the Patch Tester

Contact Dermatitis | Haptens | Patch Testing

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THE EU ISSUE

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

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CHEMOTECHNIQUE DIAGNOSTICS

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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 twentieth issue comprises 48 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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David Alsheimer-Niklasson & Steve Lee

Will all EU member states risk the same severely compromised supply of Patch Test haptens as Germany?

A comment on the: "Severely compromised supply of Patch Test allergens in Europe hampers adequate diagnosis of occupational and non-occupational contact allergy. A European Society of Contact Dermatitis (ESCD) European Academy of Allergy and Clinical Immunology (EAACI) European Academy of Dermatology and Venerology (EADV) task forces 'Contact Dermatitis' and 'Occupational Skin Disease' Position Paper"

by Swen Malte John and 28 other authors,
https://doi.org/10.1111/cod.14580

In a previous edition of The Patch Tester, the topic of regulation, and in particular the requirements for the registration of medical products, has been discussed. Now with the publication by the ESCD legal task force focus on the potentially serious situation in which allergic contact dermatitis might become the subject of underdiagnosis if regulators deny easy access of patch test materials.

The objective of the ESCD legal task force is to suggest ways forward to promote and ensure availability of high-quality patch testing substances for the diagnosis of Type IV allergies throughout Europe amongst others. In their recently published position paper "Severely compromised supply of Patch test allergens in Europe hampers adequate diagnosis of occupational and non-occupational contact allergy. A European Society of Contact Dermatitis (ESCD) European Academy of Allergy and Clinical Immunology (EAACI) European Academy of Dermatology and Venerology (EADV) task forces 'Contact Dermatitis' and 'Occupational Skin Disease' Position Paper" the task force convey why patch testing is essential for public health; they outline the legal framework in which haptens are regulated in the EU and they finally finish with a "call to action" on their suggested actions to ensure haptens availability throughout the EU.

At Chemotechnique, we are genuinely grateful for the active support and pragmatic solutions proposed by the task force. The international collaborations at the core of patch test progression, dating back to the ICDRG's formation in 1966, continue to be exemplified by this dedicated group.

However, from our perspective as a hapten manufacturer supplying clinics in Europe and around the world, some of the claims in the position paper, however require further clarification. One of its main premises is that hapten availability is scarce across the EU. While this may be true in countries such as Germany—where physicians are limited by a restricted range of registered SmartPractice haptens—and Italy (in which the AIFA pioneering adaptation of the CMDh's allergen guidelines has resulted in a temporary limited access), hapten availability from Chemotechnique remains unaf-

fected in most parts of EU, as they are still available using national implementations of Article 5 of Directive 2001/83/EC.
What could pose a long-term threat to hapten availability is the implementation of regulatory harmonisation as proposed by the CMDh within the EU if not handled with caution at a national level.

While the final outcome is still uncertain, it appears increasingly likely that EU member states will require individual marketing authorizations (MA) for each hapten based on concentration and active ingredient (based on the German precedent) in contrast to Canada, where we have registered all of our haptens under just four (4) MA's based on the pharmaceutical form.

Although the difference may seem minor, the implications are significant. Even if legislators adopt all of the ESCD task force's proposed regulatory changes, there is a crucial factor that neither clinicians nor regulators possibly can take into account when speculating the possible outcome of a change in regulation – namely the impact of regulatory fees when manufacturers decide whether to register a hapten for market authorization at a national level when the annual sales volume per hapten and EU member are very low. For example, a majority of our haptens has an annual sales volume of only 10-50 products per EU member state.

A telling example can be found in Germany. While we do not have access to SmartPractice's sales data for haptens in Germany, we are confident that the need for individual MAs correlates with SmartPractice's limited product offering in the country - only around one-third of its international product portfolio is available to German physicians. Their earnings can simply not justify a larger registered product offering. Bear in mind that this is in the largest EU member state by far – both in terms of population and GDP!

We are hopeful that once regulators recognise that the current situation in Germany is a "best case" scenario for hapten availability across other EU member states if the option to obtain haptens under Article 5 of Directive 2001/83/EC is removed, they will rethink their current regulatory agenda.

For the sake of patient safety, we are thankful to have the ESCD standing with us in this fight.

Additionally, it is important to note that in the European Commission's "Impact Assessment Study on Fragrance Labeling on Cosmetic Products," it was suggested that compulsory labeling of additional fragrance haptens would generate sufficient demand to trigger commercial production of patch test haptens. However, to date, this has not been the case, nor is it likely that such demand will materialize in the future due to the cost of registration of such initially at least very small volumes of these haptens. This further underscores the need for a practical regulatory approach that ensures the continued availability of essential diagnostic tools for allergic contact dermatitis.

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.

Lanolin
– just how much of a Hapten is it really?

Based on article "Lanolin"
by Blair A. Jenkins & Donald V Belsito,
in DERMATITIS, Volume 34, No. 1, January 2023.
https://doi.org/10.1089/derm.2022.0002

'Lanolin'' was first identified as a potential allergen in 1922 in a patient with a ''skin reaction'' to a cream containing wool alcohols. Since then, there have been numerous reports of ''lanolin'' allergy, with the first positive patch test reported in 1929. Nonetheless, the prevalence and severity of allergy to ''lanolin'' have been hotly debated. Controversy as to lanolin's allergenicity began in the 1920s and remains an issue. Claims have been made, by authoritative experts, that lanolin allergy is a figment of the imagination of over-zealous patch testers. Indeed, it is claimed that no one has succeeded in sensitizing animals or humans to lanolin or wool wax alcohols, and that most of the case reports of sensitivity to lanolin are false positives, in association with the Angry Back Syndrome. Nevertheless, the potential for ''lanolin'' to cause contact allergy in humans has been well documented in innumerable reports in the literature.

There may well exist in rare patients a real-life sensitivity to lanolin on damaged skin, but when patch tested on the usual intact skin of the same patient, then there is no response.

Another confounding situation is where patients with a positive patch test to lanolin (so on normal intact skin) may tolerate use of lanolin on normal skin. How can that be??

The most appropriate patch test preparation(s) for detecting allergy also remain disputed.
False negative reactions can occur when lanolin is tested on normal skin, even though the patient may indeed have ACD from a ''lanolin''-containing product applied to damaged skin. Identification of those patch test negative patients reacting to ''lanolin'' on damaged skin is challenging.

So what exactly is Lanolin?

Historically the term ''lanolin'' was derived from the Latin words for wool (''lana'') and oil (''oleum''). Lanolin is a complex mixture of high molecular weight esters, aliphatic alcohols, sterols, fatty acids, and hydrocarbons that has been widely used for centuries for its emollient properties. The purification of crude lanolin into lanolin wax and the processing of this wax into various derivatives began in 1882 and continue to this day with newer highly purified anhydrous lanolins. Lanolin is a complex mixture of high molecular weight esters, which constitute around 87% of ''typical'' lanolin. The remainder consists of 11% free compounds (aliphatic alcohols, sterols, fatty acids, and hydrocarbons) and 2% unidentified compounds. Since lanolin is composed primarily of high molecular weight esters, it is classified chemically as a wax, not as a fat. Sheep rely on its waxy protective properties to shed water from their wool.

Hapten of the Quarter

Wool allergy?
Since ‘‘lanolin’’ is derived from sheep’s wool, many incorrectly assume that individuals allergic to ‘‘lanolin’’ would also be allergic to wool. It is known that small amounts of unrefined wool wax may be left by clothing manufacturers in wool clothing, to retain its tactile softness. However, a comprehensive literature review showed that contact allergy from ‘‘lanolin,’’ chromium, or formaldehyde is highly unlikely to be seen with modern wool garments, though cutaneous irritation from wool does occur due to the high diameters of the wool fibres (30–32 um), which activate C-fibres, thereby causing itch. Importantly, modern wool-based textiles do not contain ‘‘lanolin’’, so allergic patients need not avoid wool (unless irritated by the fibres of the coarser wools.

Occurrence of lanolin
Lanolin and its derivatives are ubiquitous in human environments.

1. Lanolins are used as water/oil emulsifiers, emollients, occlusive moisturisers.
2. Importantly, lanolins are used as vehicles in cosmetics and pharmaceuticals designed for topical use on skin, lips, nails, and hair, as well as an ocular emollient. The principal cosmetic and pharmaceutical derivatives of lanolin include lanolin oil, lanolin wax, lanolin acid, lanolin alcohol, acetylated lanolin, acetylated lanolin alcohol, hydrogenated lanolin, and hydroxylated lanolin.
3. Lanolins are also used for industrial purposes. Wool wax has been applied to metallic surfaces to prevent corrosion, added to ink to prevent crystallization, incorporated into furniture polish, and used in leather and shoe polishes to enhance pliability and water resistance. Lanolin has also been reported to contaminate paper within leather bound books treated with neatsfoot oil and lanolin.

What component(s) of lanolin is the sensitiser?
A study of 75 individuals with known contact allergy to ‘‘lanolin’’ (most with associated Stasis Dermatitis), showed that the allergens of ‘‘lanolin’’ were the free fatty alcohols, rather than the total alcohols. Furthermore, it was noted that the incidence of allergy was increased by the simultaneous presence of detergent. Among these ‘‘lanolin”-sensitive patients, removal of both free fatty alcohols and detergent from ‘‘lanolin’’ reduced the incidence of detectable hypersensitivity by 96%. These lanolin alcohols are produced by lanolin ester hydrolysis, which releases sterol fragments and various long-chain alcohols. It is possible that the reactive electrophiles generated from this process could cause protein and lipid modification, leading to tissue damage and spurring irritant and allergic reactions.

Gas chromatography mass spectroscopy has been used to identify the allergenic fractions of hydrogenated lanolin as alkane-a,b-diols and alkane-a.o-diols. This was confirmed by patch testing these -diols. It had long been suspected that alkane-a,b-diols were the common allergens across all lanolin derivatives; however, this study showed that only the free diols are the allergens. This explains why lanolin and its ester derivatives possess lower allergenicity than lanolin alcohol. In contrast, only hydrogenated lanolin contains alkane-a.o-diols, which is another potent allergen. Therefore, among lanolin derivatives, hydrogenated lanolin is predicted to be most reactive.

Hydrogenated lanolin has been shown to be more allergenic than lanolin alcohol, whereas lanolin wax, lanolin acid, and lanolin esters exhibit lower allergenicity. Other researchers have suggested that oxidation of ‘‘lanolin’’ could produce other haptens, as the researchers showed that the antioxidants had the capacity to neutralise the allergenic properties of lanolin. They then hypothesised

that if an antioxidant could abolish the allergenic properties of lanolin, the peroxides formed by exposure to air during use might conversely accentuate the allergenic properties.
There are many grades of ‘‘lanolin’’ with varying degrees of purity and safety available. These range from crude industrial grades to highly purified medical grade anhydrous (HPA) lanolin. Medical grade ‘‘lanolin’’ may contain up to 2.5% free lanolin alcohols. Although HPA lanolin is ultra-refined to remove free lanolin alcohols to a level lower than 1.5%, and to lower detergent residues to a negligible level, the presence of any level of free lanolin alcohols could induce, and certainly elicit, ACD, especially when HPA lanolin is applied to damaged skin.

The lanolin used in patch tests will be of the pharmaceutical grade.

Note that Chemotechnique have three different lanolin-based patch test substances:
1. Lanolin Alcohol
2. Amerchol L101
3. Softisan 649

SmartPractice AllergEAZE has 4 lanolin-based patch test substances:
1. Lanolin Alcohol
2. Amerchol L101
3. Wool Alcohols Ointment
4. Wool fat

Note that Amerchol L101 (Chemotechnique hapten A-004) is the trade name of product containing lanolin alcohols, which is obtained from the hydrolysis of lanolin.

So which is the best patch test substance/allergen/hapten for screening for lanolin allergy?
The question arises as to whether the ‘‘lanolin’’ chosen for patch tests is representative of ‘‘lanolin’’ encountered by patients in their real life situations, whether at home or in an occupational environment.

Various studies over the years have produced varying results, though the consensus to adequately identify ‘‘lanolin’’ allergy seems to be 50% Amerchol L101 in petrolatum, and/or 30% lanolin alcohols in petrolatum, and/or the patient’s own products should be tested, possibly along with a standard allergen series. It is also said that he ROAT, as already described, can be extremely helpful in guiding patients patch test positive to ‘‘lanolin”.

Many authors of published literature on lanolin allergy support the notion that, at the very minimum, both lanolin alcohols (30% pet.) and Amerchol-L101 (50% pet.) should be tested simultaneously; however, others suggest that other lanolin derivatives and/or the patient’s products need to also be tested when allergy is suspected.

Regarding patch test positive patients, ROAT can be extremely helpful in (1) assessing whether ‘‘lanolin’’ allergic patients might be able to use ‘‘lanolin’’ on normal skin and (2) whether a weak positive patch is allergic or irritant, especially in the case of Amerchol-L101, which contains the potential irritant, mineral oil. Thus, there appears to be no single patch test preparation to accurately assess ‘‘lanolin’’ allergy. However, since the principal allergens in ‘‘lanolin’’ are the free alcohols (especially alkane-a,b-diols and alkane-a.o-diols), industrial and academic researchers interested

in lanolin allergy need to undertake an analysis of our current patch test materials for the presence of these, and other potentially allergenic substances (e.g., low molecular weight oxidized organic derivatives formed during different manufacturing processes). These studies may well lead to the introduction of newer patch test preparations with improved specificity and sensitivity for detecting ‘‘lanolin’’ allergy.

Prevalence of Lanolin allergy

Although lanolin is a weak sensitiser and the frequency of contact allergy to it is reported to be 0.4% in the European population, there are high-risk concomitant conditions:

- Stasis Dermatitis
- Leg ulcers
- Perianal/genital Dermatitis
- Atopic Dermatitis

Children and the elderly are also at greater risk of developing contact allergy to lanolin, partly because of comorbidities (AD and Stasis Dermatitis/leg ulcers, respectively).

A study of 24,449 patients undergoing patch testing for suspected ACD from 1982 to 1996 were all tested with 30% lanolin alcohols in pet. The mean annual rate of sensitivity to this allergen was 1.7%. The highest prevalence of allergy to lanolin alcohols was among patients with lower leg dermatitis (6.0%), followed by those with anogenital dermatitis (3.2%)

Other studies using 30% lanolin alcohols in pet., have reported a positivity rate among dermatitis patients ranging from 1.6% to 6.6%. More recent NACDG summaries from 1994 to 2006 have found reactions to lanolin alcohol 30% pet. ranging from 2.2% to 3.3% with an estimated clinical relevance of 83.4%. During the most recent test cycle of the NACDG survey (2009-2010) when lanolin alcohol 30% in pet. was used as its screening allergen, 2.5% of patients tested had a positive reaction to this allergen, of which 90.6% were deemed to be clinically relevant.

Only 2.24% of the positive reactions were linked to occupation; all the rest were due to the use of medicines or healthcare products, or household items.

It is important to consider that these prevalence figures quoted above are based on a positive patch test reaction, indicating contact allergy to lanolin, but they do not actually indicate that the patient has ACD to ‘‘lanolin’’ (which is why clinical relevance is critical). Secondly, the rates of contact allergy are those for diseased patients, not the general population. It has been estimated that the annual incidence of ‘‘lanolin’’ allergy in the general European population ranged from 1.46 to 8.75 cases per million; that is 0.00146% to 0.00875%. This is of course far below the usual threshold for the inclusion of this hapten in a standard screening panel.

However, in a multicentre European study (2 centres in Germany and 1 each in Sweden, Netherlands, Portugal, and Italy) of 3,119 volunteers who were representative of the local population, the prevalence of contact allergy to wool alcohols was 0.4% - as shown with the use of TRUE Test® with a hapten concentration of 1.0 mg/cm2.

What segments of the population are most at risk of lanolin allergy?

It is well documented that certain medical conditions confer a much higher risk of sensitisation to lanolin. These conditions are Stasis Dermatitis / Chronic Venous Insufficiency, chronic leg ulcers, perianal and genital dermatitis, atopic dermatitis, amongst children, and amongst the elderly.

1. Stasis Dermatitis / Chronic Venous insufficiency

Wound dressings are a common cause of sensitisation for persons with this condition.
One study showed that secondary ACD was found in 78% of such patients, with the most frequent allergen being lanolin alcohols (30% pet.) in 33% of all patients.

2. Chronic leg ulcers

Along with *Myroxylon pereirae* and Fragrance Mix I and benzalkonium chloride, Lanolin Alcohol and Amerchol L101 have been found to be the major exacerbating factors in patients with chronic leg ulcers. The incidence may however be decreasing in recent years due to the use of improved wound care products.

For example, a French study showed that among 354 patients, 59.6% had at least 1 positive patch test reaction to 1 of the dressings, and 19% had at least 1 sensitisation to a component of the wound dressing. After benzalkonium chloride (0.1% pet.; 7.1%), Amerchol-L101 was the next leading allergen (50% pet.; 5.4%). The study authors concluded that sensitisation, even to more ‘‘modern’’ dressings, was not rare in this population.

A recent German study of the IVDK on 5,264 patients with leg ulcers associated with Stasis Dermatitis/Chronic Venous insufficiency from the years 2003 to 2014 and compared these data with an historical control group and a current control group (n = 55,510) found that although ACD was diagnosed less frequently in the study group than in the historical control group (16.9% vs 25.9%), and contact sensitisation to most allergens had declined over the period, the allergen spectrum remained largely unchanged. The 4 most frequent allergens were *Myroxylon pereirae* (14.8%), Fragrance Mix I (11.4%), Amerchol L-101 (50% pet.; 9.7%), and lanolin alcohol (30% pet.; 7.8%).

3. Perianal and genital dermatitis

A prominent study reported that the most frequent sensitising active principles were local anaesthetics and corticosteroids, whereas lanolin alcohols were the most frequent culprits among the vehicle components. They concluded that the local conditions (e.g., occlusion, sweating, moisture) in the ano-genital region encourage skin sensitisation to the topical medications used to treat various skin diseases in that location.

4. Atopic dermatitis

The retrospective multicentre NACDG data on 36,937 patients patch tested from 2001 to 2018 included lanolin alcohols (30% pet.) which was used to screen for ‘‘lanolin’’ allergy from 2001 to 2010, as well as Amerchol-L101 (50% pet.) which was used from 2011 to 2018. Among these 36,937 adults tested to one or other of the ‘‘lanolin’’ screening allergens, 313 of the 8,336 (3.8%) AD patients versus 671 of the 28,601 (2.3%) non-AD patients had a positive reaction. Thereby, ‘‘Lanolin’’ was the 18th most frequent and the 10th most relevant allergen among adults with AD.

5. Children

However, in the same NACDG study quoted above, the authors state that this association between AD and lanolin allergy was not found amongst children (< 18 years of age). This is a rather strange statement, as their own figures indicated that there was indeed a correlation between AD and lanolin allergy. Specifically: of the 1,647 patients <18 years old tested to one of the ‘‘lanolin’’ screening allergens, 38 of 847 (4.5%) AD patients versus 22 of 800 (2.8%) patients without AD had a positive reaction to ‘‘lanolin’’. In addition, ‘‘lanolin’’ and its derivatives were the 10th most frequent and the

4th most clinically relevant allergen in children with AD.

Another study of a retrospective analysis of children (aged <18 years) patch tested by the NACDG from 2005 to 2012 compared their data from 2001 to 2004. Among the children (n = 883) tested during the study period, 62.3% had one or more positive patch test and 56.7% had one or more clinically relevant positive patch test. ‘‘Lanolin’’ was the 5th leading cause of ACD in these children: 5.5% had a positive patch test reaction to the ‘‘lanolin’’ screening allergen (lanolin alcohol, 30% pet., 2001–2010; Amerchol-L101, 50% pet., 2011–2012) and, in 5.1%, the reaction was considered relevant (92.7% of the ‘‘lanolin’’ reactions). These results in children did not differ significantly from the adults during the same time period, nor did they differ from those children tested during the 2001–2004 cycles.

However, in a subsequent more comprehensive review of the NACDG data from 2001 to 2018, allergic reactions to ‘‘lanolin’’ were in fact more common in children (4.5%) than in adults (3.2%). Hand Eczema in children is particularly associated with sensitisation to lanolin. NACDG data from 2000 to 2016 showed of 1,634 paediatric patients, 14.5% had involvement of the hands. Final physician diagnoses included ACD (49.4%), AD (37.1%), and ICD (16.9%). The 5 most common currently relevant allergens in the hand eczema cohort were nickel, methylisothiazolinone, propylene glycol, decyl glucoside, and ‘‘lanolin.’’ HE in children was associated with significantly higher odds of currently relevant reactions to ‘‘lanolin,’’ followed by quaternium-15, *Compositae* mix, thiuram mix, 2-mercaptobenzothiazole, and colophony. ‘‘Lanolin’’ was again singled out as an important allergen in the paediatric population.

6. The elderly

There is indeed a correlation between lanolin sensitivity and the elderly, but this may well be due to the increase amongst the elderly of the prevalence of chronic venous insufficiency, leg ulcers and dermatitis. For example, among their elderly with leg ulcers, the frequency of contact sensitisation to at least 1 allergen (57.4% vs 40.7%) or to multiple allergens (34% vs 16.7%) was higher than the reactivity of all elderly patients). Logistic regression analysis (gender, age, and history of atopic diseases) showed an independent association between elderly patients with leg ulcers and risk of sensitization to lanolin alcohols.

The authors of the original review article conclude as follows:
Since the principal allergens in ‘‘lanolin’’ are the free alcohols (especially alkane-a,b-diols and alkane-a.o-diols), industrial and academic researchers interested in lanolin allergy need to undertake an analysis of our current patch test materials for the presence of these substances, and other potentially allergenic substances such as low molecular weight oxidised organic derivatives formed during different manufacturing processes. These studies may well lead to the introduction of newer patch test preparations with improved specificity and sensitivity for detecting ‘‘lanolin’’ allergy.

Patch Test Hapten from Chemotechnique

Art no	Name	Conc.	Veh.
A-004	Amerchol L-101	50%	pet
S-016	Softisan 649	100%	pet
W-001	Lanolin alcohol	30%	pet

The Significance of Dose for the Patch Test Reaction

by Magnus Bruze, et al.,
CONTACT DERMATITIS, 2024; 1-2
https://doi.org/10.1111/cod.14628

Patch testing is a highly standardised procedure that involves several potential variable factors, each of which will affect the results of the patch test and therefore undermine the validity of the clinical diagnosis. One of these factors is the volume of the hapten used in the patch test chamber.

The main relevant factors are:

1. Choice of hapten; be it a salt or some other compound of the intended test substance.
2. The vehicle containing the hapten, most usually petrolatum.
3. The concentration of the hapten in the vehicle, expressed as % or e.g., mg/mm^2.
4. The volume (dose) of the hapten in the vehicle in the chamber, usually expressed as mg of weight.
5. The chamber used, such as IQ Ultra or IQ Ultimate, or Finn, etc.
6. The location of the test chambers on the patient.
7. The time period of occlusion; most usually 48 hours (D2).
8. The reading time of the test results, most usually D3 or D4 and ideally also D7.
9. The evaluation criteria for the various grades of positivity.
10. The recording of the test results.
11. The interpretation (possibly by another clinician) of the reported grades of test result.

As complicated as this sounds, there are also other factors that may be involved, such as woman's hormonal cycle, pregnancy, concomitant immunotherapy or other medicinal treatment, and many more. In fact, it's almost a miracle that the *in vivo* patch test works at all!!

This study focuses, very tightly, on the factor of dose / volume of the test hapten.

In order to select patients for the core of the study, 47 patients were shown to exhibit doubtful or weak positive reactivity to *Myroxylon pereirae*, Fragrance Mix I and/or MDBG (1.0%).
The three sensitiser haptens were chosen as the routine patch testing with these haptens in the clinic of the authors frequently gives reactions around the threshold between doubtful and weak positive reactions.

This test criterion of doubtful/weak positive was chosen because this level of reactivity is around the threshold of positivity.

The study authors define these terms as:

- A doubtful reaction is with only erythema on the patch test area, or erythema with infiltration not covering the whole test area.
- A weak positive reaction with only erythema and infiltration covering the whole test area.

In the study, adult dermatitis patients with suspected allergic contact dermatitis were routinely tested with the Swedish Baseline Series and an additional petrolatum preparation with methyldibromoglutaronitrile at 1.0% wt/wt prepared within the author's clinic laboratory.
Finn Chambers were used, with a diameter 8 mm.

The chambers were applied on the upper back and secured with Scanpor tape. The patches were removed after 48 h and the test was read on D3 or D4 according to ICDRG protocol.
Of the 47 selected patients, 40 gave a doubtful reaction and 7 gave a weak positive reaction to the petrolatum preparation of either *Myroxolon pereirae*, Fragrance Mix I or MDBG 1%.
On these 47 patients, additional patch testing was performed the same day with a set of three Finn chambers filled with 40 mg, 20 mg, or 10 mg of the respective sensitiser hapten.
These additional tests were again occluded for 48 h and read on D3 or D4.

20 mg is the standard recommended dose, as recommended by both global manufacturers of patch test haptens, so this study evaluated a half-dose and a double-dose, alongside the standard dose of 20 mg.

When the 20 mg dose was repeated on the same patients, just 34% (16/47) of all patients repeated the same level of test response.

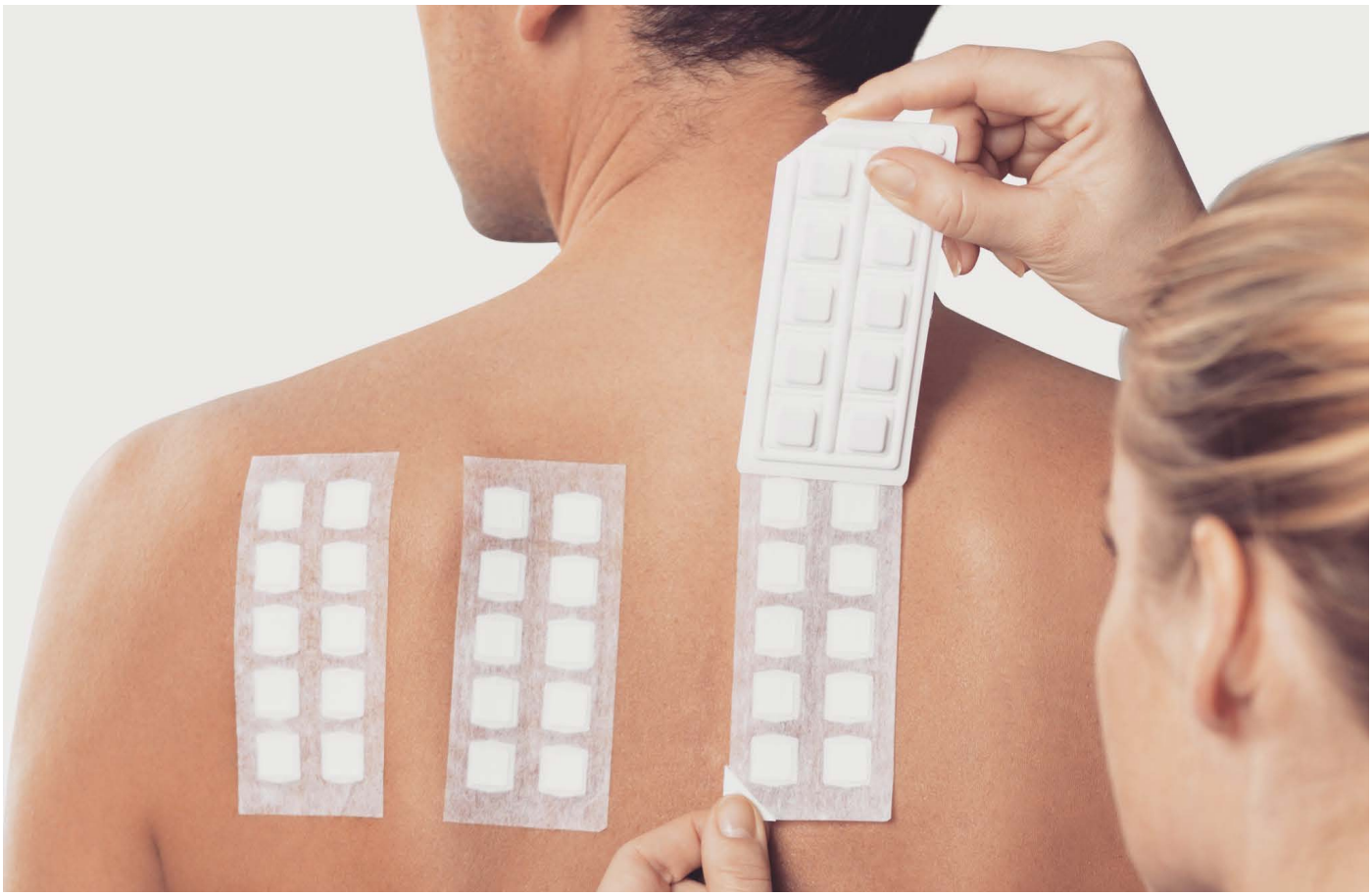
Now 15% (6/40) of doubtful reactors tested positively. For the seven patients with an initially weak positive reaction, the double-dose (40 mg) gave 25% (10/40) positive reactions.

For the forty patients with an initially doubtful reaction, the half-dose (10 mg) gave 10% (4/40) positive reactions.

For the seven patients with an initially weak positive reaction, the rates of positive reactions with different amounts of petrolatum preparations were as follows:
- 40 mg = 57% 4/7
- 20 mg = 29% 2/7
- 10 mg = 14% 1/7.

Statistically, there were significant differences between 40 mg and 20 mg ($p = 0.031$), as well as between 40 mg and 10 mg ($p = 0.0039$).

As could be expected, the results from this study demonstrate that there are differences in test response depending on the amount of petrolatum preparation with a sensitiser hapten.
Significantly, more contact allergy in this study was detected with the 40 mg petrolatum preparations. However, petrolatum doses from 25 mg (equivalent to 50 mg/cm^2) and higher give too many reactions with a major spreading outside the test area. That is one good reason why 20 mg (which is equivalent to 40 mg/cm^2) is the recommended dose.



This study also demonstrates that doubtful reactions must not automatically be regarded as irritant reactions, but may in fact represent weak positive reactions that do not quite fulfil the minimum requirements to be classified as allergic reactions.

Editors Note:
Note that the Finn Chambers were used in the study. The authors claim that all patch test manufacturers recommend 20 mg topical hapten per chamber. The Chemotechnique recommended dose is however 25 mg to achieve a dose per areas of 36 mg/cm^2.

In order to produce a 40 mg/cm^2 dose using an IQ Chamber, 27 mg of topical hapten preparation is needed. When the dose is increased the authors note that the hapten spreads outside the intended test area as it is hard to confine the haptens to the chamber while using a Finn Chamber. While this is not emphasized in the article, it is important to note that the concept of dose per area relies on a chamber that do not easily leak - such as the IQ chambers with an adhesive chamber rim.

Chromium and Cobalt in Leather: A Danish market survey

by Mikkel Bak Jensen, et al.,
CONTACT DERMATITIS. Online Version of Record before inclusion in an issue. July 2024; 1-6.
https://doi.org/10.1111/cod.14643

Nickel, cobalt and chromium are common metal allergens that cause Allergic Contact Dermatitis in individuals exposed to either a high concentration over a short period of time or a low concentration over a prolonged period.

After nickel, cobalt is the second most common metal allergen in ACD patients, though determining the clinical relevance of a positive patch test reaction to cobalt is often challenging due to insufficient knowledge about exposure patterns, because the presence and concentration of cobalt in various items is not yet clearly established or mapped.

Leather has been a significant source of chromium allergy in Denmark since the 1990s. More recently, cobalt allergy has been identified in leather as a source of Allergic Contact Dermatitis.

Several studies in recent years have suggested that contact with bio-available cobalt in leather goods may induce contact allergy through skin contact. Although there is a growing body of evidence confirming the presence of cobalt in leather products, only a few studies have systematically investigated the presence of cobalt in the leather and the amount of cobalt released from such leather products.

In May 2015, the European Union (EU) implemented a regulation limiting the content of Cr (VI) in leather to a maximum of 3 mg/kg. In 2021 a proposal was made to further reduce the EU-enforced limit of Cr (VI) from 3 to 1 mg/kg, to be implemented in 2026.

This study aimed to determine the levels of chromium, Cr (VI), and cobalt present in leather goods available to consumers in Denmark.

A total of 89 leather samples were collected, all tanned in Europe, from 5 suppliers, and of various colours.

To determine the presence and levels of cobalt and chromium in the samples, a handheld X-ray fluorescence (XRF) device was used to screen for the presence of chromium and cobalt. Then, the 20 leather samples with the highest concentrations of cobalt and chromium were tested using ISO standards (International Organization for Standardization). Note though that there was a significant discrepancy in the values measured by XRF and ISO methods, due to intrinsic differences in the different chemical forms that are measured by the two test systems.

Depending on intrinsic antioxidant content, environmental conditions, as well as the age of the leather, leather tanned with chromium might release both trivalent or hexavalent forms of chromium [Cr (III) or Cr (VI)] when coming into contact with the skin, both capable of causing ACD. Cr(VI) is of particular concern due to its potent allergenic properties, lower elicitation thresholds, and higher skin penetration rates.

The results of the study showed an important insight into the prevalence and concentrations of chromium and cobalt in leather samples from Danish importers. The detection of chromium with XRF in 83.9% of the 89 samples aligns with previous studies indicating widespread use of chromium in the leather tanning process. However, Cr (VI) was detected in 7 out of the 20 samples with the highest concentration of chromium (35%) with concentrations of 0.33–4.2 mg/kg, with 1 out of the 20 tested samples (5%) exceeding the current regulatory restriction limit of 3 mg/kg. Three out of the 20 samples (15%) exceeded the proposed 2026 restriction level of 1 mg/kg.

It is important to note that most of the chromium present in leather is in the trivalent form, Cr(III), though this can oxidise to the more toxic Cr(VI) on the surface of the leather in dry air.

Cobalt was detected in 59.7% of the samples, yet there is currently no EU legislation on permitted levels. This indicates a potential regulatory gap. Although cobalt is less frequently discussed in legislation, its proven presence and variable concentrations could pose a risk similar to that of Cr(VI). Therefore, the detection of cobalt in leather goods may mean that, in terms of consumer safety, it should be managed in the same way as Cr(VI).

Previously published research papers reported on the prevalence of chromium-induced ACD due to leather exposure from Danish leather samples and, in particular, the risks associated with Cr(VI). In that study from 2002, approximately 35% of leather articles on the Danish market had detectable levels of Cr (VI) exceeding 3 mg/kg, with concentrations ranging from 3.6 to 14.7 mg/kg. This very substantial reduction in both prevalence and concentration of chromium levels most likely demonstrates the effectiveness of the EU regulation on reducing the presence and concentration of chromium in leather goods, thereby reducing much of the public health risks associated with leather goods.

As regards cobalt; a previously published investigation of the association between cobalt allergy and leather-induced dermatitis found a significant association due to non-occupational leather exposure, highlighting leather as a notable source of cobalt. This is consistent with the finding in the current study of detectable levels of cobalt in leather goods, and supports the hypothesis that leather goods may serve as a significant source of exposure to cobalt, potentially leading to ACD. It has previously been suggested by researchers that the presence of cobalt was tannery-dependent, which would indicate that it should not be difficult to eliminate cobalt from the tanning process.

There is currently no EU legislation on the permissible concentration of cobalt in leather goods and so further research is needed to establish levels that induce sensitisation.

It has ben demonstrated that Cr (III) release decreases with usage time, while Cr (VI) increases or remains unaltered. Future research should therefore focus on longitudinal studies to monitor chromium and cobalt levels in leather goods over time, especially considering the evolving EU regulations and developments in tanning practices.

Editor's Note:
Making leather is a complicated process. The tanning process involves five different stages: Pre-Tanning, Tanning, Selecting, Dressing and Finishing. Each of these processes is complex and requires many steps. Here is an overview of some of the more important points in each step.

Step 1: Pre-Tanning
Soaking: When the leather reaches the tannery, it can be soaked to squeeze out the salt used to preserve the leather. Washing in water to remove impurities and folds from the hides. This is done in a rotating drum that can hold up to 200 hides.
Pressing: The pressing process is to eliminate excess water and stretch the hides.
Splitting: The grain - the outer surface of the hide - is mechanically separated horizontally from the split.

Step 2: Tanning
This is the process of converting pre-tanned leather into leather.
Common tanning methods include mineral tanning, vegetable tanning, synthetic tanning, oil tanning, combination tanning, etc.

Step 3: Selecting
After the tanning step, excess water is removed from the leather. The leathers are then graded according to the natural characteristics and flaws.

Step 4: Dressing
Leather dressing includes the following steps:
Shaving: The entire surface of the hide acquires a uniform thickness.
Dyeing: The key point in the process, lending the hide softness, colour and stability.
Drying: Removing the water via vacuum suction using special equipment made of steel plates.
Trimming: Cutting, selecting and dividing the hide.

Step 5: Finishing
The purpose of finishing is to improve the overall performance of the leather, and to protect the leather from wetting and soiling, to minimize the appearance of grain blemishes without losing the natural beauty of the leather product. Further modify the surface properties (gloss, shadow, etc.).
The above information taken from this webpage.

Tanning Process
Tanning chemicals include calcium hydroxide, sodium sulphide, sulphuric acid, formic acid, hydrogen sulphide, aniline-based dyes, and various solvents (dichloromethane, benzene, ethanol, tetrachloroethane, trichloroethylene).
Finishing chemicals include formaldehyde, aniline, nitrocellulose, and resins.
Leather tanning chemicals can be divided into four groups:

1. **Vegetable tanning**
2. **Chrome tanning**
3. **Chrome-free / aldehyde tanning**

4. Zeolite-based tanning.

1. Vegetable tanning

Vegetable tanning is the oldest tanning method. It uses extracts from wood, and nuts of trees and shrubs. Responsible suppliers ensure these come from a sustainable source. It usually takes longer to tan leather using this method, but the result is a leather with a distinctive aesthetic and handle, which ages beautifully. Its naming, as well as the tanning materials used, make it seem as if vegetable tanned leather is more 'eco-friendly'. However, we need to take the entire balance across the whole process into account, to make a more meaningful comparison with other methods. For example, vegetable tanning uses a few times the amount of tannins than for chrome-tanned leathers. The effluent produced also requires more treatment before it can be discharged. However, it has the benefit of using natural, sustainable, and renewable raw materials.

2. Chrome tanning

About 75% of leather made today is tanned by chromium. The process uses trivalent chromium (Cr III). Chrome tanning produces consistent leathers that can be used or worn, year after year, without any loss of properties. It is sometimes suggested that hexavalent chrome, or chromium VI (Cr VI) is used for tanning leather, and that it is carcinogenic. Chromium VI is not used in the manufacturing of leather, but it may form due to oxidation of Cr III on the surface of the leather in dry air conditions. The process of chrome tanning is constantly being upgraded, as its uptake is improved, less of it needs to be used, there is comprehensive recycling, reduced water consumption and careful management of waste. The chemicals used in chrome tanning do however put a strain on the environment.

3. Chrome-free / aldehyde tanning

There is a number of other tanning methods, known by different labels. They are usually grouped and referred to as 'chrome-free'. Chrome-free leathers are usually made for a specialised performance requirement, or often specified for automotive use. The most common is aldehyde tanning, which utilises glutaraldehyde. Leathers made with this tanning agent require relatively more chemicals after tanning, to improve the leather properties. For this reason, the effluent of a glutaraldehyde-based chrome-free process will require additional treatment before it can be discharged.

4. Zeolite-based tanning

A new innovation in tanning chemicals is the use of zeolites. Zeolites have a unique property in that they can absorb or release water, depending on the temperature. Water absorption is an important part of leather comfort, and a tannage that allows water absorption (without swelling) is a desirable characteristic. Zeolite-based tanning is chrome-free, aldehyde-free and heavy metal-free and does not compromise on leather performance.
The above information taken from this webpage

Chrome tanning

A modern electric tanning drum in Germany
Chromium(III) sulphate ($[Cr(H_2O)_6]_2(SO_4)_3$) has long been regarded as the most efficient and effective tanning agent. Chromium(III) compounds of the sort used in tanning are significantly less toxic than hexavalent chromium, although the latter arises in inadequate waste treatment. Chromium(III) sulphate dissolves to give the hexa-aqua-chromium(III) cation, $[Cr(H_2O)_6]^{3+}$, which

at higher pH undergoes processes called olation to give poly-chromium(III) compounds that are active in tanning, being the cross-linking of the collagen subunits. The chemistry of $[Cr(H_2O)_6]^{3+}$ is more complex in the tanning bath rather than in water due to the presence of a variety of ligands. Some ligands include the sulphate anion, the collagen's carboxyl groups, amine groups from the side chains of the amino acids, and masking agents. Masking agents are carboxylic acids, such as acetic acid, used to suppress formation of poly-chromium(III) chains. Masking agents allow the tanner to further increase the pH to increase collagen's reactivity without inhibiting the penetration of the chromium(III) complexes.

Collagen is characterised by a high content of glycine, proline, and hydroxyproline, usually in the repeat glyprohyprogly. These residues give rise to collagen's helical structure. Collagen's high content of hydroxyproline allows cross-linking by hydrogen bonding within the helical structure. Ionized carboxyl groups (RCO^{2-}) are formed by the action of hydroxide. This conversion occurs during the liming process, before introduction of the tanning agent (chromium salts). Later during pickling, collagen carboxyl groups are temporarily protonated for ready transport of chromium ions. During basification step of tanning, the carboxyl groups are ionised and coordinate as ligands to the chromium(III) centres of the oxo-hydroxide clusters.

Tanning increases the spacing between protein chains in collagen from 10 to 17 Å. The difference is consistent with cross-linking by poly-chromium species, of the sort arising from olation and oxolation.

Further information on the tanning process can be obtained by following this link.

Titanium Allergy: A Retrospective Review of 166 Patch Tested Patients

by Camila N. Fontane Hoyos, et al.,
DERMATITIS, Volume 35, No. 3, May/June 2024, pp 245-248.
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Nickel is the most common contact allergen identified with patch testing, and suspicion of a nickel allergy is typically the indication for patch testing prior to the implantation of any metal-containing prosthesis such as in knee joints or hip joints. Titanium-based systems are often considered an alternative option in metal-allergic patients; due to their supposed reduced incidence of sensitisation to the metal compared to other metals that may be used in prostheses. However, only a few studies have been published on titanium allergy, and practitioners may be unaware of the incidence and clinical adverse reactions to a titanium allergy, and the allergic reactions to titanium in implants may be overlooked in clinical practice.

Although titanium allergy is uncommon, surgeons, dermatologists, and allergists should be aware of its existence as a significant knowledge gap seems to exist.

Even in cases wherein allergy to a titanium implant is likely to be relevant, it is essential to weigh decisions about further surgery carefully against various case-specific factors; unfortunately, removal of a suspected implant culprit does not guarantee resolution or improvement of the symptoms.

Consequently, it may be necessary to have more broad contact allergen avoidance strategies and/or other interventions such as immunomodulators.

Previous published studies on titanium allergy provide the following data:

- In 2015, Wood and Warshaw completed a review on hypersensitivity reactions to titanium, including 19 cases of titanium implant allergy published between 1980 and 2013.
- In 2018, De Graaf et al published a retrospective chart review of 458 patients evaluated between 2004 and 2017. They found an overall titanium patch test positive (PTP) rate of 5.7% and 7.9% for titanium (IV) oxalate hydrate, specifically. Of the 26 titanium PTP patients, 2 had ‘‘complete’’ and 14 had ‘‘partial’’ relevance.
- In 2020, Tam et al published a retrospective review of 150 patients patch tested for metal allergy between 2006 and 2017 and found a 0.7% positive rate to titanium oxalate 5% petrolatum.

This study under review was based upon a single institution’s experience with titanium patch testing and evaluation of titanium allergy. A retrospective medical record review of 177 patients evaluated for titanium contact allergy was conducted in the Brigham and Women’s Hospital Contact Dermatitis and Occupational Dermatology Program between January 2018 and August 2023. Patients were

A cell phone with a titanium frame

referred for pre-implant testing, post-implant testing, or testing unrelated to metal implants. Of the 177 records reviewed, 11 were excluded if they did not receive titanium testing or lacked in-person reading between 72 and 120 hours. The remaining 166 records were evaluated as an overall group. In addition, records were compared between those patients' patch tested between 2018 and 2020 with those tested between 2021 and 2023.

Titanium substances used in the patch testing included titanium (IV) oxalate hydrate or titanium (III) oxalate decahydrate (titanium oxalate) 5% petrolatum, titanium 10% petrolatum, titanium (III) nitride 5% petrolatum, and/or titanium (IV) oxide (titanium dioxide) 10% petrolatum.
Patch testing with a full Metal Series that includes titanium allergens was performed in 99 (59.6%) of the 166 patients and was done in cases where further information was needed about other potential metal allergens. The remaining patients were tested only for titanium or titanium plus other allergens, such as our standard series, due to a clinical suspicion of additional allergens unrelated to the implanted metal.

PTP was defined by the ICDRG methodology and criteria, which included reaction strengths of 1+ or greater; questionable (?) and irritant reactions were excluded.

Previously published diagnostic criteria for metal hypersensitivity reactions to metallic implants comprise 4 major criteria:

- Eruption overlying the metal implant
- Chronic dermatitis beginning weeks to months after metallic implantation
- Positive patch test reaction to a metal used in the implant

Complete recovery after removal of the offending implant and 6 minor criteria:

- Unexplained pain and/or failure of the offending implant
- Dermatitis reaction is therapy resistant
- Morphology consistent with dermatitis
- Systemic allergic dermatitis reaction
- Histology consistent with allergic contact dermatitis
- Positive *in vitro* test to metals.

In this study, the authors designated an implant as "likely relevant" to the underlying presentation if it met at least 3 of the 4 major criteria, "possibly relevant" with 2 major criteria, and "not likely relevant" with 1 major criterion.

The results of the patch testing were as follows:

- Of the 166 patients in our cohort, 67 were referred for pre-implant patch testing and 64 for post-implant patch testing; 35 were tested for reasons unrelated to an implant.
- Twenty-six of the 166 patients were patch test positive (PTP) to titanium (15.7%) with all 26 were PTP to titanium oxalate, and 1 also reacted to titanium dioxide.
- Overall, titanium PTP rates increased from 13.6% (6/44) in 2018 – 2020 to 16.4% (20/122) in 2021 – 2023.

- Titanium PTP rates were higher for post-implant cases (28.1%, 18/64) than for pre-implant cases (6.0%, 4/67).
- When considering postimplant testing only, titanium PTP rates increased from 15.0% (3/20) in 2018 – 2020 to 34.1% (15/44) in 2021 – 2023.
- Among 18 titanium PTPs identified for the 64 post-implant cases, 8 were likely relevant, 8 were possibly relevant, and 2 were not likely relevant.
- For the 8 likely relevant cases, the average time between symptoms or dermatitis likely as sociated with implant allergy and patch testing was 26.3 months (range 4 – 132 months).
- 4 of the 8 cases improved with removal of the offending prosthesis (“explantation”), 1 is considering explantation, 2 started dupilumab, and 1 plans to start dupilumab due to continued dermatitis after explantation.
- PTP rates were higher for patients referred post-implant when allergy was suspected, compared with patients undergoing pre-implant metal allergy screening.
- There were no statistically significant differences in overall titanium PTP rates between 2018–2020 and 2021 – 2023 or between these periods when considering post-implant testing only. However, both comparisons showed trends toward greater titanium PTP rates during 2021 – 2023.

The PTP rates for titanium are likely higher in this study than in the general population, because the clinic upon which this study was based was a tertiary referral centre and received local, regional, and national referrals.

When considering which titanium preparation would be the most suitable to detect sensitisation to titanium, in this study, titanium oxalate was the most common titanium allergen, which is consistent with the published literature. Patch testing to titanium dioxide, titanium 10%, and titanium nitride did not add additional useful clinical data beyond titanium oxalate in our series. Prior studies have indicated the limited usefulness of patch testing to titanium dioxide, which may be explained by its inability to penetrate intact skin. Similar limitations may exist when testing with titanium 10% and titanium nitride.

The study authors recommend that further studies should be performed to evaluate the incidence of allergy to titanium implants and continue the surveillance of any changes in the rate of sensitisation.

Art no	Name	Conc.	Veh.
P-014A	Potassium dichromate	10%	pet
P-014B	Potassium dichromate	5%	pet
T-040	Titanium dioxide	10%	pet
T-041	Titanium(IV)oxalate hydrate	5%	pet
T-042	Titanium	10%	pet

Screening Series:

MET-1000	Metal Series
METE-1000	Metal Extended Series
IMP-1000	Implant Series

Less efficient Skin Penetration of the metal allergen Pd^{2+} compared to Ni^{2+} and Co^{2+} from Patch Test preparations

By Konstantin Simon, et al.
CONTACT DERMATITIS, Volume 90, Issue 6, July 2024, pp 11-21.
https://doi.org/10.1111/cod.14569

Contact allergies are T-cell mediated diseases that affect up to 20% of the general population, with nickel being the stand-out most common sensitising hapten.

Palladium allergy has rarely been diagnosed in the general population, which may be a true reflection of the very low incidence of sensitisation to palladium, which may be due to the poor penetration of palladium ions into the dermis both in normal life and in patch test situations, or it may be a result of using sub-optimal patch test haptens based on palladium.

Compared to the frequency of Allergic Contact Dermatitis caused by sensitisation to nickel or cobalt, reactivity against palladium is rare, yet palladium has been shown to activate a greater T cell fraction *in vitro*, suggesting that the penetration of palladium into the skin is inefficient.

Although patch testing is the one and only current diagnostic standard to confirm Allergic Contact Dermatitis and to identify the offending haptens, the test has several limitations.

Patch testing is supposed to induce the elicitation phase of ACD by delivering a critical amount of allergen into the dermis to activate immune cells located within a small test area. Antigen-specific tissue-resident memory T cells emerge during sensitisation and become re-activated by renewed allergen exposure, for example, during patch testing with the sensitising hapten. Tissue-resident memory T cells predominantly reside in the epidermis near the dermal junction, or in the dermis.

Patch test preparations of metals (such as palladium) are undissolved metal salts dispersed in petrolatum. Various patch test preparations of different compositions used globally can potentially deliver varying amounts of metal ions into the skin, with subsequent most likely different patch test results, thereby exacerbating the evaluation of the prevalence of the allergy to that hapten. Substance properties, including particle size and solubility of the metal salt, have a significant impact on the release and penetration of the metal ions into the skin. Therefore, using a sub-optimal permutation of the hapten, for example a particular salt or a particular concentration, can lead to false positive or false negative patch test results, which can ultimately result in incorrect allergy diagnoses.

For example, the ESCD guideline recommends the use of undissolved palladium chloride $PdCl_2$ in petrolatum as a patch test preparation. However, as $PdCl_2$ is poorly soluble in water, it is possible that not enough Pd^{2+} is migrating into the skin during patch testing. This can lead to false negative results when employing $PdCl_2$ as the test substance. As an alternative for palladium-

based patch test preparations, the water-soluble Na_2PdCl_4 has been suggested. Positive patch test results obtained with $PdCl_2$ were generally confirmed by Na_2PdCl_4, plus additional patients were diagnosed with palladium allergy using Na_2PdCl_4 as the patch test hapten. The results were obtained despite the fact that $PdCl_2$ was applied to the skin in dissolved form and yet Na_2PdCl_4 was applied dispersed in petrolatum.

This study was designed to determine the metal ion penetration during a 48-hour period, into pig skin, (as a surrogate of human skin), of the ions of the salts

- Nickel sulphate $NiSO_4$
- Cobalt chloride $CoCl_2$
- Palladium chloride $PdCl_2$
- Sodium tetrachloropalladate(II) hydrate Na_2PdCl_4

The test haptens were not only the commercially available haptens obtained from Chemotechnique, but also metal salt solutions in PBS.

The pig skin was divided into five different compartments (of different depths) as well as “receptor fluids” at 24 hours and at 48 hours, in order to analyse the penetration characteristics of each test substance.

The tests gave some very interesting results:

- The proportion of the applied ions that was detected in the entire skin after 48 hours did not differ significantly between the metals. However, the distribution in individual skin compartments was very different.
- Ni^{2+} and Co^{2+} from $NiSO_4$ and $CoCl_2$ patch test preparations penetrated the subcutaneous layer and the viable skin much more efficiently than Pd^{2+} ions from $PdCl_2$ or Na_2PdCl_4 patch test preparations. This can be explained by the different metal salt-water solubilities, which are reported to be in the molar range for $NiSO_4$ and $CoCl_2$ but measured to be in the mid to low millimolar range for the two palladium salts.
- A major difference between natural sensitisation to metal ions and the patch test situation is the fact that in patch test preparations, the metal salts are dispersed in petrolatum, while for skin penetration, it is feasible to assume there is a dissolution of the metal ions in an aqueous medium such as sweat prior to being taken up into the skin.
- The higher water solubilities of Ni^{2+} and Co^{2+} salts compared to Pd^{2+} salts contribute to higher recoveries of Ni^{2+} and Co^{2} in the different subcutaneous layers and the remaining skin layers.
- The water solubility of metal salts was not the only factor leading to a lower skin penetration of Pd^{2+} into the skin. Previous research on the skin penetration of dissolved metal salts indicates that metal ions are retained in the subcutaneous layers. According to previous research, the middle and lower subcutaneous layers have been shown to provide a barrier to metals, for example chromium. Histidine-rich filaggrin proteins strongly chelate nickel, which is hypothesised to hinder and slow down skin penetration. The effective retention of metal ions in the subcutaneous layers may therefore be attributed to the barrier effect of filaggrin.

- This study showed that he majority (>90%) of the metal ions remain in the donor compartment and do not penetrate the skin.
- The difference between the penetration of Ni^{2+} and Co^{2} on the one hand and Pd^{2+} on the other hand must at least partially be due to physico-chemical differences in the ions, such as radius or complexation behaviour, and biochemical properties that determine or at least affect their interactions with the skin.
- The authors of this study hypothesise that the difference in charge of the different metal ion complexes contributes to the observed differences in penetration rates through the skin. This difference can be explained by the pH gradient that exists between the different layers of the skin: the skin surface pH is acidic, ranging from 4.1 to 5.8, whereas in deeper cell layers, the pH rises to about a neutral pH of 7. In those deeper layers, the negatively charged Pd^{2+} complexes are strongly retained while the positively charged Ni^{2+} and Co^{2} complexes are able to penetrate more readily through the skin into the receptor fluid, which is at a physiological pH of 7.4.

Of the three metals analysed, Pd^{2+} had the lowest concentration in the remaining skin, regardless of whether patch test preparations or a metal salt in PBS solution were applied. This suggests that even though Pd^{2+} has the ability to activate a large portion of the T cell pool, only a very small fraction of Pd^{2+}-specific T cells become engaged at the low Pd^{2+} concentrations in the skin. This may explain why palladium allergies are less common than nickel allergies, in addition to a generally lower real-life dermal exposure.

However, individuals may become sensitised to higher Pd^{2+} concentrations (for example, in case of skin injury), whilst patch test preparations of $PdCl_2$ may not deliver enough ions to give a positive patch test result and therefore enable diagnoses. This deficiency may lead to false negative results when employing $PdCl_2$ in a patch test preparation. Previous research has suggested a greater reliability with patch tests utilising Na_2PdCl_4 instead of $PdCl_2$, proposing the availability and use of the water-soluble Na_2PdCl_4 for patch testing.

For full information on this very complex and thorough research study, please read the original article in CONTACT DERMATITIS.

Occupational Allergic Contact Dermatitis to Marijuana

by S. Heyne, et al.
CONTACT DERMATITIS, Volume 91, Issue 2, August 2024, pp 168-169
https://doi.org/10.1111/cod.14567

This paper describes a single case report of occupational dermatitis identified as being caused by physical contact with marijuana.

Cannabis is a hemp plant which belongs to the family *Cannabaceae* and order *Rosales*. The three major species are *C. sativa, C. indica* and *C. ruderalis. C. sativa* and *C. indica* are commonly used in industry and for medical and cosmetical purposes. Fibres for the textile industry and for the production of hemp-based ropes are obtained from the stem, while the cannabinoids Delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are extracted from the resin-containing flowers. Marijuana is a drug made from the dried flowers and leaves of the female hemp plant and contains the psychoactive substance THC. CBD is used as food supplements and in cosmetics, for example hemp seed oil.

Marijuana is an increasingly consumed recreational drug with possible side effects, type I sensitisation and, as shown here, also type IV sensitisation.

An aerogenically-transmitted type IV sensitisation can be difficult to distinguish from atopic dermatitis. Therefore, a detailed personal and occupational history and a diagnosis with appropriate patch tests are extremely important for the correct diagnosis.

Several reports of type I sensitisation to cannabis plants (contact urticaria, anaphylaxis) have been published previously. Only a few individual cases have been reported to date about allergic contact reactions to hemp seed oil containing CBD: For example, a young female patient developed eczema in the areas where she applied *C. sativa* seed oil. A type IV sensitisation was confirmed by a positive patch test and Repeated Open Application Test.

A case of airborne allergic contact dermatitis in the facial area due to consumption of medical marijuana was recently published.

This study presents a rare case of an occupational type IV sensitisation to aerogenic transmitted marijuana, that mimicked an atopic dermatitis.

A 24-year-old woman presented to the outpatient clinic with severe eczematous skin lesions. Atopic dermatitis had been initially diagnosed in childhood but had improved by early adolescence. In addition, she had a rhinoconjunctivitis with a type I sensitisation to rye, grasses, and Mugwort/*Artemisia*. She also had a type IV sensitisation to nickel-containing costume jewellery.

The eczematous skin lesions developed after starting to work as a medical technical assistant in the

laboratory of the criminal police department. She presented with macules and papules in the face, neck, shoulders, elbows, wrists and back of the hands, with a similar distribution to atopic dermatitis. She described severe itching (8/10 numeric rating scale [NRS]) and sleep disturbance (5/10 NRS). Local therapy with topical corticosteroids of class II resulted in a only short-term improvement. During her occupation, she had to wash her hands frequently, she used hand disinfection, and she was wearing nitrile gloves. The substances she examined mainly included marijuana, 3,4-methylenedioxy-N-methylamphetamine (MDMA) and N-methylamphetamine.

The patient was patch tested with a standard panel, plant components, disinfectants, and Rubber Series, as well as the gloves she used at work and marijuana 5% or 10% in petrolatum. MDMA and N-methylamphetamine were not tested.

The patch tests showed a double-positive patch test reaction at 48 and 72 h to marijuana 5% and 10% (pet.) and a single-positive patch test reaction to nickel sulphate at 72 h.

Allergic Contact Dermatitis due to type IV sensitisation to aerogenic transmitted marijuana was diagnosed. The type IV sensitisation to nickel sulphate was confirmed, though this was only relevant in the past, as the patient avoided all contact with costume jewellery.

The employer subsequently took actions for the patient to avoid contact with marijuana. In addition, the patient was prescribed a local therapy with TCS class II/III, followed by topical calcineurin-inhibitors (TCI), which resulted in an improvement of the Allergic Contact Dermatitis.

Allergic Contact Dermatitis caused by Colophonium in Resin Creams

by Susan Leivonen, et al.
CONTACT DERMATITIS, Volume 91, Issue 1, July 2024, pp 70-72.
https://doi.org/10.1111/cod.14545

Colophonium, also known as colophony or rosin, is a common contact allergen with an incidence in European patch tested patients during 2015 – 2018 of 3.11%.

At the Finnish Institute of Occupational Health (FIOH) in 2002 – 2017, as many as 4.6% were patch test positive to colophonium of the patients with suspected occupational ACD.

Exposure to colophonium can occur both at work and in private life. Common products containing colophonium used in domestic but also in occupational settings include adhesive plasters and tapes, wound dressings, various types of cosmetics and timber. More recently, in Finland, over-the-counter resin creams seem to have gained popularity, especially for the treatment of small skin lesions, which may well be causing an increase in contact dermatitis due to the colophonium in those resin creams.

Colophonium from coniferous trees is a mixture of resin acids of abietane-type or pimarane-type structures (90%) and neutral components (10%). The abietic-type acid is the major resin acid and the main allergen in colophonium. Resin cream prepared from purified resin of Norway Spruce (*Picea abies*) has been shown to have antimicrobial effects against bacteria (Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus* species) and fungi *(Trichophyton rubrum, T. tonsurans* and *T. mentagrophytes*). Resin cream is a medical device that contains 10% Norway Spruce resin, and it is used in professional wound care for chronic wounds. Resin creams and other preparations typically containing 5 – 30% Spruce resin are also used for topical self-treatment of various skin conditions, for instance scratches, sores, sun burns, onychomycosis and paronychia.

However, it is important to be aware of the potential sensitising effect of the products, especially due to their colophonium component. The risk of sensitisation to colophonium is likely to be even greater if the resin cream is applied to already damaged skin with impaired skin barrier as compared to healthy skin.

The increased popularity of resin cream containing colophonium use might increase the prevalence of colophonium allergy, which is concerning.

In this study, 26 of the 479 (5.4%) patch tested patients were diagnosed with contact allergy to colophonium. Of them, 10 patients (38%) reported previous use of resin cream, and it was determined that 6 of the 10 were most likely to have become sensitised to colophonium by their use of resin cream. They all reacted positively to colophonium with either strong (++) or extreme (+++) positive

reactions. Five of them had a positive reaction (++ or +++) to abietic acid and three had a doubtful reaction (?+) to it, while two were not tested with abietic acid. Three of the 10 patients with a history of resin cream use were diagnosed with current or previous occupational allergic contact dermatitis caused by colophony. Three patients were considered previously sensitised to colophonium by exposure to oil colours, adhesive plaster, cardboard, or pine wood dust that contained colophonium, and subsequently developed recurrence of allergic contact dermatitis while using resin cream. One patient initially developed eczema while using resin cream, and his eczema then recurred at work where he handled cellulose fibres that contained colophonium. One patient was a nurse that had used resin cream for treating patients. Her colophonium allergy was considered possibly occupational, though of no current relevance. Seven of the patients had noticed their eczema was related to their personal use of resin cream.

In a previous report on occupational contact allergy to colophonium, the majority of the patients worked in the wood industry, in machinery, soldering or agriculture. It should therefore be considered that there is a significant risk that sensitisation to colophonium from resin cream use in private life may affect the ability to continue to work in the wood industry and any other where colophonium occurs.

Although this is at present just a theoretical risk, even in the highly selected patient material of this patch test clinic involved in this study, consisting of patients with suspected occupational contact dermatitis, as many as 38% of patients with colophonium contact allergy had a history of resin cream use, and in 23%, the resin cream was considered the probable source of sensitisation.

The current EU cosmetics regulation does not prohibit or restrict use of unmodified colophonium in cosmetic products, such as resin creams. However, the results from this study indicate the potential benefit of a review of the regulation to ensure consumer safety regarding colophonium content in resin creams.

Comparison of Patch Test positivity after 24 and 48 hours of occlusion time in Patients of Allergic Contact Dermatitis: A prospective study

By Rhea Ahuja, et al.,
In CONTACT DERMATITIS, Volume 90, Issue 6, June 2024, pp 54-59.
https://doi.org/10.1111/cod.14543

The Patch Test is of course the gold standard for the confirmation of suspected Allergic Contact Dermatitis and the identification of the offending allergen/hapten.

Conventionally, according to the recommended procedures of the ESCD and the NACDG, the patches loaded with the test hapten are applied for a period of 48 hours/2 days, before being removed and the test sites having their initial inspection.

However, for several reasons there would be a case for the removal after just 24 hours:

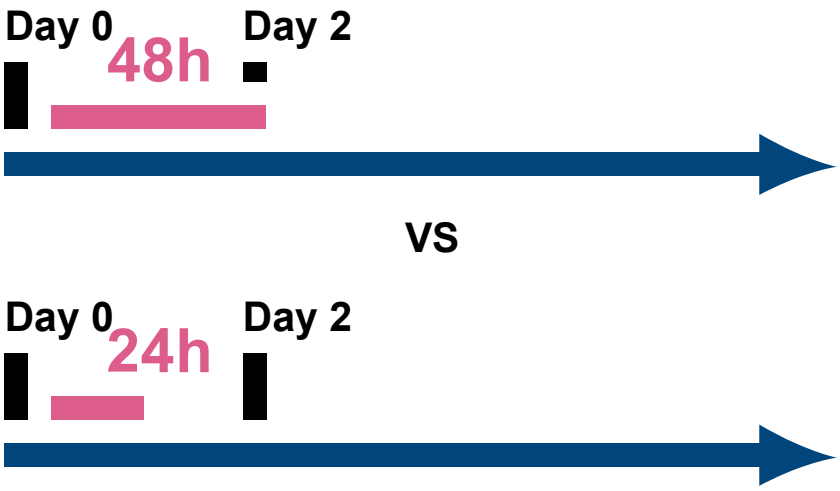
1. In more humid / tropical climes, where excessive sweating can lead to irritation.
2. Convenience, due to the need to avoid bathing if using non-water-resistant chamber strips.
3. Risk of loss of adhesion of the chamber strips, resulting in repeat testing.

The authors of this India-based study therefore investigated if the results after just 24 hours occlusion on the skin could be comparable to the standard 48 hours occlusion, for common allergens/haptens, at their standard concentrations.

Ninety seven clinically suspected ACD patients were tested with the Indian Standard Series of 25 haptens (See here for more information on the Indian Standard Series), plus parthenium acetone extracts in 3 different concentrations (1:50, 1:100 and 1:200 dilutions), as well as patients own materials.

Patches were applied to the patients back, in duplicate on either side, using a random number table. One set of patches was removed after 24 hours and the other set after 48 hours. Readings were performed at 48 hours and at 96 hours, independently by two Dermatologists who were blinded to the period of occlusion.

Editor's note:
It would have been interesting if a reading had also been done on the 24-hour patches at 24 hours, rather than just at 48 hours and 96 hours.



The results showed almost complete agreement between patches occluded for 24 hours or 48 hours.

Of the 48-hour occluded patches, a total of 133 patches showed positive reactions at 48 hours and 142 at 96 hours reading time.

Of these, 117 (87.9%) and 132 (92.9%) were positive and concordant after just the 24-hour occlusion period. The Cohen's Kappa Coefficient were 0.94 for 48-hour and 0.97 for 96-hour readings.

Editor's note:
The study authors made two interesting statements in their conclusion, which are partially contradictory:

1. There is no significant difference in patch test positivity among haptens/allergens of the Indian Standard Series after either occlusion period.

2. When reactions of all haptens/allergens are considered (Indian Standard Series + parthenium acetone extracts + patient material are analysed together, then the 48-hour occlusion period performs significantly better compared to 24-hour occlusion.

This initial study does however raise awareness of this important technical issue and should be followed up in other studies using different standard series of haptens/allergens, and a larger number of patients.

Patch Test Results amongst Older Adults: A Retrospective Analysis of the NACDG Data (2009-2020)

by JiaDe Yu, et al.,
DERMATITIS, Volume 35, No. 3, May/June 2024, pp 236-242.
https://doi.org/10.1111/cod.14545

Allergic Contact Dermatitis in older adults (OA) represents a significant health burden, but there are few studies that examine the prevalence and characteristics of contact allergy and ACD in this population.

Within just 5 years from now, more than 20% of the U.S. population will be over the age of 65.

Older Adults are defined in this study as over the age of 65 years, whereas YA are defined as 19 to 64 years and children as 18 years and under.

As this shift toward an older population unfolds, it is essential to further our understanding of skin disease, including ACD, in OA.

This study provides an updated understanding of patch test results in OA as compared with YA and children. We found that patient characteristics, patch test reaction proportions, clinical relevance, and final diagnoses differed between the three age groups.

Some of the earlier studies initially showed a lower incidence of ACD amongst older adults. Some experts were of the opinion that ACD was less common in older adults. An older theory hypothesised this may be due to senescence of the immune system with an observed decrease in both pro-inflammatory cytokines as well as the density of Langerhans cells in the aging epidermis.
For example, a 2003 European study of 2,776 patch tested patients with suspected ACD found the prevalence of patch test reactivity to be lowest (34.9%) among patients older than age 70 years and highest (62.0%) in children up to 10 years.
However, more recent reports in the literature suggests a higher prevalence of ACD in OA. For example, a previous analysis of 31,942 patients (1994 – 2008) found that the proportion of at least 1 positive patch test reaction was highest in OA (‡65 years old) (67.3%), followed by younger adults (YA, 19–64 years old) (66.9%) and children (>18 years old) (62.9%).
Similarly, a smaller retrospective analysis published in early 2022 involving 169 OA (‡65 years old) found a PPT reaction proportion of 84.6%.

In addition, a 2023 study of 4199 patients found that OA (‡65 years old) were also more likely to have a clinically relevant positive patch test result (67.7%) compared with a Young Adult group (18 – 64 years old) (51.6%).
An important question is ...is this perceived change in the prevalence of ACD in the Older Adult

group a real change or just a quirk of statistics. This question is not answered by this report.
In this study, patients referred for suspected ACD were patch tested by NACDG members between 2009 and 2020 with a standardised screening series containing 70 or 80 allergens. The method of patch testing, data entry, and analysis were performed according to established NACDG guidelines.

Numerous points of interest were revealed by the analysis of this study:

- Of 28,177 patients included in this study, 19.0% (n = 5,366) were OA, 75.7% (n = 21,343) were YA, and 5.2% (n = 1,468) were children.

The relative frequency of patch testing for ACD amongst OA (19.0% compared to YA (75.7%) and Children (5.2%) gives a clear indication of the significance of ACD to OA, as the 19.0% corresponds almost exactly to the proportion of OA in the general population. This would indicate that the incidence of ACD amongst OA is no less, nor no greater, than amongst YA and Children.

- OA were more likely than YA to be male and to identify as white.
- OA were less likely than YA to have occupation-related ACD.
- Compared with children, OA were more likely to identify as white, but were less likely to have history of AD.
- The most common primary site of dermatitis in OA was the face (28.1%), followed by scattered generalised (25.9%) and hands (10.1%).

Compared with YA and children, OA had higher proportions of dermatitis affecting the trunk, scalp, anogenital region, and ‘‘under clothing,’’ but had lower proportions of dermatitis affecting the face not otherwise specified, lips, and feet.

When compared with YA only, OA had higher proportions of dermatitis affecting the legs, ears, eyes, and a scattered/generalized distribution, but had lower proportions of dermatitis affecting the hands and eyelids. When compared with children only, OA had lower proportions of dermatitis affecting the arms and exposed areas.

There was no difference in the proportion of either PPT (positive patch test reactions) reactions or RPPT (clinically relevant patch test positive reactions) between OA and YA. However, OA were significantly more likely than children to have a PPT reaction and/or RPPT reaction.

The most common allergens (for both PPT and most usually also RPPT) for OA were as follows:

- Fragrance mix I
- Methylisothiazolinone (MI)
- Hydroperoxides of linalool (Lin-OOH)
- Benzisothiazolinone (BIT)
- *Myroxylon pereirae* resin (balsam of Peru) (BoP)
- Methylchloroisothiazolinone/methylisothiazolinone (MCI/MI)
- Nickel
- Formaldehyde
- Iodopropynyl butylcarbamate (IPBC)
- Neomycin

- Bacitracin

Compared with both YA and children, OA had higher odds of an RPPT reaction to Fragrance Mix I, BoP, formaldehyde, BIT, and IPBC.

OA had lower odds of an RPPT reaction to nickel as compared with YA and Children.

Compared with YA only, OA had higher odds of an RPPT reaction to Lin-OOH.

Compared with children only, OA had higher odds of an RPPT reaction to MI.

The top 5 allergen SPIN scores for OA were Fragrance Mix I (622), Lin-OOH (544), MI (541), MCI/MI (501), and BoP (425).

The most common specified sources for the allergens with the top 5 SPIN scores in OA were:
- Fragrance Mix I = moisturisers, shampoos/conditioners, and perfumes/colognes.
- Lin-OOH = shampoos/conditioners, perfumes/colognes, and moisturisers.
- MI = shampoos/conditioners, moisturisers, and soaps/detergents.
- MCI/MI = shampoos/conditioners, moisturisers, and liquid/lotion/bar soap.
- BoP = food products, perfumes/colognes, and moisturisers.

The most common final primary diagnosis after patch testing in OA were ACD (50.8%), ‘‘other dermatitis’’ (18.3%), and ‘‘other dermatoses’’ (10.2%).

In comparison with both YA and children, OA were more likely to have a final primary diagnosis of ACD, other dermatitis, other dermatoses, nummular eczema, seborrheic dermatitis, and stasis dermatitis, whereas OA were less likely to have a final primary diagnosis of irritant contact dermatitis and AD than either YA or Children.

The significance of concomitant Atopic Dermatitis (AD) also showed real differences between the three age groups. OA were less likely to have a history of AD compared with YA and children (16.0% vs 30.4% vs 58.2%) and/or a final diagnosis of AD (5.3% vs 13.9% vs 30.3%) after patch testing. This finding is expected as AD onset is common in early childhood, and many symptoms resolve by adulthood. However, the burden of AD in OA is now increasingly recognised, with recent data suggesting a prevalence of 2 – 10%. As AD and ACD may be morphologically indistinguishable, anatomic distribution, clinical history, and potential patch testing are all important for a differential diagnosis, an accurate diagnosis and effective management.

In summary, this 11-year study of >28,000 patch tested patients showed that OA were just as likely and statistically possibly even more likely to have a final diagnosis of ACD as compared with younger age groups.

These results should be carefully considered when evaluating ACD in older adults, and may help guide patch testing.

In addition, further research is needed to better understand the development of contact allergy, and subsequently ACD, across the lifespan.

Patch Testing and Allergic Contact Dermatitis in Pregnancy

by Magnus Bruze, et al.,
In CONTACT DERMATITIS, Volume 91, Issue 3, September 2024, p1
https://doi.org/10.1111/cod.14543

Pregnancy is a very common condition, that can coincide with Allergic Contact Dermatitis, yet there has been very little research or investigation into the topic of patch testing the pregnant woman, and the influence of the hormonal status and changes of the pregnant ACD patient.

ACD can cause significant distress and morbidity, which necessitates a need for better future guidelines on the optimal care of expectant mothers with ACD.

During the course of pregnancy, the body undergoes complex immunologic and hormonal changes, which consequently lead to changes in the immunologic processes in dermatologic disorders such as ACD, sometimes improving and other times worsening the disease condition.

Of the various allergic disorders that can be seen in pregnancy, ACD is less often discussed in the literature despite its relatively common prevalence of ACD in the general population.

Current patch testing guidelines state that while there is no known risk with patch testing during pregnancy, it is recommended out of an abundance of caution, and perhaps also lack of knowledge, that patch testing is avoided to be avoided as a precautionary measure.

In this study, a PubMed literature search (on 1/4/2024) using search keywords of ‘allergic contact dermatitis’, ‘patch testing’ and ‘pregnancy’ were used to evaluate all English-language articles discussing patch testing and ACD in pregnancy. All articles were screened by abstract and only two papers were found to satisfy the selection criteria.

One study described two patients who underwent patch testing, one of whom was in the third trimester of pregnancy, and the other was a postpartum patient who was breastfeeding. Both patients were found to have positive reactions that then guided subsequent treatment recommendations. This article seems to be the only report of patch testing in pregnancy for ACD. It suggests that patch testing could be a safe procedure if indicated. However, the study gives no information the true efficacy of performing such testing that may be affected by unclear false-positive results that could theoretically occur due to the altered immunologic state of pregnancy.

The second published study summarised several allergic disorders seen in pregnancy. Interestingly, they described the fact that whilst ACD is more common in females, there is no epidemiologic or statistical information on ACD among pregnant females. They recommended therapies used in atopic dermatitis (AD) to also be used also in ACD given that both have similar treatment options in the general population, with mild topical corticosteroids as first-line treatment.

In summary, there is currently very little literature on patch testing and ACD in pregnancy.

The study authors suggest that, in order to obtain more useful data and information to bridge the current knowledge gaps, they make a call to action for data collection under the guidance of the European Society of Contact Dermatitis. They propose the establishment of a data registry where clinicians may submit de-identified details on pregnant patients who had undergone patch testing (e.g., gestational age at the time of testing, test results, suspected false negatives, etc.) which may develop into a valuable shared clinical resource).

The study authors also suggest that when and if controlled prospective studies may be performed, comparing patch testing results during pregnancy and after can provide useful data. While a prospective study involving patch testing during pregnancy might be difficult for approval by the ethics committee (unless the ACD of the individual patient is severe enough to warrant patch testing whilst pregnant), patch testing during the post-partum period would be more easily permitted.

A re-assessment of the value of markers of Corticosteroid contact allergy in the Spanish Baseline Series: Clobetasol propionate in the spotlight

by Pedro Mercader-García, et al.,
In CONTACT DERMATITIS, Volume 91, Issue 3, September 2024, p228-236
https://doi.org/10.1111/cod.14639

The Spanish National Baseline Series of 29 haptens/allergens is of course widely used by Spanish Dermatologists in their routine patch test screening. It includes Tixocortol-21-pivalate (0.1% pet) and Budesonide (0.01% pet).

Since the 1990s, contact allergy to topical corticosteroids has been recognised as a common clinical problem, with several studies reporting a high prevalence of contact allergy, up to 5%. Although frequent, allergy to corticosteroids may be easily overlooked, because the clinical presentation is not specific and often manifests as a worsening of the condition for which the corticosteroid is prescribed to treat. In addition, systemic corticosteroids may cause sensitised patients to react with generalised reactions.

Accordingly, in 2000, two corticosteroid allergy markers were included in the European Baseline Series; Tixocortol pivalate and Budesonide. Different classifications of topical corticosteroids based on the cross-reaction patterns and molecular structures of corticosteroids have emerged in recent decades. The first of these classifications was established by Coopman and Degreef in 1989 and classified corticosteroids into four groups A, B, C and D. Thereafter, Matura and Goossens have modified this classification and subdivided group D into sub-groups D1 and D2. Most recently, Baeck et al. reorganised corticosteroids into three groups:

> **Group 1**: the non-methylated, mostly non-halogenated corticosteroids, which included the previous groups A, D2 and also Budesonide.
> **Group 2**: the halogenated molecules with a C16/C17 cis ketal/diol structure corresponding to Group B corticosteroids.
> **Group 3**: the halogenated and C16-methylated molecules, encompassing groups C and D1.
> Tixocortol pivalate is a marker of allergy to Group 1 corticosteroids, especially hydrocortisone.

Budesonide is also a marker of allergy to Group 1 corticosteroids; though it can also detect sensitisation to Group 2 corticosteroids.

However, these two markers (Tixocortol and Budesonide) are not as useful for detecting sensitisation to Group 3 corticosteroids; consequently, patients sensitised to any of the Group 3 corticosteroids may be overlooked.

Clobetasol propionate is a Group 3 corticosteroid that is commonly prescribed in Spain. It has therefore been previously suggested as a marker for sensitisation to all Group 3 corticosteroids.

Editor's Note:
Clobetasol propionate is currently to be found in the following series:

- Corticosteroid Series
- North American Series
- International Comprehensive Baseline Series
- North American Comprehensive 80 Series
- American Core Series 90
- New Zealand Baseline Extended Series

This study aimed to ascertain the prevalence and relevance of positive patch test reactions to two Clobetasol propionate preparations (0.1% ethanol and 1% petrolatum) and to compare them with those of Budesonide and Tixocortol pivalate in a Spanish population evaluated for suspected Contact Dermatitis.

Throughout 2022 and 2023, 4,338 patients attending the 22 public hospital clinics of the REIDAC (Spanish Registry of Research in Contact Dermatitis and Cutaneous Allergy) were patch tested with an extended Spanish Baseline Series that included Clobetasol propionate in 0.1% ethanol and 1% petrolatum.

The various patch test haptens were obtained from either Chemotechnique or SmartPractice AllergEAZE, or SmartPractice TRUE test (which contains both Budesonide and Tixocortol), in the different clinics. Different chamber types were also used in the different clinics.

Editor's note:
These two factors are unwelcome variables in the study design, which may have affected the results obtained. Readings were also taken on variable times, with most but not all readings being on D2 and D$ but some also on D7.

The following snippets of data and information can be taken from the published paper:

- In a previous study conducted in Spain to determine the sensitivity and specificity of corticosteroid allergy markers, all patients attending the centres involved for patch testing were tested with a Corticosteroid Series in addition to the Spanish Baseline Series. In that study, 45.4% of patients sensitised to any of the corticosteroids included in the dedicated Corticosteroid Series showed negative tests to corticosteroid allergy markers (Budesonide and Tixocortol) that were included in the Spanish Baseline Series. The rate of false negative results was higher for Group 3 corticosteroids; with 76.9% of patients sensitised to Clobetasol propionate testing negative for the Spanish Baseline Series markers of Budesonide and Tixocortol. This earlier study therefore indicates that the inclusion of Group 3 corticosteroid representatives in the Spanish Baseline Series is advisable, with clobetasol propionate being the best candidate marker for Group 3 corticosteroids.

- The prevalence of corticosteroid allergy in Spain has historically been low; in this study just 1.15%, which is similar (1.46%) to a previous study by the same authors in 2018.
- In contrast to the reported low frequency of corticosteroid allergy in Spain, a higher prevalence has been reported in other countries such as Denmark (2.7%), New Zealand (4.4%) and the United States (4.12%). These differences can be explained not only by the different prescription habits and differences between the populations studied, but also by the different methodologies of patch testing.
- Late readings were performed in all patients, revealing 28.1% of new positives on D7. Some researchers have shown that up to 28% – 38% of corticosteroid-positive test results may be missed if D7 readings are not performed, whereas other researchers did not find a significant increase in positives with a D7 reading. Although the guidelines recommend D7 readings for all patients, this recommendation is difficult to implement in many clinics for logistical reasons. Most of the patients in this current Spain study were advised to return to the clinic if they observed new positive results after 7 days, especially if there was a suspicion of corticosteroid allergy. With this approach, their results for Budesonide (0.55%) were similar to those of another recent Italian study that performed D7 readings in all patients (0.6%).
- In New Zealand, patch testing is a limited service in state hospital clinics, and only the most severe cases are accepted for testing.
- In the United States, more corticosteroid allergy markers, such as hydrocortisone butyrate, triamcinolone acetonide and clobetasol propionate, are used in the various American baseline series, resulting in an increased ability to detect corticosteroid-sensitised patients. Additionally, macular erythema is considered to be a positive reaction in American studies and is reported as positive; whereas such reactions are considered doubtful and so are not included in prevalence estimations in most European studies.
- No irritant reactions were detected to any of the corticosteroid markers, but doubtful reactions were frequent, especially with clobetasol propionate 0.1% ethanol. The high number of doubtful tests may be caused not only by the characteristics of topical corticosteroids themselves but also by the vehicle used, as there were more doubtful reactions with ethanol than with petrolatum. Corticosteroids can themselves cause reactive vasodilation, which can be interpreted as a weak or doubtful reaction. The anti-inflammatory effect of corticosteroids can make the patch test results difficult to interpret with false negatives or weak positives with ‘edge effect’. It is therefore possible that some doubtful reactions reported in this study may, in fact, be weak positives.
- Budesonide is widely used in Spain, though not in creams. Instead, it is a common component of inhalers, nasal sprays and enemas, which may be sources of sensitisation.
- The most common corticosteroid allergy identified was to Budesonide (0.55%). When compared separately, the results for Budesonide 0.01% in petrolatum (0.65%) are slightly higher than those previously reported by the European Surveillance System on Contact Allergies (ESSCA) using data from 2019 to 2020 (0.49%). Therefore, its inclusion in the Spanish Baseline Series is obvious.
- Tixocortol pivalate allergy was the least frequently detected (0.21%), with only two positives

among 2,164 patients tested (0.09%), which is lower than the results of the ESSCA study (0.34%). These data questions its usefulness as a marker of corticosteroid allergy in Spain. This low prevalence is likely related to prescribing patterns. In Spain, it is not possible to buy low-potency corticosteroids without a medical prescription. In contrast, in other countries where over-the-counter corticosteroids can be purchased, the prevalence of Tixocortol pivalate allergy is higher (1.6% in Denmark and 4.7% in the United States). Despite the greater incidence in USA, some American authors have recently recommended the withdrawal of Tixocortol pivalate from their various baseline series owing to the low rate of cross-reactions with other corticosteroids.

- Clobetasol propionate is one of the most prescribed topical corticosteroids in Spain and its relevance is easier to establish than that of other allergens. However, although the relevance that we found was high (56.52%), it was similar to that of Budesonide and far from that reported in the United States (78%).

- The British Association of Dermatologists reviewed corticosteroids for use in their Corticosteroid Series at 16 centres in the United Kingdom and Ireland. They reported a very low prevalence of contact allergy to Clobetasol propionate 1% petrolatum (0.12%) but found more positives when patch testing was performed with a commercially available cream containing the corticosteroid (1.68%). In New Zealand, a clobetasol propionate cream and ointment were also used for patch testing, with more positives than clobetasol propionate 0.25% in petrolatum. The disadvantage of performing patch tests using a commercially available preparation is that the reaction may possibly be caused by an excipient. Therefore, although using a commercially available cream preparation is a suitable approach for a specific series, it does not seem to be the most appropriate for use in a baseline series.

- There are several arguments in favour of the use of ethanol as an excipient for corticosteroids in general, as opposed to petrolatum. Although ethanol is less stable, the storage of patch test substances in ethanol does not seem to affect patch test reactions because the allergen is not the steroid itself but a degradation product. Patch test reactions with ethanol develop earlier than with petrolatum, and the distribution of the allergen is logically more uniform in ethanol. Despite these arguments, it is still much easier obtain allergens in petrolatum from suppliers/ manufacturers. Clobetasol propionate 1% in petrolatum has been used in the NACDG/ Baseline Series since 2003, and the prevalence of contact allergy was similar to that of our study (0.32%). Furthermore, the proportion of doubtful reactions found in our study with ethanol as a vehicle was much higher than that with petrolatum. In addition, if the substance is in ethanol, it cannot be pre-loaded onto the chambers, whereas petrolatum-based haptens such as Clobetasol propionate can indeed be preloaded onto chamber strips for storage and later use.

- The study authors concluded that Budesonide is the main marker for corticosteroid allergy in Spain. In contrast, Tixocortol pivalate shows limited utility in detecting corticosteroid allergy in Spain and its inclusion in the Spanish Baseline Series seems questionable. In addition to the fact that Clobetasol propionate is a widespread allergen in our environment, the prevalence of positive test reactions to clobetasol propionate, high relevance of the tests and few cross-reactions with current markers make the inclusion of Clobetasol propionate in the Spanish Baseline Series advisable. Of the two concentrations studied, the study authors recommend the use of 1% in petrolatum because it causes fewer doubtful reactions and is readily commercially available.

2024 ESCD

In this twentieth issue of “The Patch Tester” we are taking a look at the ESCD Congress in Dresden Germany on the 4th to 7th September 2024. Chemotechnique participated in the trade exhibition at this prestigious and focused key event of the year.

The scientific program covered a broad range of topics in the field, including the latest advances in basic and translational research, updates on diagnostic and prevention of contact dermatitis, allergic and inflammatory skin diseases, current and emerging therapies, and presentations on the latest clinical studies and their implications for patient care.

Experts in the field presented topics of broad relevance in 15 Plenary sessions. 18 further sessions provided comprehensive knowledge in specific fields of irritant and allergic contact dermatitis, as well as inflammatory diseases.

Special attention was given to the regulatory status of patch test products in the EU in presentations by both prof. Vera Mahler and the ESCD Task Force, represented by Prof. Swen Malte John, giving good insight in their aproach to the upcoming changes in regulation.

It was as always a pleasure meeting with all dedicated patch test clinicians in our booth and we look forward to meeting with you in congresses to come!

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 Dermatolologic 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

Dermatology - International

25th – 28th September 2024
EADV Congress 2024
Amsterdam, Netherlands
https://eadv.org/events/calendar/

18th – 21st June 2025
International Society of Dermatology
Rome, Italy
https://www.icd2025rome.org/

21st - 26th June 2027
ILDS - World Congress of Dermatology
Guadalajara, Mexico
https://www.ilds.org/what-we-do/world-congress-of-dermatology/

The webpage at www.waset.org/dermatology-conferences-in-2023 is one potentially very useful source of information of Dermatology congresses in 2024.

WASWT is the World Academy of Science, Engineering and Technology. Their webpage states numerous dermatology-related congresses and conferences for 2024.

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