, with article number C-059.

The deep red of carmine found in food, cosmetics, textiles and others.

Art-no	C-059
Concentration	2.5%
Vehicle	Petrolatum
Molecular Formula	C22H20O13 (Carminic acid)
Molecular Weight	492.4 g/mol (Carminic acid)
CAS	1390-65-4
INCI Name	CI 75470

Carmine is now included in the recently announced American Core Series of 90 haptens, with article number AC-1000.

Due to the very recent creation of this 2020 American Core Series, and its inclusion of many other new clinically important haptens, and its sheer number of haptens compared to earlier-designed American and International Series, the authors expect that the American Core Series will gain ever-increasing adoption amongst not only American Dermatologists but also internationally.

For further information on the American Core Series see the article entitled "What's New in Patch Testing" in this issue #9 of The Patch Tester.

Dear Reader, if you have any particular article or book or website that you would like to have reviewed in a future issue of The Patch Tester, then please contact the Editor here.

Nickel Barrier Cream

NIK-L-BLOK™

The most innovative barrier cream on the global market.
Designed and created specifically for nickel-sensitive persons.

Nickel is by far the most commonly-encountered contact hapten causing Allergic Contact Dermatitis, and so is of great importance to nickel-sensitised persons and to their Dermatologists.

Unfortunately, despite decades of regulation by various authorities in many countries around the world to limit the use of nickel in common every-day articles, it is still very difficult or impossible for members of the public as well as certain categories of workplace professionals to avoid coming into contact with nickel.

Until now, the best and most commonly-expressed advice that medical professionals have been able to give to their nickel-sensitised patients has been to "avoid nickel" in order to avoid subsequent signs and symptoms of allergic contact dermatitis.

But now, with the unique **NIK–L–BLOK** product, there is an alternative option for the nickel-sensitive patient or person.

Chemotechnique Cosmeceuticals have developed and made available to the public our nickel barrier cream **NIK–L–BLOK**, for the every-day skincare routine of nickel-sensitised individuals.

NIK–L–BLOK is the world's first patented, active barrier cream that encapsulates nickel ions, blocking them from penetrating the skin when in contact with metal objects that contain nickel.

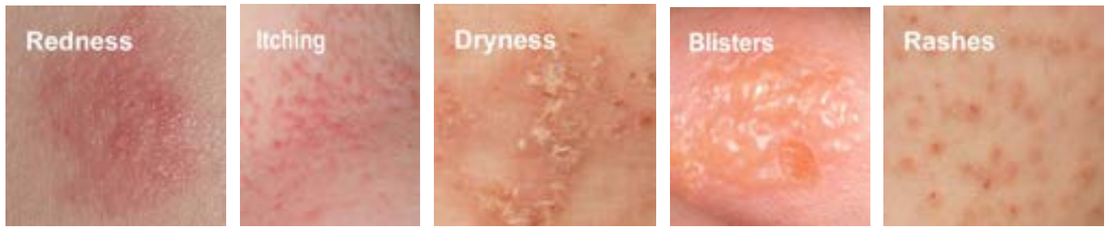
Active ingredients in the cream work effectively to protect the skin both internally and externally, thereby preventing the development of allergic reactions such as eczema, dryness, blisters, redness and itching.

Nickel Allergy

When your skin is exposed to nickel, even nickel in a mix of other metals, free nickel ions penetrate the outer skin layer (stratum corneum) and bind to proteins in the dermis layers. The haptens of zinc ions then become allergens. When the accumulated exposure to nickel surpasses a critical threshold, then the person's immune system treats the nickel bound in skin proteins as a threat, and then causes the development of the various signs and symptoms of allergy to the nickel. The person is then sensitised against nickel. This sensitisation threshold varies greatly among individuals.

Unlike most other types of allergies (such as respiratory allergy to house dust mites or pollens or animal danders), the signs and symptoms of contact allergy, such as to nickel, are not immediate but are called delayed reactions, usually presenting 12-48 hours after exposure to the substance. Once a person responds with an allergic reaction to nickel, any future exposure of nickel to the skin may result in an allergic reaction.

There are several different signs of an allergic reaction, as shown in the 5 illustrations below



How NIK–L–BLOK Works

Nickel ions trigger allergic reactions only after having penetrated into the skin.
NIK–L–BLOK is a revolutionary active skin barrier cream based on a patented chelating formula using the active ingredient DTPA to capture free nickel ions. When the skin is in contact with metal objects containing nickel, the DPTA then blocks the nickel ions from permeating into the skin. In total, the ingredients in the cream work effectively to protect the skin both internally and externally, thereby preventing the development of allergic reactions such as eczema, dryness, blisters, redness and itching.

By using **NIK–L–BLOK** regularly on exposed skin areas that may come into contact with nickel (either in the occupation or work, or in daily life), sensitisation towards nickel will be prevented, as the skin remains protected against nickel-induced Allergic Contact Dermatitis.

Chemotechnique - Nickel Detection - Chemo Nickel Test

Chemotechnique does not only provide leading diagnostic solutions within the field of contact allergy, and nickel protection, but also a test to detect the presence of nickel in metal objects. The **Chemo Nickel Test** has been the first choice of medical practitioners in the detection of free nickel in metal objects since its introduction in 1995. As a testament to its proven quality, the **Chemo Nickel Test** is the only one-step nickel detector sold through retail pharmacies in Sweden. The test consists of an ammoniacal solution of Dimethylglyoxime (DMG) for the detection of nickel in various metallic objects. DMG produces a bright, reddish-pink insoluble salt with nickel. The Chemo Nickel Test detects free nickel down to a limit of 10 ppm (parts/million). The sensitivity threshold of most nickel allergic patients is above 11 ppm. However, some strongly-allergic patients may react to objects releasing amounts of nickel below the threshold of the test.

Tea Tree Oil

In the May/June issue of Dermatitis is an interesting article by Maria Michela Lauriola and colleagues of on two cases of Allergic Contact Dermatitis Due to “Therapeutic Uses” of Tea Tree Oil on the Lips and Toenails

See Dermatitis: 5/6 2021 - Volume 32 - Issue 3 - pp40-41.

This is just the most recent reminder of the importance of sensitisation to this naturally occurring allergen / hapten that is being increasingly utilised in the production of various cosmetics, medical products and household products.There are several other articles in the literature over the last decade that have provided useful information and insights into this sensitiser.

Origin

The oil is extracted from the leaves of the tea tree via steam distillation. Tea Tree Oil is a pale-yellow essential oil extracted from the leaves of the *Melaleuca alternifolia* plant of the Myrtaceae family; the Myrtles. This native shrub grows on the north-eastern Australian coast, often alongside bodies of water.

The Tea Tree Oil (TTO) comes from leaves’ distillation of the Australian native *Melaleuca alternifolia* or tea tree. It is rumoured that the name “tea tree” was attributed to this plant by Captain James Cook, a discoverer of Australia, who obtained an infusion from this tree that was similar to a spiced tea.

A search online will reveal photographs that are labelled Tea Tree but are very obviously of widely differing trees/shrubs visually, and with widely differing leaf morphology, and so are most probably also of widely different phylogeny. In other words, beware of alternatives and imitations.

Properties

TTO is well known for its proven medicinal properties of being antiseptic, antifungal, antiviral and anti-mite.

Commercialisation

The oil from the crushed leaf was first used as an aromatherapy agent by the indigenous Australian Bundjalung tribe to treat upper respiratory tract infections. This essential oil possesses a sharp camphoraceous odour followed by a menthol-like cooling sensation.

In the 1920s, researchers Penfold and Grant published the first reports of the potential antiseptic activity of tea tree oil, describing it as 11 times more active than phenol.

Commercial production continued until the mid-1940s, when it was slowly phased out with the introduction of more effective oral antibiotic medications and topical antiseptics.

With the increasing popularity of “natural” products in the 1970s, however, commercial farming of *M. alternifolia* began on large plantations in the eastern Australian states of New South Wales and Queensland. Currently, these production facilities not only grow tea trees but also steam-distil the

leaves on-site to manufacture a uniform product.

Composition of TTO

Tea tree oil is composed of more than 220 chemical components.

The composition of tea tree oil has been regulated since 1996 by the International Organization for Standardization (ISO); the oil is labelled “oil of Melaleuca—terpinen-4-ol type (tea tree oil).”

The ISO specifies the top 15 compounds needed for the product to be labelled “tea tree oil”. See the table below. Of note, the international classification does not require that the oil be produced from *M. alternifolia*, and there have been reports that oils that meet the international standard requirements have been produced from other Melaleuca species (such as *Melaleuca dissitiflora* and *Melaleuca linariifolia*).

Component	Minimum %.	Maximum %
α Pinene	1.0%	6.0%
Sabinene	Trace	3.5%
α -Terpinene	5.0%	13.0%
d-Limonene	0.5%	1.5%
ρ-Cymene	0.5%	8.0%
1,8-Cineol (Eucalyptol)	Trace	15.0%
Γ-Terpinene	10.0%	28.0%
Terpinoline	1.5%	5.0%
Terpinen-4-ol	30.0%	48.0%
α-Terpineol	1.5%	8.0%
Aromadendrene	Trace	3.0%
Ledene (viridioflorene)	Trace	3.0%
Β-Cadinene	Trace	3.0%
Globulol	Trace	1.0%
Viridifloral	Trace	1.0%

- The allergenic compounds in TTO have been investigated and include the following haptens:

1,8-cineole
D-limonene
aromadendrene
terpinen-4-ol,
α-phellandrene
ρ-cymene
α-pinene
terpinolene
α-terpinene.

Unfortunately, the evaluation of tea tree oil as a potential contact allergen is incredibly challenging because tea tree oil consists of more than 100 distinct compounds (220!) but also because the oil is often mislabelled or does not meet ISO guidelines.

Furthermore, the most sensitising components may not be chemicals in the oil itself but rather degradation / oxidation chemicals that are formed after the oil is applied to the skin, either immediately or over time. Oxidised tea tree oil has been found to be a more potent contact allergen than the fresh form of the oil, suggesting that oxidation products may be the likely allergens.

Fresh oil is a weak allergen, but its composition changes after oxidative degradation (from exposure to light, oxygen, and heat), and its sensitising capacity becomes approximately 3 times stronger.

Usage

Most commonly used as an ingredient in topical products, it is used at a concentration of 5% to 10%.

Natural essential oils are currently proposed as a panacea to treat almost any disease and body site. Among all those essential oils, TTO has been responsible for the most allergic reactions reported in the literature, since the first cases were described in 1991. This is because this essential oil is gaining popularity in Europe and North America.

Tea tree oil is an increasingly popular ingredient in not only claimed therapeutic products but also in a variety of household and cosmetic products, including shampoos, massage oils, skin creams, nail creams, and laundry detergents.

Since 2002, the European Cosmetic and Perfumery Association has recommended TTO be used in concentrations of less than 1% in cosmetics, use in association with antioxidants, and use with packaging designed to minimise exposure to light.

Clinical Conditions

Although generally considered a safe product when used topically, tea tree oil is considered toxic when swallowed. Reactions to ingestion of the oil range from vomiting and diarrhea to hallucinations and coma. Gynecomastia has also been reported.

The main safety concern with topical tea tree oil preparations is however their potential to induce allergic contact dermatitis.

A number of cases of ACD from tea tree oil are cited in the literature over the years. The reported presentations are variable and range from erythema and pruritus to eczematous plaques at topical application sites to bullous and erythema multiforme–like reactions. Of note, there has been 1 reported case of linear immunoglobulin A induced by tea tree oil.

Reactions have been reported as occurring equally in males and females, and there does not appear to be a preferred site of involvement. Although patients as young as 17 years and as old as 76 years have been reported, most patients were in their 50s to 70s and had previous exposure to products containing TTO.

Approximately three-quarters of cases are attributed to the use of neat (100%) oil or that in concentrated forms, particularly on the injured skin.

Prevalence of Sensitisation

The latest available data from the North American Contact Dermatitis Group indicate a low prevalence of 1.4%. However, there are other reports of sensitisation rates up to 3.5%.

In a selected population of healthy volunteers of whom 63% had prior exposure to tea tree oil, the prevalence of ACD reactions to a 10% dilution ranged from 2.9% to 4.8%, respectively, not including or including “indistinguishable reactions.”

However, Lisi and colleagues tested 725 consecutive patients suspected of having ACD with undiluted, 5%, 1%, and 0.1% tea tree oil preparations in petrolatum; nearly 6% of the patients had patch-test reactions to the undiluted preparation, whereas only 1 patient had a true positive reaction to the 1% dilution. The high reactivity rate with the undiluted preparation suggested that irritancy may occur with the concentrated product, whilst lower concentrations may not “capture” all allergic patients.

In summary, although the prevalence of tea tree oil allergy is low, it should remain on the allergen differential for ACD especially because the oil is present in a wide variety of consumer products.

When the index of suspicion remains high, patch testing both with 5% tea tree oil in petrolatum and with the patient’s own products is recommended.

Patch Testing

TTO was originally added to the North American Contact Dermatitis Group screening panel in 1999. TTO is also present in various other screening series, such as:

Cosmetic Series C-1000
International Comprehensive Baseline Series ICB-1000
Australian Baseline Series ABS-1000
North American 65 Extended Series NAE-65
North American 80 Comprehensive Series NAC-80
Chinese Baseline Series CB-100
American ACDS 90 Core Series (2020) ACS-1000

Chemotechnique

Chemotechnique manufactures and markets oxidised Tea Tree Oil.

Art-no	T-035B
Concentration	5.0%
Vehicle	Petrolatum

For product information on TTO click **here**
For the Safety Data Sheet on TTO click **here**
For the Hapten Information Sheet on TTO click **here**

Severe Acute Respiratory Syndrome Coronavirus 2 Vaccines and Cutaneous Adverse Reactions: A Review

by Miguel Alpalhão, et al.
in Dermatitis, Volume 32, Issue 3, May/June 2021, pp 133-139.

We are entering a new stage of the severe acute respiratory syndrome coronavirus 2 pandemic with the initiation of large-scale vaccination programs globally. In these circumstances, even rare adverse effects of vaccines may be encountered more often, if millions of people are to be vaccinated in a short period. Vaccination has the potential for causing cutaneous adverse effects. Thus, it is paramount that dermatologists worldwide are acquainted with the possible skin reaction patterns to the coming vaccines. The authors conducted a review to discuss the most frequent cutaneous adverse effects of vaccines and their management, with a particular focus on the expected adverse reactions for the coming severe acute respiratory syndrome coronavirus 2 vaccines, such as local reactions, as well as immediate- and delayed-type hypersensitivity reactions, including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrosis, serum sickness–like reactions, and vasculitides. The authors also discussed the yet unanswered questions on vaccines for which we may soon be asked to provide an expert opinion.

The current severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has brought to light countless challenges to clinical practice. We are now entering a new phase of this crisis, which might become the largest vaccination movement in human history. Most countries are expecting to vaccinate most citizens within a year, with vaccines that were subject to a fast development pase, at the relative expense of long-term data on safety. Although messenger ribonucleic acid (mRNA) technology for vaccine development has been extensively studied over the last decade, only a year has separated the identification of this novel coronavirus and the approval of a new vaccine by most international drug agencies, which contrasts with the several years to more than a decade of clinical development of other recent vaccines, such as those against human papillomavirus or varicella-zoster viruses. It is thus possible that even relatively rare adverse effects of these vaccines will be seen occasionally, if hundreds of millions or billions of people are to be vaccinated, as may happen with any other vaccines under the same circumstances.

Vaccination has the potential for causing cutaneous adverse effects. Thus, it is paramount that physicians worldwide are acquainted with the possible skin reaction patterns to vaccines, which might become more frequent in daily practice in the coming months.

The authors conducted a short review on the most frequent cutaneous adverse reactions to vaccines and what may be expected from the upcoming SARS-CoV-2 vaccines (summarised in Table 1).

LOCAL REACTIONS

Local reactions are the most frequent adverse reaction to vaccines. Erythema, oedema, and tenderness at the administration site are frequent and common to all known vaccines, and usually develop within the first few hours after administration and subside after a few days. They represent a nonspecific innate immune response to foreign body injection and are usually mild and easily managed by local ice application and acetaminophen.

Local reactions to mRNA vaccines against SARS-CoV-2 have been extensively recognised.

One particular reaction to Moderna's vaccine has been popularly dubbed as "COVID arm," which should more appropriately be called "COVID vaccine arm." This reaction, which has been known since the clinical trials leading to approval, represents the development of an erythematous and oedematous patch around the administration site, which may develop 5 to 10 days after the injection of the vaccine and resolves spontaneously within days. This adverse effect has been postulated to represent a delayed hypersensitivity reaction, but the mechanism remains to be elucidated.

Uncommonly, foreign body granulomas may develop within days to weeks and may become persistent. Subcutaneous granulomatous nodules are a well-known reaction to vaccines containing aluminium, which is a frequent ingredient in vaccines to boost immune reaction. Proposed vaccine candidates against COVID-19 with aluminium in their composition include the inactivated vaccine CoronaVac (Sinovac). Often, the reaction ameliorates with time. Intralesional corticosteroids or surgery may be an option in severe cases.

Rarely, Nicolau syndrome (embolia cutis medicamentosa) may occur. This condition is not exclusive to vaccination but rather a possible complication shared by all injectable treatments. It is characterized by extreme pain after injection, followed by erythema and by a livedoid reticular or haemorrhagic patch, and may result in skin necrosis and ulceration. The pathogenesis of this reaction is yet obscure but may be related to embolisation of the administered drug or vascular collapse because of increased local interstitial hydrostatic pressure. Cold dressings may aggravate this condition by increasing arterial vasoconstriction. Treatment is usually supportive, and oral pentoxifylline and subcutaneous heparin may be helpful. Proper injection technique is paramount to prevent this avoidable complication.

IMMEDIATE HYPERSENSITIVITY REACTIONS

Immediate (Type I) hypersensitivity reactions develop within 4 hours after vaccine administration and are mediated through immunoglobulin E-dependent histamine release. These reactions may range from mild, with urticarial lesions only, to moderate, with wheezing and/or diarrhoea, to life-threatening with angioedema and anaphylactic shock. They may develop in response to any vaccine, but severe reactions are rare, with an estimated incidence of approximately 1 case per million administered vaccines. Treatment is supportive, and immediate administration of intravenous antihistamines and hydrocortisone may be considered for non-severe reactions, whereas anaphylaxis may be addressed with adrenaline injection. Monitoring patients after vaccine administration is important in individuals with a history of hypersensitivity reactions to vaccines. Patients should be referred to an allergy expert for further study after an episode of immediate hypersensitivity reactions to vaccines.

Polyethylene glycol (PEG) moieties and polysorbate-80 have the potential to cause immediate hypersensitivity reactions, as well as delayed hypersensitivity reactions (see below). Polyethylene glycol moieties, present in both Moderna's and Pfizer's vaccines, have been postulated to be responsible for anaphylactic reactions to these vaccines.

DELAYED HYPERSENSITIVITY REACTIONS

Systemic Contact Dermatitis

Delayed (Type IV) hypersensitivity to vaccine constituents often presents as systemic allergic contact dermatitis. Systemic allergic contact dermatitis usually develops after systemic administration (oral, intravenous, intramuscular, subcutaneous, inhalational, transmucosal, or transcutaneous) of a given allergen, to which an individual had become previously sensitised, usually through the cutaneous route. The clinical presentation may be diverse, with recurrence of skin lesions on previously affected areas of dermatitis or on areas of a previous positive patch test; vesicular hand dermatitis (pompholyx); symmetrical drug-related intertriginous and flexural erythema; or, less frequently, pruritic papules on extensor surfaces of knees and elbows, erythroderma, or even vasculitis-like lesions.

Systemic allergic contact dermatitis has been described as a reaction pattern not only to metals, namely, nickel, cobalt, and chrome, but also to a wide range of drugs and other substances, inclu-

TABLE 1 - Summary of the Most Frequent Reactions to Vaccines, their Characteristics, and General Management

Reaction	Mechanism	Clinics	Frequency	Management	Notes
Mild local reaction	Nonspecific inflammatory reaction to foreign body	Erythema, swelling, tenderness	Frequent	Local cold dressing; mild analgesics	
Foreign body granuloma	Granulomatous reaction to foreign body	Cutaneous/subcutaneous nodules	Uncommon	Tincture of time; intralesional corticosteroids or surgery for severe cases	
Nicolau syndrome	Vascular collapse/occlusion/embolism?	Severe pain, livedoid changes, haemorrhagic plaque	Rare	Pentoxifylline, low-molecular-weight heparin	
Immediate hypersensitivity reaction	IgE-mediated histamine release	Mild: urticaria; moderate: diarrhea, wheezing; severe: angioedema, anaphylaxis	Uncommon to rare	Antihistamines ± corticosteroids; adrenaline in severe cases	
SCD	Delayed hypersensitivity reaction	Pruritic eczematous lesions with variable distribution	Uncommon to rare	Topical or systemic corticosteroids	rvatives such as thimerosal; PEG and polysorbate 80 in mRNA vaccines may be a potential cause
Drug eruptions	Delayed hypersensitivity reaction	Any pattern of usual drug eruptions	Rare	Topical or systemic corticosteroids	
EM	Delayed hypersensitivity reaction, usually as a reaction to viral infections	Targetoid lesions on acral areas; mucous erosions may occur	Uncommon to rare	Supportive; antivirals or systemic corticosteroids may be pondered	Intact viral vaccines and adenovirus-vector vaccines may pose a higher risk
SJS/TEN	Delayed hypersensitivity reaction, usually as a reaction to drugs	Prominent systemic symptoms; erythematous macules with subsequent blistering and epidermal detachment; mucous erosions frequent	Rare	Critical patient approach; consider admission at burn unit; systemic steroids/cyclosporine A/tumor necrosis factor inhibitors could be considered	
Vasculitides	Mostly mediated by antigen-antibody complex deposition	Palpable purpura; in severe cutaneous diseases, livedoid changes or necrosis may be present; may affect other organs	Uncommon to rare	Exclude other organ involvement; rest; consider systemic corticosteroids	
Serum sickness–like reaction	Yet obscure; similar to Type III hypersensitivity reaction, but no immunocomplexes are found	Urticaria, fever, arthralgia	Rare	Supportive; antihistamines and systemic steroids may be used	More frequent in children

Frequency is reported semi-quantitatively based on the assessed evidence of published cases, as a general reference only, and may have significant publication bias or underreporting of some milder presentations.

EM, erythema multiforme
IgE, immunoglobulin E
PEG, polyethylene glycol
SCD, systemic allergic contact dermatitis
SJS/TEN, Stevens-Johnson syndrome/toxic epidermal necrolysis
SSLR, serum sickness-like reaction.

ding but not limited to antibiotics, topical anaesthetics, aminophylline, and even corticosteroids.

Vaccine constituents have been implicated in systemic allergic contact dermatitis, the most common of which being antibiotics (e.g., neomycin) and preservatives (e.g., thimerosal, formaldehyde, propylene glycol, sorbic acid). Mercury derivatives have been ubiquitous in the past, accounting for high rates of sensitisation in the general population, but have been recently abandoned for most of their uses.

Thimerosal is currently not used in most vaccines in the Western world, but it is still not banned from use according to the World Health Organization recommendations, which refer a positive benefit-risk assessment for its use. Other preservatives and antibiotics remain common, and their use is widespread. Most vaccines in development for COVID-19 have not disclosed their composition publicly, which makes it difficult to ascertain the risk for this type of reaction.

Pfizer's vaccine (COMIRNATY) lists 2-[(PEG)-2000]-N,N-ditetradecylacetamide (ALC-0159), a PEG derivative, as an excipient intended to stabilise lipidic particles.

Moderna's vaccine also features another PEG derivative, 1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000; for similar purposes. Cases of allergic contact dermatitis to PEG moieties have been described in the literature, but so far, no cases have been reported on COVID-19 vaccine administration.

Moderna's vaccine also lists trometamol as an excipient, a substance to which allergic contact dermatitis has been described, thus raising the possibility of systemic contact dermatitis in some patients. AstraZeneca's vaccine lists polysorbate-80 and disodium edetate dihydrate as excipients, both of which are known potential allergens.

It is worth mentioning that cases of cross-reactivity between polysorbate-80 and PEG moieties have been described. Most cases of cross-reactivity between these allergens presented as an immediate-type reaction in perioperative context, where PEGylated moieties are ubiquitous (antiseptic gels, bowel preparation solutions, ultrasound gel, lubricants, volume expanders, etc). Considering that reports of both immediate and delayed hypersensitivity reactions are found in the literature and the potential for cross-reactivity, testing for such allergens may be useful should a suspicion arise of allergy to any of those compounds.

Prick tests and patch tests may be necessary to accurately assess the full gamut of possible allergic reactions to these substances, according to the suspected pathophysiological mechanism, and may be complementary in selected cases. The dermatologist thus plays a pivotal role in the clinical assessment and diagnostic workup of these cutaneous adverse reactions.

Drug Eruptions

Other patterns of delayed hypersensitivity reactions are those of drug eruptions, which may range from the most frequent disseminated and symmetrical maculopapular exanthem (morbilliform eruption) to less frequent bullous fixed-drug eruptions or even potentially severe reactions, such as drug reaction with eosinophilia and systemic symptom syndrome.

Onset ranges from a few days to weeks after the administration of the vaccine, with re-exposure featuring earlier onset than the first reactions. Most of these adverse effects are non-life-threatening and easily manageable, with topical corticosteroids for limited extension disease or systemic corticosteroids for more widespread disease.

For more severe cases, hospital admission and systemic steroids may be warranted.

Referral to a dermatologist/allergist who specializes in type IV hypersensitivity reactions should be pursued for additional studies, after the resolution of the episode.

Erythema Multiforme

Erythema multiforme (EM) is a cutaneous reaction pattern, clinically characterised by erythematous papules (less frequently macules) with a target morphology, primarily affecting acral areas with symmetric distribution, and mucosal erosions in more severe cases. Erythema multiforme is a delayed hypersensitivity reaction most frequently elicited by active Herpes virus infection, but many other viral agents and atypical bacteria have been implicated in their etiopathogenesis (most frequently *Mycoplasma pneumoniae*, parapoxvirus, adenovirus, hepatitis viruses, cytomegalovirus, and HIV). Cases of EM have also been described in COVID-19 patients, and as a reaction pattern to multiple vaccines has been described, particularly in children, although confounding factors make the nexus of causality dubious in most instances.

Although virtually any vaccine may cause EM, virus-based vaccines, either live-attenuated or inactivated SARS-CoV-2 vaccines (e.g., CoronaVac, from Sinovac) or vaccines using adenoviruses as vectors (e.g., AstraZeneca's AZD122 and CanSino Biologics' Ad5-nCoV), may theoretically pose a higher risk for this adverse reaction.

Should a patient present with EM after vaccination, we recommend other more frequent causes to be excluded. Treatment is usually supportive as the disease is self-limited, but systemic corticosteroids and antivirals have been used in clinical practice in more severe cases, despite the evidence for use being low.

Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) represent a spectrum of conditions, which feature varying degrees of epidermal necrosis and detachment, accompanied by prominent systemic symptoms with significantly associated morbidity and mortality. Clinically, a prodrome of malaise and/or fever predates the onset of rapidly progressing erythematous exanthem with subsequent blistering and epidermal detachment in some areas. Target lesions may be present, but unlike EM, SJS/TEN affects preferentially the torso and face, and mucosal involvement of the mouth, conjunctiva, and/or genitals is very frequent. Epidermal detachment may be elicited through tangential mechanical stress with a finger (Nikolsky sign).

Stevens-Johnson syndrome/TEN is a delayed hypersensitivity reaction typically caused by drugs, which promote immune activation with cytotoxic damage of keratinocytes, but infections have infrequently been implicated as etiological agents. These entities have rarely been described after vaccine administration, and the nexus of causality is thus highly dubious. Stevens-Johnson syndrome/TEN is, however, a severe condition that requires prompt diagnosis and management. Careful assessment of these patients is advised, and hospital admission is frequently necessary. Electrolyte imbalance is frequent, and hypocalcaemia may be a cause of sudden death in these patients. Epidermal detachment of more than 30% constitutes indication for admission at a burn unit. Treatment is still a matter of discussion, but more severe cases may benefit from systemic corticosteroids, cyclosporine A, and/or antitumour necrosis factor α therapy (e.g., Etanercept), in addition to skin care and supportive hydration and nutrition, which have been reviewed extensively elsewhere.

Vasculitides

Vasculitides are a heterogeneous group of diseases, which share the common feature of endothelial damage secondary to inflammation.

Some vasculitides have been recognised as a reaction pattern to infectious or xenobiotic stimuli. The most frequent form of vasculitis, hypersensitivity (leukocytoclastic) vasculitis, usually presents with palpable purpura of the lower limbs, because of antigen-antibody complex deposition (Type III hypersensitivity reaction) in the small vessels under a gravity gradient, but other organ involvement has been acknowledged, most frequently affecting the kidney, intestines, and joints. Several cases of leukocytoclastic vasculitis, Henoch-Schönlein purpura, and even anti-neutrophil cytoplasmic antibodies-associated small-vessel vasculitis have been described in association with vaccines against viral diseases, namely, influenza and human papillomavirus, but more severe cases of medium-vessel vasculitis, such as Kawasaki disease, have also been reported. These reactions seem to be more frequent in children, adolescents, and young adults, but the relative risk of vaccination to vasculitis development seems to be low.

Incidentally, vasculitis seems to be a feature of COVID-19, as well in some cases. This raises the question whether the coming vaccines against SARS-CoV-2 may feature vasculitis as possible adverse reactions.

Management of vasculitis should focus on the exclusion of organ involvement other than the skin. Most patients without evidence of other organ lesion in small-vessel vasculitis with palpable purpura only may be discharged under topical or systemic corticosteroids, according to disease extension. Symptomatic measures to alleviate pruritus and rest with elevation of lower limbs should be proposed. Patients with skin necrosis, livedoid changes, or other organ involvement should be promptly referred to specialised hospital care with a multidisciplinary team.

Serum Sickness-Like Syndrome

Serum sickness-like reactions (SSLRs) are so described as they share overlapping clinical manifestations with serum sickness disease (a Type III hypersensitivity reaction), but no circulating immunocomplexes are found. This entity is more frequently found in children after administration of certain antibiotics, such as cefaclor, but cases of SSLRs after vaccination have been described. Clinically, an SSLR is characterised by urticarial lesions, arthralgia, and fever, days to 3 weeks after relevant exposure. Additional symptoms, such as generalised lymphadenopathy, nausea, vomiting, glomerulonephritis, and neurological symptoms, may be present in a few cases. Treatment is usually symptomatic with complete resolution after cessation of the offending agent. In more severe cases, systemic corticosteroids may be used, although evidence to support this approach is lacking.

Other Reaction Patterns

There have been reports of lichenoid eruptions, Sweet syndrome, Gianotti-Crosti syndrome, acute generalised exanthematic pustulosis, and bullous pemphigoid after vaccination. However, these cases are rare and make a causative relationship hard to establish.

Special Considerations and Unanswered Questions

Vaccines against SARS-CoV-2 are truly ground-breaking and disruptive of the usual process of vaccine development, assessment, and distribution. Although this allows for a fast development and an expedited bench-to-the-patient time, it also raises significant questions.

mRNA vaccines have long been postulated as favourable candidates for large-scale immunisation as they feature fast and simple production, and promote both humoral and cellular immunity against viral antigens. However, this is the first time that this kind of vaccine will be used in humans.

Although the available data for efficacy and safety for these vaccines, which are relatively scarce, point toward general safety, the profile of cutaneous reactions is still unclear. It is known whether these vaccines are strong stimulators of both the innate and adaptive immune responses, with increased production of interferon, the consequence of which to the skin is yet unclear.

So far, most reports of cutaneous adverse reactions to vaccines have been local or Type I hypersensitivity reactions, but other adverse reactions may come to light over time.

Viral vector-based vaccines may represent a further risk for cutaneous adverse reactions. Adenoviruses are a recognised precipitant of many cutaneous reaction patterns as described previously. Some voices have also advocated for caution when dealing with adenovirus 5 vectors, as previous research has raised the possibility that these vaccines may put some individuals at increased risk for other viral diseases, namely, HIV. These authors suggest that Ad5 immune complexes may activate the dendritic cell-T-cell axis, which could potentiate HIV-1 replication in CD4 T cells. Furthermore, Ad5-specific CD4 T cells have been suggested to feature increased susceptibility to HIV infection.

Perhaps one of the most pressing questions for dermatologists and allergists on vaccination would be on the appropriate course of vaccination should a cutaneous adverse reaction occur. Most vaccines currently marketed or at phase III in development require 2 doses, except for Janssen's Ad26.COV2.S and CanSino's Ad5-nCoV, which require only 1 dose. It is known that reactions at second dose tend to be more frequent and more severe. Should a patient develop an adverse skin reaction, these specialists would be called to ascertain whether a second dose should be administered or withheld. On the one hand, withholding the second dose may compromise vaccine efficacy; on the other hand, a second dose may cause more severe reactions. As a rule of thumb, mild local reactions pose no contraindication to second dosage. Severe reactions should be assessed on a case-by-case basis. As per the current Centers for Disease Control and Prevention guidelines, individuals with a known diagnosis of PEG/polysorbate immediate-type allergy or allergy to any mRNA vaccine should not receive vaccination with another mRNA vaccine against SARS-CoV-2, unless deemed otherwise by a specialised allergist, and only under strict medical observation. As most immediate hypersensitivity reactions are due to excipients, initiating and completing the approved posological schedule of a different vaccine with distinct composition may become an option, but as of now, there are no formal recommendations on this aspect. For severe adverse skin reactions, such as SJS/TEN or systemic vasculitides, it is our opinion that a rechallenge poses inadmissible risks. One-dose schemes may obviate this dilemma, but that does not mean that they are necessarily safer. Furthermore, these severe adverse reactions are infrequent at most, and thus should not dictate public health policies on vaccinal schemes.

Last, physicians will be asked to provide opinion on the vaccination of patients with chronic severe skin diseases and those under immunosuppressant or immunomodulating therapies. To date, until data are available, there is no evidence to support any course of action, and advice should be provided based on expert consensus and individual characteristics of the patients.

Conclusions

Vaccination against SARS-CoV-2 will represent a significant progress toward ending this pandemic crisis. Physicians should be aware that large mass vaccination may lead to a rise in certain reactive dermatosis, which should be promptly identified and appropriately managed. Nevertheless, the individual risk for any such adverse reaction will be probably low and should not be considered a valid argument against vaccination, in most cases. Detailed data on safety from the available clinical trials and long-term surveillance of adverse effects are paramount to identify possible risks, thus allowing for adequate prevention. Nationwide databases to register adverse effects should be encouraged as a primary pharmacovigilance strategy.

Patch testing with Carmine 2.5% in Petrolatum by the NACDG 2011-2012

by Erin Warshaw, et al.
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Systemic Contact Dermatitis (SCD) describes the hypersensitivity reaction following systemic re-exposure of the inciting allergen in previously sensitised individuals. A multitude of substances have been reported in the literature to be capable of eliciting Systemic Contact Dermatitis. These substances can be separated into metals, drugs, plant products, chemicals, edibles, and several other categories. Recently, emerging in the “edibles” category is a lesser-known cause of SCD, carmine.

The aim of the study was to analyse patch test reactions to carmine (2.5% in petrolatum) and characterise carmine-positive patients, by conducting a retrospective analysis of North American Contact Dermatitis Group data compiled between 2011 and 2012.

Of 4,240 patients patch tested to carmine, 132 (3.1%) had reactions with a final interpretation of “allergic” (positive).

Carmine-positive patients were significantly more likely to be female (77.7% vs 68.3%; P = 0.0237) and have a final primary diagnosis of allergic contact dermatitis (74.8% vs 47.2%; P < 0.0001).

As compared with carmine-negative patients, carmine-positive patients were significantly more likely to have involvement of all facial sites combined (48.1% vs 29.9%; P < 0.0001) and the lips (7.6% vs 3.6%; P = 0.0166).

At final reading, most carmine reactions were weak (+; 64.9%). Approximately half (53.4%) were currently clinically relevant. Identified sources were primarily personal care products (77.1%), especially makeup (31.4%) and lip products (8.6%).

Weak patch test reactions to carmine should be interpreted with caution. Allergic contact dermatitis to carmine should be suspected in women with facial and/or lip dermatitis, especially those using carmine-containing cosmetics. In a 7-year study (2005–2012), the North American Contact Dermatitis Group (NACDG) tested a total of 87 allergens in patients aged 0 to 18 years. Of the 883 children who were tested, 62.3% had at least 1 positive patch test. Of those tested in the 0- to 18-year age range, 3.8% had positive patch tests to carmine.

There is a rather clear delineation of sensitivity reactions to carmine, to localised symptoms and to systemic symptoms of Contact Dermatitis. This is most likely a consequence of the different immunological response pathways to carmine, illustrating Type I and Type IV hypersensitivity.

Localised Contact Dermatitis

The NACDG Patch Test Results from 2011–2012 found 66.8% of all referred individuals had contact sensitivity to at least 1 allergen. Of patients who tested positive, 49.5% were diagnosed with ACD.

Carmine in cosmetics

In their recent report, the NACDG made 4 changes to their screening series. Of the initial 70 allergens, glycerol thioglycolate and dimethylol dihydroxyethyleneurea were removed and subsequently replaced by carmine 2.5% petrolatum and ethyl 2-cyanoacrylate 10%, respectively. It should be noted that carmine has been removed from the list of allergens currently tested by the NACDG.
The NACDG reported a 3.1% (131/4230) positive rate for carmine, of which two thirds of the reactions to carmine were mild.

Further stratification of reaction relevance demonstrated 1.5% definite, 13.7% probable, and 38.9% possible.

Occupational asthma has been reported in industries that use carmine in the production of consumer products including textiles, dyes, cleaning supplies, cosmetics, animal health, farming, food (especially sausage making), health care, and construction.

This 2003 study recognised rates of carmine sensitisation and occupational asthma of 48.1% and 18.5%, respectively. To date, in 2021, the Centers for Disease Control and Prevention has yet to include carmine as a hazardous substance in the workplace.

There are few case reports of localised ACD to carmine.

Sarkany et al reported the first cases of allergic contact chellitis secondary to carmine exposure in 3 patients in 1961. There were several other reports of such sensitivity during the next few decades.

In 2009, Shaw reported an especially interesting case in which a 28-year-old woman experienced a flare of dermatitis 6 to 24 hours after application of her eye shadow and lipstick containing carmine. Her allergy was confirmed with a patch test utilising 2.5% carmine in petrolatum. Following carmine allergy diagnosis, after incorporation of carmine-free cosmetic products, the patient experienced no further carmine reactions. In conjunction with her reaction following exposure to carmine-containing products, this patient also tested positive for immunoglobulin E (IgE) against cochineal proteins. The combination of Types I and IV reactions suggests the potential for a concomitant protein contact dermatitis (PCD) and classic delayed hypersensitivity pathway to the low-molecular-weight carminic acid and/or high-molecular-weight cochineal protein, but also may open a door to gain insights into juxtaposition points of both the innate and adaptive immune system pathways.

Similarly, Suzuki et al reported another case in 2011, where a 52-year-old woman without a history of atopic dermatitis or allergic rhinitis presented with scaly erythema secondary to application of carmine-containing blush. Two years prior, she experienced a pruritic erythema on her cheeks bilaterally that improved with avoidance of carmine-containing cosmetics. After patch testing the patient with her personal cosmetic products, only the blush tested positive. This patient's allergy was confirmed by patch testing utilising 0.2% carmine in petrolatum.

- Machler and Jacob recently reported a 4-year-old atopic girl who presented with recurrent intermittent bouts of generalised systematised dermatitis associated with severe facial involvement and periorbital swelling. She was initially prescribed a hypoallergenic routine (with very limited personal care products), tacrolimus 0.1% ointment, and a 7-day course of prednisolone 15 mg every morning (0.8 mg/kg). Fourteen days later, she was patch tested, which showed a clinically relevant 2+ reaction to carmine that appeared by 48 hours and persisted. The clinical relevance of carmine was sourced to candies, juices, and, most notably, red velvet cupcakes, which had temporal association with the flares.

Although a prevalence of 3.1% of individuals testing positive places carmine sensitisation in the top 40 NACDG allergens, carmine (along with several others) remains absent from T.R.U.E. Test.

As a consequence, when considering the reported prevalence of sensitisation and widespread use of carmine in consumer products, it is highly likely that many reactions are unrecognised and therefore carmine sensitisation is underreported.

Systemic Contact Dermatitis

There are few case reports of systemic ACD to carmine.

- Greenhawt and Baldwin noted definitive cases of IgE-mediated anaphylactic reactions occurring immediately after exposure to carmine. However, they also stated there are cases in which reactions occur several hours later. In addition, skin prick tests were often found to react at 30 minutes, as opposed to the typical 10 to 15 minutes. Greenhawt and Baldwin acknowledged the reason is unclear; however, there is likely a systemic PCD association that allows for Type I symptoms on the timeline of a delayed-type response. As discussed earlier, this phenomenon is likely attributed to the immunologic crossroads between Types I and Type IV hypersensitivity.
- Ferris et al described a case of SCD in which a woman in her 50s with a childhood history of atopic dermatitis and flexural dermatitis presented with periorbital erythema and edema, perioral plaques, and erythematous scaly plaques on her neck, ears, back, and buttocks. On patch testing, the patient demonstrated sensitivity to formaldehyde, formaldehyde releasers, and carmine. After extensive review of her regular cosmetics and medications, it was discovered that her lip balm and chewable multivitamin contained carmine. Although the patient practiced avoidance of her confirmed allergies, her dermatitis remained recalcitrant. It is theorised that her yeast microbiome may have been a factor in her continued dermatitis flares and underscores the multifactorial nature of chronic dermatitis in patients.
- Chung et al outlined a case report of 3 women demonstrating episodic urticaria, angioedema, and/or anaphylaxis 3 to 5 hours after consumption of carmine-containing food products. Patient 1 was a 32-year-old woman who experienced these symptoms 3 to 5 hours after consuming artificial crab or ruby red grapefruit juice. Patient 2 was a 27-year-old woman who presented to the emergency room after ingesting carmine-coloured ice on a stick. She experienced nausea within minutes; however, the corresponding pruritus, urticaria, hypotension, and tachycardia occurred later within 3 hours of ingestion. Lastly, after facial application of blush coloured with carmine, she reported immediate, pruritic, erythematous eruption. The third patient reported several episodes of angioedema and/or urticaria 4 to 5 hours after ingestion of artificial crab containing carmine. Patient 1's allergy was confirmed through a combination of skin prick testing and single-blind, placebo-controlled food challenge to carmine. Patient 2's allergy was confirmed by Prausnitz-Küstner test (used to identify presence of IgE antibodies), and patient 3's allergy was confirmed by skin prick testing and a double-blind, placebo-controlled food challenge to carmine. Notably, after avoidance of carmine-containing products, all 3 patients experienced no further episodes of recurrent anaphylaxis, urticaria, or angioedema. Most importantly, Chung et al noted that commercial carmine contained

proteinaceous material from the cochineal insect. Immunoblot assays determined that no 2 patients reacted to the same protein bands derived from pulverised cochineal extract and carmine liquid. While the same proteins were present in both, their concentrations differed. Furthermore, immunoblotting assays noted that the smallest protein found in these patients was approximately 21.5 kd, an observation consistent with the development of PCD in some individuals.

- Baldwin et al described a case of a 27-year-old woman with a history of allergic rhinitis and positive skin prick tests to various aeroallergens presenting to the emergency department with anaphylaxis. More specifically, she experienced nausea, pruritus, urticaria, and hypotension 3 hours following consumption of a popsicle containing carmine. Prior to her anaphylactic episode, this patient reported a previous episode of an immediate pruritic and erythematous eruption following application of her normal cosmetic products on her face, which were found to have carmine. Interestingly, when her cosmetics were applied to her forearm, no reaction was noted. However, the reported patient did exhibit a positive skin prick test and Prausnitz-Küstner test to carmine-specific IgEs.

- Baldwin et al noted that topical sensitisation was not a well-documented pathway for the development of an IgE response. However, Spergel et al demonstrated that protein allergens are capable of eliciting localised allergic dermatitis and bronchial hypersensitivity through an IgE-mediated antibody response. These findings support the IgE-bound Langerhans cell activation of B and T cells, with priming of IgE for the mast cell response.

- Kägi et al described a 34-year-old woman with a history of atopy presenting with anaphylaxis 15 minutes following consumption of orange juice mixed with Campari. Her reaction consisted of sneezing, conjunctivitis, rhinitis, pruritus, urticaria, Quincke's oedema, dyspnoea, bronchospasm, nausea, vomiting, diarrhea, and chills. A thorough history yielded that the patient had previously experienced reactions to cosmetic products containing carmine, as confirmed by skin prick tests. Follow-up with this patient showed that this patient continued to experience minor allergic reactions to food products containing carmine.

- Similarly, DiCello et al presented 2 women, aged 27 and 42 years, who developed similar reaction following consumption of a carmine-containing yogurt and Campari. Notably, each of these women had previous reactions to cosmetics containing carmine. Sensitivity to carmine was positive via skin prick testing. The combination of epidermal reactions to carmine-containing compounds with associated IgE-mediated symptoms suggests the potential PCD. Topical sensitisation occurs with IgE-bearing Langerhans cells that travel to the lymph node, where B cell–dependent CD4 T-cell activation occurs. Maturation of B cells to plasma cells allows for immunoglobulin production and mast cell activation, capable of eliciting the above reaction.

- In another case reported by Greenhawt et al, a 47-year-old woman with a history of mild persistent asthma, allergic rhinitis to pollen and dander, and oral allergy syndrome presented for evaluation of her swelling and respiratory distress. The patient had a history of facial angioedema in response to red raspberry yogurt, facial and tongue swelling, and respiratory distress secondary to consumption of red tortellini and facial dermatitis and swelling after application of red eye makeup. Of note, all 3 substances contained carmine. Forty-five days after the initial evaluation, the patient presented with facial itching and eye swelling 90 minutes after the consumption of a generic azithromycin pill. To confirm allergy, carmine dye, crushed and dried cochineal insects, crushed tablets, generic azithromycin, and crushed coatings were utilised in epicutaneous skin prick testing. Notably, she tested positive to the carmine dye, but negative to cochineal extract. The authors noted that her skin prick test results may be the result of cochineal processing, in which cochineal proteins may have become converted to an allergenic form.

- Miyakawa et al reported a case of a woman who used dark red eyeliner or orange eye shadow almost daily for 3 years. A year prior to this report, she had developed mild type I hypersensitivity symptoms (itching swelling and redness of body) 1 hour after consuming a pink macaroon. At a later time, she developed itching, swelling, and redness on her face, eyelids, and body; pharyngeal tingling; and collapse 15 minutes after consumption of either a raspberry and white chocolate–flavoured chocolate biscuit or strawberry flavoured latte. In this particular situation, it appears that the patient was sensitised by her daily cosmetics, and her oral ingestion triggered the anaphylactic reaction. This reaction parallels the pathogenesis of SCD described previously. Daily cutaneous carmine exposure led to DC activation of naive T cells and differentiation of B cells capable of eliciting types IV and I hypersensitivity reaction, respectively. These sensitized T2 cells and B cells primed in the gastrointestinal mucosa elicited the anaphylactic response upon re-exposure to dietary carmine.

- Tabar-Purroy et al recorded cases of occupational asthma in present (24) and past (1) employees who processed natural dyes. Positive skin test results from these employees yielded 41.7% positive to carmine, 29.2% positive to cochineal, and 4.2% positive to carminic acid.

Occupational asthma has been reported in industries that use carmine in the production of consumer products including textiles, dyes, cleaning supplies, cosmetics, animal health, farming, food especially sausage making, health care, and construction.

The assemblage of SCD, anaphylaxis, asthma, and gastrointestinal allergic reactions in the context of carmine exposure highlights carmine's ability to trigger multiple immunologic pathways.

Carmine remains a highly prevalent substance in consumer products and the sensitisation to carmine is likely underreported, due to its absence from almost all current testing panels.

In individuals with recalcitrant dermatitis and a positive carmine intolerance history and/or patch test, it is important to consider a trial topical and dietary elimination of carmine-associated products and foods.

The significance of positive patch test is confounded by the potential for carminic acid and cochineal protein sensitisation. While both appear capable of contact sensitisation, the allergenic molecule(s) used in consumer products is unknown.

Additional studies are necessary to further investigate the patho-immunologic mechanism behind carmine-associated SCD.

As always, for further information, pleae read the original article.

Chemotechnique

Due to the increasing recognition of carmine as a sensitising substance causing allergic contact dermatitis, Chemotechnique has now made available this substance as a commercially available hapten, with article number C-059, and included in the ACDS Core Series, AC-1000.

Patch Testing with a New Composition of the Mercapto Mix. A Multicentre Study from the International Contact Dermatitis Research Group

By Marlene Isaksson, et al.
In Dermatitis, Volume 32, Issue 3, May/June 2021, pp 160-163.

Occurrence

Mercaptobenzothiazole compounds are associated with allergic contact dermatitis caused by rubber products.

Mercaptobenzothiazole compounds are primarily used as accelerators in rubber products and are secondarily used as fungicides and in machine coolants. They are first and foremost associated with allergic contact dermatitis caused by rubber products.

Substances

With more mercaptobenzothiazole derivatives being used as accelerators, new screening substances were introduced for patch testing. In the 1970s, MBT was replaced in the ICDRG Baseline Series by a mix, which comprised:

MBT
N-cyclohexyl-2-benzothiazyl sulphonamide
2,2′-dibenzothiazyl disulphide
2-(4-morpholinyl) mercaptobenzothiazole.

This mix, commonly known as the Mercapto mix, has since been used in different compositions and concentrations in different baseline series over the years. To investigate possible allergic rubber dermatitis, 2-mercaptobenzothiazole (MBT) in 2% petrolatum (pet.) was included in the very first baseline series proposed by the International Contact Dermatitis Research Group (ICDRG) in 1968.

Mainly, 3 different Mercapto mixes have been used:

A 3-part mix consisting of 0.33% each of the 3 substances mentioned above but no MBT (total concentration, 1.0%)

A 4-part mix consisting of 0.25% of each of the aforementioned haptens (total concentration, 1.0%)

A 4-part mix consisting of 0.50% of each of the aforementioned haptens (total concentration, 2.0%).

In many baseline series, both the Mercapto mix at 2% (wt/wt) pet. and MBT 2% (wt/wt) pet. are tested in parallel, for example, in the ICDRG Baseline Series decided in 2000.

Study

The aim of this study was to investigate whether a Mercapto mix at 3.5% (wt/wt) could replace the 2 preparations Mercapto mix at 2.0% pet. and MBT at 2.0% pet. In other words: does the mix at 3.5% detect as many positive patients as patch testing the 2 preparations Mercapto mix at 2.0% pet. and MBT at 2.0% pet., respectively, in parallel?

Replacing the two tests with just one test would enable additional space to test a more relevant hapten in a screening series.

Twelve ICDRG member dermatology clinics took part during the period of January 1, 2017, until the middle of 2018. The participating clinics were located globally.

Results were based on the consecutive patch testing of 7,103 dermatitis patients with suspected allergic contact dermatitis, 5,097 women and 2,006 men (mean age: men, 43.5 years; women, 44.0 years; age range: men, 1–97 years; women, 6–94 years).

7,103 dermatitis patients in 12 International Contact Dermatitis Research Group dermatology departments were patch tested with 2-mercaptobenzothiazole 2.0% petrolatum (pet.), Mercapto mix 2.0% pet., and Mercapto mix 3.5% pet.

Materials Used

The preparations containing MBT 2.0% (wt/wt) pet. and Mercapto mix 2.0% (wt/wt) pet. were acquired from Chemotechnique Diagnostics (Vellinge, Sweden) and distributed to the participating clinics. The preparation of Mercapto mix 3.5% (wt/wt) pet. was prepared by the Malmö Department by spiking the commercial preparation of mercapto mix 2.0% (wt/wt) pet. (Chemotechnique Diagnostics) with MBT.

This implied a final concentration of 2.0% MBT and 0.5% of the other 3 constituents of the regular MBT mix 2.0% to get the MBT mix 3.5%. All participating clinics used patch test preparations from the same batches.

Patch Testing

Patch testing procedures followed the routine of the participating clinics.

Finn Chambers (8-mm diameter; SmartPractice, Phoenix, AZ) on Scanpor tape (Norgesplaster, Vennesla, Norway) were used in all centres except Montreal and Ottawa, which used IQ Ultra chambers (8 × 8 mm; Chemotechnique Diagnostics) on a hypoallergenic surgical tape, and Leuven, which used the AllergEAZE test system of patch test chambers.

The 20-mg dose for the Finn Chambers and the 25-mg dose for the IQ Ultra chambers were applied. Chambers were applied on the back and occluded for 2 days. Readings were classified according to the ICDRG guidelines. The common reading day was day 3 (D3) or D4. A positive reaction on D3 or D4 was registered, and the results were based on these readings. The definition of “positive” was +, ++, and +++ reactions only, excluding doubtful and irritant reactions.

Only test results from individuals tested with the 3 preparations simultaneously were registered. An individual test protocol designed for the study was filled in for each patient with patch test reactions (allergic, doubtful, or irritant) to at least one of the test preparations. It was emphasised that all patch test reactions without an obvious morphology of an allergic or irritant nature must be classified as doubtful. Late reactions beyond D8 were also to be reported.

Results

Contact allergy to the 3 test preparations varied among the 12 centres:

2-mercaptobenzothiazole 2.0% pet. (0–2.4%),
Mercapto mix 2.0% pet. (0–4.9%),
Mercapto mix 3.5% pet. (0–1.4%).

2-Mercaptobenzothiazole 2.0% and Mercapto mix 2.0% detected a few more positive patients compared with Mercapto mix 3.5%, but the difference was statistically insignificant.

Numerically, Mercapto mix 2.0% pet. as well as MBT 2.0% pet detected a few more patch test–positive patients than Mercapto mix 3.5% pet, but the difference was statistically insignificant.

When both Mercapto mix 2.0% pet. and MBT 2.0% pet. were tested in parallel and both were positive, the difference with respect to Mercapto mix 3.5% was also statistically insignificant.

Distribution of exclusive and concurrent positive test reactions to Mercapto mix 2.0% (wt/wt) pet., Mercapto mix 3.5% (wt/wt) pet., and MBT 2.0% (wt/wt) pet. in 49 individuals. The number of patients with a positive test reaction to the respective test substance were:No sex difference was seen.

Few doubtful reactions were seen:

for MBT 2.0%	= 9/7103	= 0.13%
for Mercapto mix 2.0%	= 7/7103	= 0.10%
Mercapto mix 3.5%	= 5/7103	= 0.07%.

No or few irritant reactions were registered:

for MBT 2.0%	= 0/7103	= 0.00%
for Mercapto mix 2.0%	= 2/7103	= 0.03%
for Mercapto mix 3.5%	= 1/7103	= 0.01%.

A limitation to this study is the small sample size and with some centres having no positive reactions.

Discussion

The patch test preparations in the baseline series have all been tested extensively and are optimised to give a minimum of false-positive and false-negative reactions as possible, that is, they are tested in non-irritant and non-sensitising concentrations.

When raising a test concentration, there is always a risk that the new concentration will lead to false-positive reactions. To pre-empt this possibility, a pre-study was conducted at the Malmö department in consecutive dermatitis patients in a stepwise manner using incrementally increased concentrations of MBT in the Mercapto mix, such as that previously reported by the Swedish Contact Dermatitis Research Group.

This study may be classified as a high-quality study. Several previous studies have compared patch test results with MBT 2.0% pet. and Mercapto mix 2.0% pet.

- In 2006, The European and Environmental Contact Dermatitis Research Group concluded that both MBT 2.0% and Mercapto mix 2.0% should be included in the European Baseline Series. In that study, a total of 32,475 patients were tested, and 0.22% (73/32.475) were positive only to mercapto mix 2.0%, 0.20% (66/32.475) were positive only to MBT 2.0%, and 0.58% (188/32.475) were positive to both preparations.
- In 2014, the North American Contact Dermatitis Group presented concomitant reactions between MBT 2.0% pet. and Mercapto mix 2.0% pet. in a total number of 30,880 patients.

They reported that 0.31% (98/30.882) were positive only to Mercapto mix, 0.62% (192/30.882) were positive only to MBT 2.0%, and 0.76% (235/30.882) were positive to both preparations and concluded that MBT ought to be the preferential screening hapten for mercapto compounds.

Conclusions

Mercapto mix 3.5% pet. is not better than 2-mercaptobenzothiazole 2.0% and Mercapto mix 2.0% by a difference that is significant.

By using only 1 test preparation (Mercapto mix 3.5%), an additional new hapten in a series could be tested.

The general recommendation is that a sensitiser should be included in a baseline series when the contact allergy rate in consecutively tested dermatitis patients is 0.5% or higher. Even if our rate for 2 of the 3 preparations was less than 0.5%, it does not necessarily mean that an MBT test preparation should not be present in a baseline series. It is debatable whether Mercapto chemicals have a place at all in the baseline series. The conclusion from the Swedish study was that until better markers for this type of rubber allergy are present, the replacement of the Mercapto mix 2.0% pet. with the Mercapto mix 3.5% pet. should take place.To conclude, Mercapto mix 3.5% pet was not better than MBT 2.0% with or without Mercapto mix 2.0% to detect this contact allergy, but the difference in patch test results was insignificant. By testing with only one test preparation (Mercapto mix 3.5%), one hapten of higher relevance could be placed in the ICDRG baseline series.

As a result of this study, the members of the ICDRG decided beginning in 2019 to replace MBT 2.0% pet. and Mercapto mix 2.0% pet. with Mercapto mix 3.5% pet. in the ICDRG baseline series.

Chemotechnique

Chemotechnique offer the Dermatologist the following relevant mixes and individual haptens:

Mercapto mix	1.0%	pet	Mx-05B
Mercapto mix	2.0%	pet	Mx-05A
Mercapto mix	3.5%	pet	Mx-05C
Mercapto mix Mx-05B (1.0%) comprises the following components:			
Dibenzothiazyl disulfide (MBTS)	0.33%	pet	D-003
N-Cyclohexyl-2-benzothiazolesulfenamide	0.33%	pet	C-023
2-(4-Morpholinylmercapto) benzothiazol (MOR)	0.33%	pet	M-016
Mercapto mix Mx-05A (2.0%) comprises the following components:			
2-Mercaptobenzothiazole (MBT)	0.5%	pet	M-003A
Dibenzothiazyl disulfide (MBTS)	0.5%	pet	D-003
N-Cyclohexyl-2-benzothiazolesulfenamide	0.5%	pet	C-023
2-(4-Morpholinylmercapto) benzothiazol (MOR)	0.5%	pet	M-016
Mercapto mix Mx-05C (3.5%) comprises the following components:			
2-Mercaptobenzothiazole (MBT)	2.0%	pet	M-003A
Dibenzothiazyl disulfide (MBTS)	0.5%	pet	D-003
N-Cyclohexyl-2-benzothiazolesulfenamide	0.5%	pet	C-023
2-(4-Morpholinylmercapto) benzothiazol (MOR)	0.5%	pet	M-016

Positive Patch Test Reactions to Carba Mix and Thiuram Mix: The North American Contact Dermatitis Group Experience (1994–2016)

by Erin Warshaw, et al
in Dermatitis, Volume 32, Issue 3, May/June 2021, pp 173-184.

Occurrence

Carba mix (CM) and thiuram mix (TM) are allergen mixes of commonly used rubber vulcanisation accelerators. Carba mix and Thiuram components are important occupational allergens, especially in rubber gloves.

Chemicals

Carba mix is composed of the following chemicals:

- 1,3-diphenylguanidine
- zinc dibutyldithiocarbamate (ZDBC)
- zinc diethyldithiocarbamate (ZDEC).

Thiuram mix is composed of 4 organo-sulphur compounds:

- tetramethylthiuram monosulphide (TMTM)
- tetramethylthiuram disulphide (TMTD)
- tetraethylthiuram disulphide (disulphiram, TETD)
- dipentamethylenethiuram disulphide (DPTD).

Recent evidence suggests that dithiocarbamates/diphenylguanidine may be more important as allergens than thiurams in gloves.

Thiurams and dithiocarbamates are theorised to cross-react, because they are closely related structurally and constitute a redox pair. Dithiocarbamates produce the corresponding thiuram disulphide when oxidised; reduction of a thiuram disulphide produces the analogous dithiocarbamate structure.

Although the North American Contact Dermatitis Group (NACDG) Screening Series, American Contact Dermatitis Society Core Series, and T.R.U.E. TEST (SmartPractice Denmark ApS, Hillerød, Denmark) all include both CM and TM, many national standard series opt to test only for TM because of these structural similarities.

In a study of 24 patients with known allergic contact dermatitis to rubber accelerators, Hansson et al found that all but one patient who reacted to dithiocarbamates also had a concurrent reaction to the equivalent thiuram compound. However, studies examining concomitant reactions to CM and TM in larger populations present mixed results. Because thiurams and dithiocarbamates have structural similarity, concomitant reactions are to be expected.

Thiurams and carbamates are primarily used in the rubber industry

As thiurams are reduced to dithiocarbamates, and dithiocarbamates are oxidised to thiurams (a redox equilibrium), a significant frequency of concomitant reactions is not surprising. Thiuram disulphides, when bonded to nickel, form lipophilic complexes that distribute easily through tissue and may penetrate the skin more easily compared with carbamates; this difference in penetration may explain different patch test results between TM and CM.

It is also important to note that, unlike ZDEC and ZDBC, diphenylguanidine is not a dithiocarbamate and does not share the same close structural relationship with thiurams. This study was limited to being able to test only CM instead of individual dithiocarbamate chemicals; it is possible that testing a mix composed of only dithiocarbamates without diphenylguanidine may have resulted in more frequent concomitant reactions than in the current study. Other studies have found significantly stronger associations between ZDEC and TM compared with CM and TM. However, many national/international screening series do not test for CM and opt to test for TM only.

Carba mix is a well-known problematic allergen, causing a large proportion of doubtful and irritant reactions when occluded on the skin. Notably, CM was removed from the European Baseline Series in 1988 after 17 years of testing because of risk of irritancy. In contrast, TM has traditionally been considered to be acceptable.

For example, the largest study involved 29,522 patients patch tested by the European Surveillance System on Contact Allergies (ESSCA) found that 31.8% of TM-allergic patients had positive reactions to CM and 21.1% of CM-allergic patients had reactions to TM.

This study by the NACDG characterises concomitant reactions to carba mix (CM) and thiuram mix (TM) in a large North American population. Patients with a final reaction interpreted as “allergic” to either CM or TM were included. Investigations of concomitant reactions to CM and TM in a large North American population have been lacking. This study characterises and analyses general trends of positive reactions to CM and TM in patients tested by the NACDG.

Haptens

The NACDG Screening Series comprises 65 to 70 screening allergens / haptens, and has included both CM and TM since 1994.

Patch test haptens / allergens used were allergEAZE (SmartPractice, Calgary, Alberta, Canada), and Chemotechnique (Chemotechnique Diagnostics AB, Malmö, Sweden).

Haptens / allergens were tested on Finn Chambers (SmartPractice, Phoenix, AZ) with Scanpor tape (Alpharma AS, Vennesla, Norway).

Patch testing was completed in accordance with the previously published NACDG protocols.

All patches were removed after 48 hours.

Timing of the final read varied between NACDG physicians, ranging from day 4 to day 8.

Results

A total of 49,758 patients were tested to both CM and TM.
A total of 3,437 (6.9%) had positive reactions to CM and/or TM, comprising the following groups:

- CM+ only n = 1,403 40.8%
- TM+ only n = 1,068 31.0%
- Both TM and CM n = 966 28.1%.

A total of 47.5% of TM+ patients were positive to CM and 40.8% of CM+ patients were positive to TM.

Male sex, occupationally related dermatitis, and hand involvement were significantly more common in individuals positive to CM and/or TM as compared with those who were negative.

More than 80% of CM+/TM+ reactions were currently relevant.

There were 2,369 total reactions to CM and 2,034 total reactions to TM.

Among TM+ patients, 47.5% were also positive to CM, whereas 40.8% of CM+ patients were also positive to TM.

In other words, 52.5% of reactions to TM would have been missed by testing to CM alone and 59.2% of CM reactions by testing to TM alone. For the subgroup of patients with strong (++ or +++) reactions to either CM, TM, or both, 57.5% of TM+ patients were also positive to CM, and 68.6% of CM+ patients were also positive to TM.

For these patients, 42.5% of reactions to TM would have been missed by testing CM alone, and 31.4% of reactions to CM would have been missed by testing TM alone.

Irritant Reactions to CM and TM

Irritant reactions included those coded as:

- “Definite irritant” CM: 414 TM: 98
- “Unknown/indeterminate” CM: 265 TM: 81
- “Doubtful, final interpretation negative” CM: 541 TM: 165
- Total irritant reactions CM: 1220 TM: 344.

This is a very significant proportion of the reactions to CM and to TM.

Trends of CM and TM

Overall, the proportion of positive reactions to both of these rubber accelerators decreased significantly since the inclusion in the NACDG screening series in 1994-1995 to 2015-2016.
In particular, there were no significant differences in the proportion of positive reactions to CM and TM in each 2-year cycle between 1994 and 2006. However, the proportion of positive reactions to CM was greater than that to TM in each 2-year cycle between 2007 and 2016.

This figure shows the prevalence of allergy to CM and TM from 1994 to 2016, based on the data adapted from the NACDG Standard Series patch test results published on a biannual cycle.

Allergen Sources of CM and TM

For positive reactions to CM and TM, the most common source category was “clothing/protective equipment”. Within this group, gloves were the most frequent (24%-64%).

However, in CM+ only patients, the proportion of allergy attributable to gloves was significantly lower than that in those positive to both and TM+ patients.

In CM+ only patients, personal care products and clothes/apparel/garments seemed to be a more common source of dermatitis compared with those in other subgroups.

Positive Reactions to CM and TM

Nearly half (47.5%) of TM+ patients demonstrated reactions to CM, and 40.8% of CM+ patients had concomitant reactions to TM; this association was greater for patients with strong (++, +++) reactions.

This study showed higher concomitant frequency compared with 2 prior ESSCA studies of 46,854 patients, which found that 36.5% of TM+ patients had reactions to CM and 28.3% of CM+ patients had reactions to TM. Buttazzo et al, in north-eastern Italy, found that 39.7% of TM+ patients had reactions to CM, and 21.0% of CM+ patients had reactions to TM. In the current study, 28.1% of patients reacting to CM and/or TM were positive to both. This percentage of CM+/TM+ reactions is also higher than that in previous studies involving at least 100 patients, which ranged from 14.5% to 22.7%.

Compared with patients allergic to one mix alone, CM+/TM+ patients were more likely to have stronger reactions to these allergens. It is possible that weaker reactions to a mix may not represent true “allergy” and thus not present with true cross-reactions to the other mix; CM especially is known to be a patch test allergen of high irritancy.

One other small study presented data on strength of reactions and concomitant reactions; in that study, 81.8% (9/11) of reactions in CM+/TM+ allergic patients were ++ or +++, compared with 69.2% (18/26) of CM+ only (18/26) and 100% (1/1) of TM+ only. In addition, reactions in patients positive to both rubber mixes were significantly more likely to be clinically relevant than reactions in patients positive to only one rubber mix. No other studies have evaluated clinical relevance in relation to reaction strength.

Patient Characteristics

Patients positive to CM and/or TM were significantly more likely to be male, have an occupationally related dermatitis, or have dermatitis involving the hands compared with patients negative to CM and/or TM. As thiurams and carbamates are commonly used in rubber gloves used by workers in healthcare, household services, and other industries, these results are consistent with an expected higher likelihood of glove exposure in these categories of workers.

Trends

Frequency of positive reactions to both CM and TM has significantly decreased since their addition to the NACDG Screening Series in 1994. However, the proportion of positive reactions to CM remained relatively consistent between 2001 and 2016, whereas the proportion of positive reactions to TM decreased more so during the same period, which is consistent with previous reports. The

Most Common Sources Overall Associated with CM and TM (Since 2001*)

	CM+ n=1,065	CM+ in (CM+/TM+) n=659	TM+ in (CM+/TM+) n=659	TM+ n=729
Clothing, wearing apparel, protective equipment, and textiles	**43.0%**	**73.4%**	**74.8%**	**56.9%**
Gloves	23.6%	63.4%	63.9%	41.3%
Undergarments and swimwear	8.1%	1.5%	1.4%	3.4%
Shoes, boots, sandals, and slippers	4.1%	4.2%	4.6%	6.4%
Shirts, pants, socks, stockings, belts, hats, textiles, accessories, and others	2.1%	0.6%	0.8%	1.0%
Personal care products (including Band-Aids and health devices)	**18.7%**	**6.8%**	**5.9%**	**8.9%**
Miscellaneous health aids and devices	0.8%	1.1%	1.5%	0.4%
Tapes, Band-Aids, and adhesive aids	0.4%	0.2%	0.2%	0.8%
Building and construction materials, tools, equipment, and supplies	**2.4%**	**2.3%**	**2.1%**	**1.8%**
Machinery and vehicles	1.3%	1.7%	1.7%	1.5%
Miscellaneous	**0.3%**	**0.8%**	**0.8%**	**2.6%**
Personal grooming devices and applicators	0.3%	0.8%	0.6%	2.2%
Others†	**3.4%**	**3.6%**	**3.9%**	**4.3%**
Unknown/not classified elsewhere	30.9%	11.4%	10.8%	24.0%

*Sources available from 2001.
†Includes glasses/jewellery, safety equipment, essential oils, aromatherapy, chemicals/chemical products, furniture/structures, drugs/medications/alcoholic beverages, and soaps/detergents/cleansers/laundry aids.

CM = carba mix; TM = thiuram mix.

For the subgroup of patients with ++ or +++ reactions to CM, TM, or both, clothing/protective equipment remained the most common category. Gloves remained the most frequent source within the clothing group.

ESSCA found that frequency of positive reactions to TM significantly decreased and positive reactions to CM significantly increased from 2004 to 2012. This has been considered partly because of glove manufacturers changing production practices and rubber additives in recent years.

Sources

Consistent with prior studies, gloves were the most common source associated with reactions to CM and/or TM. Although thiurams have historically been the most commonly identified source

of rubber allergy, carbamates have been more frequently used in rubber gloves in recent years, which likely explains the increasing frequency of positive reactions to CM. An analysis of manufacturer-reported ingredients completed in 2018 found that carbamates were reported by manufacturers in nearly 91% of gloves, compared with thiurams in 5.8%.

An interesting finding of the current study is that allergic contact dermatitis in CM+ only patients was related to gloves only 24% of the time, compared with 63% in CM+/TM+ patients and 41% in TM+ only patients. However, this difference was smaller for patients with ++/+++ reactions to CM, TM, or both; CM+ only patients had allergy related to gloves 33.3% of the time, compared with 63% in CM+/TM+ patients and 40% in TM+ only patients.

Confounding factors include that virtually all glove and rubber products are not formally labelled as to rubber additive composition, and many manufacturers consider complete composition disclosure to be proprietary. Cao et al found that there were discordances between patch test results for glove chemicals and glove swatches, and between available information on chemicals used during glove production and chemicals used during chemical analysis of gloves. Similarly, a recent chemical analysis of 16 “accelerator-free” medical gloves found that all contained accelerators (DPTD found in 16, ZDBC in 5, TMTM in 3, 1,3-diphenylguanidine in 2, TETD in 1, TMTD in 1). Allergen content may also be a moot point in certain circumstances, as oxidation of zinc dithioethylcarbamate to TETD may occur when gloves come into contact with strong oxidising disinfectants (e.g., iodine, hydrogen peroxide, bleach).

Limitations

1. This retrospective study has a number of limitations. Most importantly, CM includes diphenylguanidine (a non-dithiocarbamate) in addition to 2 dithiocarbamates, ZDEC and ZDBC. True co-reactivity between dithiocarbamates and thiurams would require testing a dithiocarbamate mix without diphenylguanidine.

2. This study analysed reactions to rubber accelerator mixes; results of testing individual components of these mixes, if performed, were not collected. In addition, it is likely that patients allergic to CM and/or TM had been exposed to, and sensitised to, both rubber accelerator groups, so distinguishing co-reactivity from cross-reactivity is not possible.

3. The population analysed in this study primarily consists of patients seen at tertiary referral centres, so the data are not necessarily indicative of trends in the general population.

Summary

This study demonstrated concomitant reactions to CM and TM, with more than 40% of individuals positive to one and positive to the other. This relationship was stronger for those with ++/+++ reactions, with more than 55% of individuals positive to one and positive to the other. Positive reactions to CM and TM were clinically relevant in more than 70% of patients and most commonly associated with gloves. The frequency of reactions to both CM and TM significantly decreased during the study period.

Conclusions

Carba mix and Thiuram mix remain important, clinically relevant allergens. Although significant concomitant reaction frequency was demonstrated, more than half of the patients reacting to either

CM or TM would have been missed if both had not been tested, underscoring the importance of testing to both in any screening series.

This study is extensive and comprehensive, and provides much more data and information than can be stated in this brief review. Therefore, for full information, the reader is recommended to access the original article.

The epidemic of contact allergy to methylisothiazolinone – An analysis of Danish consecutive patients patch tested between 2005 and 2019

by Martin Haymose, et al.
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Preservatives are widely used additives in industrial and consumer products to prevent bacterial decomposition. Although these properties are beneficial to both manufacturers and consumers, preservatives tend to have a sensitising potential, thus posing a risk of sensitisation and subsequent allergic contact dermatitis (ACD).

Introduction of new preservatives has historically led to outbreaks of contact allergy. This has been seen previously for formaldehyde in the 1960s, methyl bchloroisothiazolinone (MCI) in combination with methylisothiazolinone (MI) in the 1980s, methyl dibromo glutaronitrile (MDBGN) in the 1990s, and most recently with MI as a stand-alone preservative in the 2000s.

In 2005, methylisothiazolinone (MI) was allowed as a stand-alone preservative in cosmetics. This resulted in an epidemic of allergic contact dermatitis to MI, mainly affecting women exposed to leave-on cosmetics. Consequently, a regulation of Annex V in the European Union in 2017 banned the use of MI in leave-on cosmetics and reduced the allowed concentration in rinse-off products.

MI was introduced on the market in the 1980s as an ingredient in a series of biocides known as Kathon in a 3:1 ratio of MCI and MI. Around the millennium, with the expiration of the patent for Kathon, MI as a stand-alone preservative was applied in industrial settings.

The first case reports of ACD to MI in workers were published in 2004 and 2006, describing reactions to wallcovering glue and paint. Despite these early cases, the Scientific Committee on Cosmetic Products and Non-Food Products (the predecessor to the Scientific Commission On Consumer Safety [SCCS]) deemed MI safe in cosmetic products, and MI was subsequently adopted in Annex V (list of allowed preservatives in the European Union) in 2005, permitted in concentrations of 100 ppm.

The first case reports of consumers affected by MI contact allergy from cosmetics emerged in 2010, describing reactions to wet wipes and make-up remover. The same year, a retrospective analysis of MI contact allergy from 2006 to 2010 found that 32% of the cases were caused by exposure to cosmetics. From then on, a dramatic increase in the prevalence of MI contact allergy arose across Europe. In Germany the prevalence increased from 1.9% in 2009 to 6.0% in 2012, mainly affecting female patients exposed to MI-containing cosmetics. In Finland, Portugal, and the British Isles, the prevalence exceeded a staggering 10% by 2012 to 2013.

This increase in the prevalence urged the European Society of Contact Dermatitis in 2011 to write a letter to the European Commission, to sound the alarm of an ongoing epidemic. This was responded to with ”no priority”, inspiring an editorial in the Contact Dermatitis journal to draw on the Great Fire of Rome, famous for the inactions of the political power of the time. It was not until 2013

that the SCCS revised its opinion on the safety of MI, recommending that no safe limit existed for leave-on cosmetics and only concentrations up to 15 ppm to be used in rinse-off products. In 2015, this was settled in a final opinion, and by February 2017 this change was adopted in Annex V.

The purpose of the study was therefore to analyse the temporal trends in contact allergy to MI in Danish patients in relation to key events including European regulations over time.

Methods

The reported study was a retrospective study of consecutive patients who were patch tested with methylisothiazolinone from 2005 to 2019. Demographics and clinical characteristics in terms of MOAHLFA (male, occupational, atopic dermatitis, hand dermatitis, leg dermatitis, facial dermatitis and age >40 years), sources of exposure, and clinical relevance were analysed in relation to key historical events.

Patch Test Products Used: A test concentration 1,000 ppm aq. (0.1%) MI was used in 2005, whereas a concentration of 2,000 ppm aq. (0.2%) was used for the remainder of the study period. Patch testing was performed with Finn Chambers (Epitest, Tuusula, Finland and SmartPractice, Phoenix, Arizona) on Scanpor tape (Norgesplaster, Alpharma, Venesla, Nor,way) applied on the upper back.

Reading was done at days 2, 3, 4, and 7.

A reaction of +, ++, or +++ was considered positive, whereas a negative, irritant, or doubtful reaction was considered negative.

Results

Three hundred eighty of 12 ,494 patients (3.0%, 95CI: 2.7–3.4%) tested from 2005 to 2019 were sensitised to MI. An increasing trend in the prevalence of MI contact allergy from 2005 to 2019 was observed, although a decline in the absolute number of patch-test positive patients was seen from 2013 and onward. A reduction in leave-on cosmetics as a source of exposure was observed following the legislative ban in 2017, from 24.8% from in 2010 to 2013 to 6.2% in 2017 to 2019.

Data from 12,494 consecutive MI patch tests performed between 2005 and 2019 were available (Table S1). These originated from 12091 individual patients; 456 patients (3.6%) were patch tested more than once. In the study populat,ion, 11,543 patients were tested one time, 417 patients were tested two times, 27 patients were tested three times, four patients were tested four times, and one patient was tested five times.

The MI patch test positive patient tended to be female, having occupational dermatitis, hand dermatitis, facial dermatitis, and being >40 years of age. Women were mainly affected by facial dermatitis and exposed to leave-on cosmetics.

When stratifying for sex, men tended more often to have hand dermatitis, occupational dermatitis, with cutting fluids and various chemicals being the main sources of exposure.

Most patients were between 41 and 60 years of age, with significantly more male patients in this age group, whereas female patients tended to be younger: between 19 and 40 years of age.

TABLE 1. Baseline characteristics of the study population

	MI positive	MI negative	P-value
	n = 380	n = 12, 114	MI positive vs negative
Age mean years	48.9	46.9	.04
Male	27.1%	32.4%	.03
Occupational dermatitis	29.7%	20.2%	<.01
Atopic dermatitis	15.5%	20.9%	.01
Hand dermatitis	52.9%	39.2%	<.01
Leg dermatitis	2.1%	2.6%	.56
Facial dermatitis	39.5%	24.7%	<.01
Age >40	73.7%	64.4%	<.01

Overall trends from 2005–2019

During the 14-year study period, 380 of 12, 494 patients were patch-test positive to MI. The number of patch tests performed ranged from 469 in 2005 to 1136 in 2014, with a prevalence of MI allergy ranging from 1.1% in 2007 to 5.4% in 2013. A significant trend in the increase in MI allergy from 1.5% in 2005 to 3.3% in 2019 was observed. No significant trend in the prevalence was found from 2014 and onward.

The proportion of MI patch-test positive patients who were female increased from 56.8% (period I) to 72.8 (period IV), with a borderline significant trend. No significant trends were found for age groups being affected, when analysed as a whole or when stratified by sex.

Occupational dermatitis affected fewer MI patch-test positive patients, decreasing from 40.9% in period I to 25.9% in study period IV and fewer patients had hand dermatitis, with the percentage decreasing from 72.7% (period I) to 42.0%.

The authors found a decrease in the absolute number of patients with MI allergy and a reduction in prevalence from 2013 and onward; however, this change was not statistically significant. Nevertheless, both the numbers of MI allergic patients and MI patch-tested patients were declining in absolute terms, indicating that the epidemic is waning. This was further supported by a decline in MI patch-test positive patients with current relevance from 70.1% in 2010–2013 to 43.2% in 2017–2019, and the number of patients with a debut of contact dermatitis within 1 year of patch testing from 46.9% in 2010–2013 to 31.4% in 2017–2019.

Considering that 96.4% of the study population was patch tested only once, the prevalence may serve as a proxy for the incidence, indicating that the rate of MI contact allergy has not yet returned to its pre-epidemic levels. This is in line with the ORs of MI allergy in relation to patch-test year, where no statistically significant difference was seen when comparing 2010-2013, 2014-

2016, or 2010-2016 with 2017-2019.

Recent multicentre studies demonstrated a significant downward trend in the prevalence of MI allergy in Europe, which is perhaps due to a larger study population or different patterns of exposure among the contributing institutions.

The decline in prevalence in our study was accompanied by a reduction in MI allergic patients with hand and facial dermatitis and with fewer being exposed to MI from leave-on cosmetics and household products. Leave-on cosmetics accounted for 24.8% of patients in 2010–2013 and 6.2% in 2017–2019 ($P < .01$), illustrating the effect of the ban in February of 2017. No reduction was observed from 2010-2013 to 2014-2016.

The exposure from household products declined from 2010-2013 to 2014-2016, perhaps because the producers of such products responded faster to the recognition of MI as an allergen or changed consumer behaviour following increased public awareness of MI as an allergen.

Recommendations

The chain of events of the MI epidemic follows a well-described pattern previously identified for other epidemics of contact allergy. As seen with the preservatives formaldehyde, MCI/MI, and MDBGN, the primary cases were occupational, subsequently followed by reports of consumers being affected, indicating a forthcoming epidemic that remains unrecognised until high numbers of consumers are sensitised. It is thought provoking, with this knowledge in mind, that from the first case reports of workers and consumers being affected in 2004/2010 and the subsequent surge in the prevalence of MI allergy up until 2013, it took until 2017 to update the status of MI in Annex V.

Despite the EC being warned about a developing epidemic in 2011, more patients were allowed to be sensitised for half a decade, before the status of MI was updated in Annex V. Although the SCCS revised its opinion in 2013, a decline in cases was first noted in 2015 and a significant downward trend only found in study period IV (2017-2019), which underscores the importance of effective processing of post-marketing evaluation and quick adaption of Annex V when necessary.

The delay of a ban of MI in cosmetics has led to an unnecessary increase in MI sensitised patients and financial burden on health care systems. The process of communicating the evidence of an emerging epidemic from the scientific community to the EC has not functioned optimally to protect the consumers from MI, delayed partly by neglect of the EC and opposing evidence by Cosmetics Europe. It has previously been suggested that preservatives be adopted in Annex V on a time-limited entry, thus requiring re-evaluation after a certain time period. It is not unreasonable to suggest that this would have limited the magnitude of the epidemic of contact allergy to MI.

The consulting group COWI has estimated the total cost of contact allergy to MI in cosmetics to be 48.4 m Euro per 1,000 cases. This gives a cost of 18.4 m Euro, just for the MI allergic patients seen at Gentofte hospital in Denmark from 2005-2019. Based on the CE-DUR method to estimate the prevalence in the general population, 0.64% (of the population in Denmark is sensitised based on a medium case scenario, potentially costing 1.80 b Euro according to the COWI estimates.

In a previous publication, the early introduction of MI in the baseline series at Gentofte hospital made it possible to show that a large proportion of patients were sensitised by cosmetics before the escalation in the prevalence of MI allergy. It may therefore be beneficial, when future preservatives are introduced in consumer products, to be proactive in routinely patch testing with these early on, whenever a reasonable doubt exists about the allergenic properties.

Limitations

1. It is a disadvantage to this study that no information is available on the reasons for referral, as the number of patch tested patients varies across the study period, consequently affecting the prevalence of MI allergy.

2. In addition, MI was only tested for in a concentration of 0.1% aq. in 2005, potentially underestimating the number of affected patients.

3. When stratifying the timeline by key events, the timing of any changes in trends may be obscured by these predefined strata. It is, however, of great value to analyse the epidemic with data from a single institution, with the same methods for patch testing throughout the entire study period.

Conclusions

MI has been included in the Baseline Series at Gentofte Hospital since 2005, as the data and conclusion in the SCCS opinion led us to believe that major problems with contact allergy to MI could be expected.

The epidemic of MI contact allergy is declining in absolute terms, although the prevalence in the patch-tested population has not returned to its pre-epidemic levels. The legislative regulation of MI in 2017 has been effective in terms of leave-on cosmetics as a source of exposure in MI allergic patients.

A reduction in MI-associated hand and facial dermatitis as well as leave-on cosmetics and household products as sources of exposure was observed.

The process of post-market risk assessment seems inefficient to cope with rapidly developing epidemics of contact allergy. A time-limited adoption of preservatives in Annex V may be a solution to this problem.

The original article in Contact Dermatitis has considerably more data than is shown in this brief synopsis. The reader is therefore recommended to read the original article.

Changes in adhesive ingredients in continuous glucose monitoring systems may induce new contact allergy pattern

by Cecilia Svedman, et al.
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Medical devices (MD) in close skin-contact for a prolonged time, such as glucose monitoring (CGM) systems, are a risk factor for contact allergy, and there has been an increase in patients using these.

Allergic contact dermatitis due to CGM systems and insulin pumps are difficult to investigate and require chemical analysis. Because of the lack of information on substances used in the production, and when changes with MDs are initiated, it is difficult to advise patients, especially since they risk sensitisation to several allergens. The use of MDs has increased and, thus, the need for increased collaboration between manufacturers, clinicians, and patient organisations.

Investigating patients with suspected allergic contact dermatitis to medical devices (MDs), such as continuous glucose monitoring (CGM) systems, intermittently scanned glucose monitoring (isCGM)/ flash glucose monitoring systems, and insulin pumps, is complicated.

The diagnosis has to be suspected and the patient must be patch tested with the right substances. The investigation should also include patch testing with the patient's own material.

This testing may, however, result in false negative reactions since the concentration of allergens in the material may actually be too low to elicit a positive reaction at ordinary patch testing, even if an extract of the product is made. Producing an extract can in itself be difficult because of the lack of material, especially if extraction solvents with different physico-chemical properties are desired.

The culprit contact allergens found have mainly been used in attachment areas, i.e., where different materials must adhere to each other, but not necessarily primarily in the adhesive patch in direct contact with the skin. Therefore, identifying and finding the optimal patch test substance and dose has been complex, as the final dose on skin exposure is not necessarily the same as where the identified substance is used.

The need for collaboration with the manufacturers of the devices has been emphasised especially as the number of patients being sensitised to several allergens found in different MDs is increasing. As product ingredients may be changed without a change of brand name or notification to the clinicians or the users, helping the user find a reliable product is made even more difficult.

In this study, the authors report three patients who reacted to the Dexcom G6, CGM system (Dexcom, Inc.), who suddenly experienced symptoms after the composition of the adhesive was changed, and in which a new allergen was found. The identification of the allergen was simplified by the fact that previous analyses of Dexcom G6 existed for comparison at our laboratory in Malmö.

The three patients were all referred because of sudden onset of problems related to efforts made by the manufacturing company to improve the adhesive in Dexcom G6.

Case 1.This patient was a 40 -year-old female office worker, with diabetes mellitus since the age of 8, rhinoconjunctivitis, but no atopic dermatitis nor asthma and no other skin diseases. She started to use an insulin pump in 2008 and had at first referral used three different brands (Medtronic, Animas Vibe, and Tandem t:slim) without the occurrence of dermatitis; however, because of dermatitis problems she had stopped using certain brands (Freestyle Libre and Dexcom G6). In 2015, she started to use the FreeStyle Libre glucose sensor. After 1 month she experienced an oozing dermatitis at the contact site for the sensor and, therefore, changed to Dexcom G4, then G5, without experiencing any problems. In October 2019 she started to use Dexcom G6. In March the following year the patient started getting an itchy dermatitis at the contact site of the sensor that gradually deteriorated. At that time, she had received a new batch of sensors with an adhesive that was more difficult to remove from the skin. At referral she could only use the sensor for 2–3 days (normal wear:10 days) before getting a severe dermatitis. She had started to use Tegaderm Transparent film style 9534 HP (3M) under the sensor adhesive, but even then, she could not use the sensor for more than 5–7 days before the dermatitis forced removal of the device. The patient was thus referred for patch testing.

Case 2. This case was a 35-year-old female, office worker, with diabetes mellitus since the age of 3, and no history of skin disease or atopy. She started to use Freestyle Libre in 2015 but developed dermatitis at the contact site for the sensor after a couple of months. In 2016 the patient started to use the insulin pump Omnipod. In March 2017, a dermatitis developed. The patient during this period used Dexcom G5 and G6 CGM without complications. The patient started in October 2017 to use the Medtrum A6 CGM and insulin patch pump system and immediately experienced problems. She was investigated because of contact dermatitis and found to have an allergic contact dermatitis. Because of the multiple contact allergies found in the earlier investigation, and the fact that the patient now had started having symptoms from Dexcom G6, she was once more referred for patch testing.

Case 3. This patient was a 44-year-old, male office worker with diabetes mellitus since the age of 29 and no history of skin disease or atopy. He started to use Freestyle Libre in 2017 but developed dermatitis at the contact site after 9 months. He had previously used a Medtronic insulin pump without dermatitis problems and was in 2018 recommended CGM system Dexcom G5 and then Dexcom G6. At referral the patient used Dexcom G6 with a Dexcom overpatch. Initially, he had no dermatitis problems, but in the summer of 2020 developed an oozing dermatitis. At referral for patch testing, he could only use his device for 2-3 days because of the dermatitis. He developed dermatitis both with and without the overpatch.

Investigation

The extracts of the adhesive patches and sensor housings tested in case 1 and case 3 were diluted 10-2,000 times and thereafter analysed by gas chromatography-mass spectrometry (GC-MS). Furthermore, ethanol extracts of the adhesive patch and sensor housing from another sensor (LOT no 5266562), as well as an acetone extract of the adhesive patch from yet another sensor (LOT no 5267489) were analysed. Previous analysis using the GC-MS existed making comparison with the extracts of the changed adhesive possible.

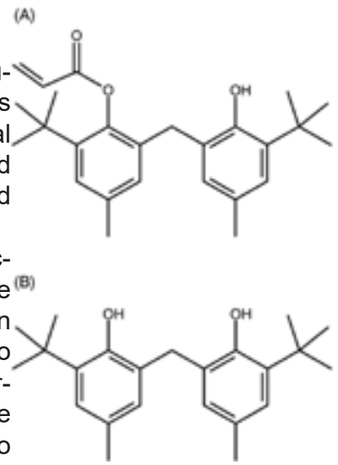
The comparison yielded several possible substances for further investigation, but it was clear that a major change in the adhesive had been made and, thus, this substance was the first to be identified.

The chemical investigations showed the presence of 2,2′-methylenebis(6-tert-butyl-4-methylphenol) monoacrylate in all extracts. For all samples, the concentrations found corresponded to a total amount of approximately 1 mg per adhesive patch and 0.03-0.08 mg per sensor housing.

All extracts also contained isobornyl acrylate (IBOA) at estimated concentrations in the same order of magnitude as those found in previously analysed sensors from older batches, corresponding to a total IBOA content of ≤1 µg/patch and ≤1 µg/sensor housing.

Furthermore, all sensors were also found to contain 2,2′-methylenebis(6-tert-butyl-4-methylphenol).

Molecular structure of:
(A) 2,2′-methylenebis(6-tert-butyl-4-methylphenol) monoacrylate
(B) 2,2′-methylenebis(6-tert-butyl-4-methylphenol)



All three patients were found positive to 2,2′-methylenebis(6-tert-butyl-4-methylphenol) monoacrylate, 0.3% with a + reaction. Case 1 was patch tested in acetone because acetone had been used in the initial analysis. When found positive in acetone the allergen was prepared in pet. and the following patients and controls where thus patch tested in pet. as the vehicle.
Case 1 was found positive for IBOA at 0.1% w/w in pet. with a + reaction and to IBOA 0.3% with a +(+) reaction, i.e., a weak to moderate reactivity. Case 2 was positive to IBOA only at 0.3% with a + reaction and only on D7, i.e., a weak reactivity. Case 3 had a +++ reaction to IBOA 0.3% and a positive reaction in dilution series of the same allergen down to 0.01%. Cases 1 and 2 both reacted to colophony, Case 1 with a doubtful reaction at 60% pet. and Case 2 with a + reaction to colophony in 20% pet.
Case 2 was further positive to hydroabeityl alcohol.

Moreover, case 1 reacted with a ++ reaction to the adhesive “as is”, and with a doubtful reaction to the adhesiCe in the alcohol extract, Case 3 with a ++ positive reaction to the adhesive “as is”, + to the alcohol extract and to the extract of the sensor.

All 20 controls patch tested negatively and with no irritant reactions to 2,2′-methylenebis(6-tert-butyl-4-methylphenol) monoacrylate, 0.3% pet., and no reported late reactions (2/2 vs 0/20; P = .0043; Fisher’s exact test, two-sided).

For the clinician, it is interesting to note the fact that the three patients were all what is usually called polysensitised. The term is complex and here, in the definition, the authors included allergens other than those found in the various baseline series. They had as a mean nine contact allergies. Multiple allergies have been discussed previously with regard to patients using the medical device Freestyle Libre, but that using a medical device, i.e., a glucose sensor or insulin pump, should be a risk factor for polysensitisation can, of course, not be argued from case reports. These patients had been patch tested in a targeted manner with substances that also might be found in the same products. The finding does, however, point to the fact that the group, because of exposure, may possibly be prone to polysensitisation.

Case 3 was positive to 2-hydroxyethyl methacrylate without any known exposure, and had a doubtful reaction to ethyl acrylate, to which an association has been indicated in Freestyle Libre-sensitised patients.

All three patients when patch tested were found to be sensitised not only to allergens from different groups related to MDs; acrylates, and colophony, but also to corticosteroids, preservatives, metals, and fragrance substances. The possible association with regard to preservatives, metals, and fragrance allergens and the MD exposure could not be determined. Neither did the patients have any other clear relevance, present or past, for these identified contact allergies. With regard to corticosteroids, it could not be determined whether the sensitisation was related to treatment of medical device-related dermatitis. Among patients with contact allergy to IBOA, sensitised due to the use of MDs (Freestyle Libre), contact allergy to sesquiterpene lactones has also been found to be overrepresented. In these cases, this was not found, however, Case 1 had a doubtful reaction to alantolactone.

The authors have previously reported on the finding of IBOA in Dexcom G6. Not only was IBOA found to be a possible culprit allergen, but also possible derivatives of colophony. As Dexcom Inc. and their Swedish distributors contacted us because users had reported dermatitis during the spring of 2020, the authors knew that some alteration had been made in the adhesive. The three patients reported here had previously been able to use Dexcom products, but now showed a reaction pattern with contact allergy to IBOA, in Case 2 contact allergy to colophony and Hydroabietyl alcohol and in Case 1 a doubtful reaction to colophony. All showed positive reactions to 2,2′-methylenebis(6-tert-butyl-4-methylphenol) monoacrylate 0.3%, while there was no reaction in the 20 controls. The latter substance has, to the best of the knowledge of the study authors, not previously been described as an irritant or as an allergen in man nor animal.

2,2′-methylenebis(6-tert-butyl-4-methylphenol) monoacrylate, (also known under the trade names Sumilizer GM, BNX 3052, and Irganox 3052), is a heat and light stabiliser and an antioxidant used in a wide range of adhesive, plastic, and elastomer materials. Unlike traditional phenolic stabilisers/antioxidants, this substance is an effective alkyl radical scavenger. This property is especially useful in processes at high temperatures and in low oxygen environments, such as during the initial mixing of adhesives. The stabilising mechanism involves trapping of polymer alkyl radicals at the double bond of the acrylate group, and subsequent hydrogen transfer from the intramolecular hydrogen-bonded phenolic hydroxyl group. This results in a stable phenoxyl radical, 2,2′-methylenebis(6-tert-butyl-4-methylphenol) monoacrylate.

2,2′-methylenebis(6-tert-butyl-4-methylphenol) monoacrylate has no harmonised classification according to the Classification, Labelling and Packaging (CLP) regulations. In the vast majority of CLP notifications provided by companies to the European Chemicals Agency (ECHA) no hazards (including skin sensitisation) have been classified. According to data in ECHA’s dossier on the substance, no irritancy was described in animal testing with the Draize test method; and it has been classified as a non-allergen in a local lymph node assay. The highest tested concentration in the local lymph node assay was 25%, although neither local irritation nor systemic toxicity were reported at this concentration.

The sensors were also found to contain 2,2′-methylenebis(6-tert-butyl-4-methylphenol), a structurally related antioxidant which, however, lacks the acrylate group present in 2,2′-methylenebis(6-tert-butyl-4-methylphenol) monoacrylate. The content of 2,2′-methylenebis(6-tert-butyl-4-methylphenol) in the adhesive patches was approximately 20 times lower than the content of methylenebis(6-tert-butyl-4-methylphenol) monoacrylate. Because of the structural similarities, simultaneous reactions based on cross-reactivity could be expected, and at least theoretically, an enzymatic hydrolysis of 2,2′-methylenebis(6-tert-butyl-4-methylphenol) monoacrylate could occur in the skin generating 2,2′-methylenebis(6-tert-butyl-4-methylphenol) and acrylic acid. Interestingly, none of the patients reacted to 2,2′-methylenebis(6-tert-butyl-4-methylphenol) tested at 1.0%, although this corresponds

to a molar concentration which is 3 times higher than that of 0.3% 2,2′-methylenebis(6-tert-butyl-4-methylphenol) monoacrylate. This may indicate that the presence of an acrylate group is crucial for the sensitising potential of 2,2′-methylenebis(6-tert-butyl-4-methylphenol) monoacrylate.

From the patients' histories it is quite clear that the initial sensitisation was to IBOA and that previous use of Freestyle Libre was the medical device that sensitised. Case 2 was further exposed to IBOA through the use of Omnipod and was most likely thereby sensitised to colophony and hydroabietyl alcohol, causing allergic contact dermatitis almost instantly when using the Medtrum devices.

The three cases are particularly interesting since they could initially use the device without experiencing any skin problems, in Cases 2 and 3, even for a prolonged time, and then subsequentially experienced dermatitis. The fact that the authors know from previous investigations and the investigations reported here, that in Dexcom G6 both IBOA and possibly colophony-related substances are present, but presumably in our cases the concentration did not initially provoke an elicitation. It was most probably the change in adhesive components that actually caused dermatitis, which could at least be partially explained by contact allergy to 2,2′-methylenebis(6-tert-butyl-4-methylphenol) monoacrylate. This substance has not been observed in previous analyses by the study authors of older Dexcom G6 sensors, but was now found in sensors from newer production batches in relatively high concentrations, while the IBOA content was approximately the same as in the sensors from previous batches.

If the patients would have been sensitised to 2,2′-methylenebis(6-tert-butyl-4-methylphenol) monoacrylate had they not had contact allergy for substances already found in the products, cannot be clarified in retrospect. The cases underline two possibly contradictory general principles when using substances which are biologically active and that may give rise to contact allergy (i.e., sensitisation) and allergic contact reactions, i.e., elicitation:

1. By keeping the concentration of substances low and possibly using different substances concomitantly, thus achieving the wanted effect, the risk of sensitisation decreases - which can be done with cosmetic consumer products;

2. In an individual already sensitised to allergens in a mixture, the more possible contact allergens there are at the same skin surface area, the higher the risk of elicitation of contact allergy.

In the Dexcom G6, IBOA has been found in low concentration and the patients could previously use the devices. In the devices used by these patients, alterations in the adhesive patch had been made and after this they experienced an oozing dermatitis leaving hyperpigmentation for a prolonged time. However, all patch test reactions, apart from that of IBOA in Case 3, were at the most found with a moderate reactivity.

With regard to colophony in Case 1 nothing but a doubtful reaction to colophony at 60% could be verified. In this patient it cannot be clarified in retrospect if colophony-related allergens in Dexcom caused the allergy or if the patient had been exposed to the allergens elsewhere. The patient had been recommended to use Tegaderm Transparent film dressing frame style 9534 HP (3M) under the adhesive and next to the skin. Tegaderm products have been found to contain abietic acid - colophony; however, as far as the authors know, is not found in the product recommended.

How can the very strong reaction to the adhesive when using the device be explained when there were no strong (+++) reactions to 2,2′-methylenebis(6-tert-butyl-4-methylphenol) monoacrylate in anyone of the patients? …… The most obvious explanation is, of course, the application time. Another possible explanation is that the substance 2,2′-methylenebis(6-tert-butyl-4-methylphenol) monoacrylate, found in a quite high concentration in the product, was patch tested at too low a concentration. In the adhesive, the concentration was calculated to 40 µg/cm^2, this can be compared to the epicutaneous patch test concentrations, where a 0.3% acetone preparation gives a dose of 90 µg/cm^2 and a 0.3% pet. preparation gives a dose of 120 µg/cm^2.

The patch test concentration was, thus, only 3-4 times higher than the concentration in the product. For many sensitisers, including preservatives, the required patch test concentration is around 20 times higher than in leave-on products, – which at patch testing may give false negative reactions. Whether an optimal patch test concentration for 2,2′-methylenebis(6-tert-butyl-4-methylphenol) monoacrylate would be around 1.5% needs to be carefully investigated in order to avoid active sensitisation. A third possible explanation is that a low-grade inflammatory reaction to IBOA, and in 2 cases colophony and colophony-related substances, caused enhanced penetration of allergens, thus inducing a greater total reaction. Another explanation could be that the reaction pattern can be defined as an example of the cocktail effect; that is, additional low reactivity allergens in a mix will enhance the reactivity by immunological mechanisms and thereby produce a reaction greater than the reactivity of the different components in themselves.

The last explanation is, of course, that the major culprit allergen has not so far been identified.With regard to patch test results for testing with own material and extracts, the patients did not always react, or react with stronger reactions to the extracts, as compared to the material "as is,". This is in agreement with previous results with regard to medical devices.

The reaction pattern of the patients with regard to extract vs material "as is" indicates that also in these cases, the extracts used were not concentrated enough. In these cases, the analysis of the material and the knowledge that the substance found was an acrylate made us, out of precaution, limit the amount of adhesive used for extracts.

Conclusion

In the reported cases, a new allergen in the CGM system Dexcom G6 is presented: 2,2′-methylenebis(6-tert-butyl-4-methylphenol) monoacrylate.

The three cases showed multiple allergies at the investigation, some with low reactivity. This emphasises the need for re-testing and re-analysing the devices chemically if a patient suddenly appears to have problems to material that has previously been negative at testing. Besides sensitisation to an already known sensitiser in the device, the possibility of increased reactivity due to exposure and sensitisation in the same skin area to a presently unknown allergen in the device should be considered.

The reactivity pattern with weak and moderate reactivity to the allergens emphasises the need for optimal test concentrations and the need for two patch test readings.

From the three cases, where two were actually patch tested with the allergen in pet. and one in acetone, the authors cannot exclude the possibility that the authors were not patch testing at the optimal concentration. These cases emphasise the importance of occlusion time when using CGMs.

You are invited to notify us If there is a website you would like to have reviewed in a future issue of The Patch Tester or if there is a society or other website that you would like to have included in these lists.

Dermatology Society Websites

ILDS:	*International League of Dermatology Societies*	www.ilds.org
ICDRG:	*International Contact Dermatitis Research Group*	www.icdrg.org
EADV:	*European Academy of Dermatology & Venerology*	www.eadv.org
ESCD:	*European Society of Contact Dermatitis*	www.escd.org
ACDS:	*American Contact Dermatitis Society*	www.contactderm.org
APEODS:	*Asia-Pacific Envmntl & Occupational Dermatology Society*	www.apeods.org
EAACI SAM:	*European Academy of Allergy & Clinical Immunology*	www.eaaci.org
BAD:	*British Association of Dermatology*	www.badannualmeeting.co.uk
AAD:	*American Academy of Dermatology*	www.aad.org
PDA:	*Pacific Dermatololologic Association*	www.pacificderm.org
APD:	*Association of Dermatology Professors*	www.dermatologyprofessors.org
NDA:	*Nordic Dermatology Association*	www.nordicdermatology.com
GDA:	*German Dermatology Society*	www.derma.de
FSA:	*French Society of Dermatology*	www.sfdermato.org
CDA:	*Caribbean Dermatology Association*	www.caribbeanderm.org
ACD:	*Australian College of Dermatologists*	www.dermcoll.edu.au
NZDS:	*New Zealand Dermatology Society*	www.nzdsi.org
DNA:	*Dermatology Nurses Association*	www.dnanurse.org
DermNET NZ:	*Dermatology Infomation Resource for Patients*	www.dermnetnz.org

Dermatology Meeting Websites

www.eadv.org
www.aad.org
www.dermatologymeeting.com
www.asiaderma.sg
www.dubaiderma.com
www.cairoderma.com

Patient Information

Yet again, a small country on the far side of the world from Europe is boxing and batting far above its weight also in the field of dermatology….we are of course talking about New Zealand.

With a population of just 5 million people, in a land mass of just 268,000 square kilometres, NZ has just 60 dermatologists, in state hospital and private practice.

The professional Dermatologists society website is at www.nzdsi.org. There is also an excellent patient-focussed website at www.dermnetnz.org which lists numerous patient-focussed external websites.

DermNet

DermNet is the world's free resource and authority on all things skin. They help thousands of people make informed, evidence-based decisions on how to care for skin conditions, by providing reliable information at the click of a button. DermNet is supported by and contributed to by New Zealand Dermatologists on behalf of the New Zealand Dermatological Society Incorporated.

The range of topics with dermatology information for patients is truly comprehensive. See https://dermnetnz.org/topics/ for details. One of the very informative sections within the DermNet website is the information for patients on patch tests.

See https://dermnetnz.org/topics/patch-tests/

External sources of information for patients

American Academy of Dermatology
- Diseases and Treatments
- For kids

huidziekten.nl – Dermatological information in Dutch
Australasian College of Dermatologists
British Association of Dermatologists
Skin the Surface podcasts
Drugs.com
Emedicinehealth
Health Ed Resources of the Health Promotion Agency (HPA) and New Zealand Ministry of Health
MedHelp International Dermatology forum for patients with skin diseases
MEDLINEplus® The National Library of Medicine's consumer information site
- Medical Encyclopedia
- Drug Information

NHS choices Health A-Z - Conditions and treatments UK
SkinCareGuide Canada
Global Dermatology information on skin disorders
International Alliance of Dermatology Patient Organizations
The Skin Site
Skin Problems and Treatments Health Center WebMD Health
SkinHelp.co.uk

Genetic Alliance UK
Lab Tests Online AU®
Skinsight – Disease Information and Pictures
Skin Deep® Cosmetics Database | Environmental Working Group
Healthline – Skin disorders
The Institute for Healthcare Improvement (IHI) and the National Patient Safety Foundation (NPSF) (US)
IHI and NSPF (Ask Me 3: Good Questions for Your Good Health)
Agency for Healthcare Research and Quality (US)
Questions To Ask Your Doctor

Image Atlas
DermIS DOIA and PeDOIA

Dermatology Diagnosis for Patients

Featured in the DermNet website is a section on “DermDiag” which is intended to be a self-help for the patient to understand their skin condition. The DermDiag tool is based on the best-selling book for doctors Differential Diagnosis in Dermatology. This tool does not provide medical advice. It is intended for informational purposes only. Awarded Book of the Year by the British Medical Association in 2015, it is now in its updated 4th edition.
Buy Differential Diagnosis in Dermatology on Amazon.

https://www.routledge.com/Differential-Diagnosis-in-Dermatology-4th-Edition/Ashton-Leppard-Cooper/p/book/9781909368729

GlobalSkin

The International Alliance of Dermatology Patient Organizations (IADPO) - also known as GlobalSkin - is a unique global alliance, committed to improving the lives of patients worldwide. They nurture relationships with members, partners and all involved in healthcare - building dialogue with decision-makers around the globe to promote patient-centric healthcare.

People living with dermatological conditions face stigma, shame and other psychosocial challenges in addition to the physical symptoms of their disease. For many patients, this is a lifelong burden. And in many cultures, this can have devastating social impacts. This must change.

Together, we can make it happen.

The International Alliance of Dermatology Patient Organizations (IADPO) – also known as GlobalSkin – is a unique global alliance serving patient organisations to improve the lives of dermatology patients worldwide. This not-for-profit organisation, based in Canada, is focused on three pillars:

1. Research
2. Advocacy
3. Support

GlobalSkin envisions a world in which people living with dermatological diseases and skin traumas can easily access the care and treatment they need, when they need it, and can live without stigmatisation, persecution, or economic disadvantages due to their conditions.

GlobalSkin is working with more than 177 patient association members ─ located in 58 countries representing more than 65 disease areas ─ to improve the lives of those affected by dermatological conditions throughout the world by:

- Initiating dialogue and advocating for access to new and existing treatments, and dermatological care to improve patients’ quality of life;
- Raising the awareness of the incidence of, and the challenges for, people living with serious dermatological diseases to create better understanding; and
- Supporting our Members, not-for-profit dermatology patient organizations, through education, global campaigning, sharing of best-practices and beneficial networking opportunities to strengthen support for patients and build a strong, inclusive movement;
- Building special focus communities; and
- Conducting patient–initiated research.

GlobalSkin appeals as one voice to the World Health Organization and other key influencers to recognise the debilitating nature of dermatological disease, so that more resources for research and treatment options are made readily available to those afflicted and in need of help.

The common thread through these important IADPO initiatives is credible data, which they will collect in the first-ever global patient-initiated ’impact of skin disease’ research project, expected to have a profound and lasting impact on key decision-makers.

By collecting data from the dermatology patient perspective to represent various real-life conditions around the world, the dermatological community will gain better awareness, making it easier to truly help patients.

Together, we are stronger.

Contact Dermatitis / Patch Testing

8th to 10th June 2022
European Society for Contact Dermatitis
Amsterdam, Netherlands
www.escd2022.com

Dermatology - International

14th to 15th January 2022
ICCDTSD 2022
Clinical Dermatology and Treatment of Skin Disorders Conference
Zurich, Switzerland*https://waset.org/clinical-dermatology-and-treatment-of-skin-disorders-conference-in-january-2022-in-zurich*

4th to 5th March 2022
ICCD 2022
International Conference on Clinical Dermatology
Barcelona, Spain
https://waset.org/clinical-dermatology-conference-in-march-2022-in-barcelona

25th to 29th March 2022
AAD 2022
American Academy of Dermatology Annual Meeting
Boston, MA, USA
https://www.dremed.com/medical-trade-shows/?--p=6182

15th to 16th April 2022
ICSDDT 2022
International Conference on Skin Disorders, Diagnosis and Treatment
Cape Town, South Africa
https://waset.org/skin-disorders-diagnosis-and-treatments-conference-in-april-2022-in-cape-town

12th to 14th May 2022
EADV Symposium
European Academy of Dermatology and Venerology
Ljubljana, Slovenia
https://eadv.org/calendar/show/335

5th to 7th July 2022
BAD 2022
British Association of Dermatologists
Glasgow, Scotland
conference@bad.org.uk

7th to 11th September 2022
EADV Congress
European Academy of Dermatology and Venerology
Milano, Italy
https://eadv.org/calendar/show/61

3rd to 8th July 2023
ILDS WCD-2023
World Congress of Dermatology
Singapore
https://www.wcd2023singapore.org

In this current era of ever-changing health and travel restrictions due to the COVID-19 pandemic, the organisation of conferences and congresses, including of course dermatology congresses, is in a state of evolution and flux.

The webpage at www.waset.org/dermatology-conferences-in-2022 is one potentially very useful source of information of Dermatology congresses in 2022. WASWT is the World Academy of Science, Engineering and Technology. Their webpage states numerous dermatology-related congresses and conferences for 2022.

A word of warning, as has been stated elsewhere in the dermatology world, (https://www.bad.org.uk/events/eventcalendar) we need to be aware of the possibility of wishful thinking, opportunism, obsolescent statements, and even misrepresentations or false advertising for congresses.