the Patch Tester

Contact Dermatitis | Haptens | Patch Testing

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THE HEMA ISSUE

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

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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 nineteenth issue comprises forty 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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Litigation in Contact Dermatitis
– old news in America, fresh news elsewhere?

Based on the article….

Characteristics of Litigations involving Contact Dermatitis: An Exploratory Analysis

by Aashka Suvamakar, et al.
in DERMATITIS, Vol 35, No. 2, March-April 2024, pp 167-172.
https://doi.org/10.1089/derm.2023.0087

A very interesting article in the DERMATITIS journal on the unfortunate fact of litigation in the American legal system highlights how there is not only a cost to industry due to absenteeism caused by occupational dermatoses, but also a very tangible cost to industry by litigation from employees due to their acquisition of dermatitis or eczema caused by their work and working conditions and environment.

The article states the cost burden for CD in the United States approaches US $ 1,000,000,000 annually. A survey by the authors found 791 cases when searching the legal database for the terms "dermatologist" or "dermatology". Of these, there were 98 cases of lawsuits by employees against employers during the 37 years prior to 2021 on that basis of employer-caused "dermatitis" or "eczema". That is an average of just 2.6 cases per year, but the financial sums involved are very significant. Of those 98 cases, 61 met the inclusion criteria of the study.

So litigation by employees (and others) against employers is hardly new but whilst it is well entrenched in the US legal system, it will be new for many other countries if the practice spreads, as it inevitably will, sooner or later to a lesser or greater extent.

As background information, it should be remembered that Contact Dermatitis accounts for 90% to 95% of all occupation-related skin disease, and 30% of occupation-related disease.

From the original article many interesting points can be discerned, as follows:

- Verdicts favoured the plaintiffs (employees), in 42.6% of case, and the defendants (employers) in 32.8%, with the remaining 24.6% of cases settled by out-of-court financial arrangements.

- If a pay-out occurred, so from the employers to the employee(s) then the mean was $246,000. This does not include the out-of-court settlements, which would have been confidential. The biggest pay-out was over $5,000,000.

- The main reason for the employee-initiated litigation was "toxic exposure". Other major reasons were "negligent business practice" and "medical malpractice".

- The common contact allergens associated with the lawsuits were latex, surgical tape, and beauty products. Also occasional causes were hair/perm products and laundry detergent.

• Seven cases (of 61, so 11%) of dermatitis were induced by psychological stress (which is definitely not included in any hapten Screening Series).

• Of the 38 cases (62%) of "toxic exposure",
14 (23%) resulted from a "reaction to a product"
10 (16%) resulted from "occupational hazard"
8 (13%) resulted from "improper cosmetic services"
6 (10%) resulted from "negligent business practices"

• 5 (13%) of the "toxic exposure" cohort resulted from exposure to the skin which was not intended for that product. This included insecticides, tar, laundry detergent, heavy-duty clean-up chemicals and other chemicals.

• 10 (26%) of the "toxic exposure" cohort resulted from occupational hazards, with the majority of them resulting from a work injury.

• Forty-one out of 61 cases (67%) received financial compensation ranging from $325 to a maximum of $5,075,000, with a mean of $246,310. The single largest payment was awarded to a plaintiff who claimed an anaphylactic reaction to latex rubber gloves used during her surgical procedure, which led to a hospital stay, which in turn led to several other complications. The plaintiff claimed permanent disability and disfigurement.

• Case outcomes more often favoured the plaintiffs; at 42.6% vs 32.8%, which is in contrast to litigation involving melanoma, carcinomas, psoriasis, and MOHS surgery, where the majority of the litigations favoured the defendants. For example, medical malpractice represented 18% of the total CD lawsuits, with a majority favouring the defendant. Furthermore, only 1 (2.4%) resulted in a monetary compensation. This contrasts with a study that reported 51% of claims for melanoma malpractice resulted in a settlement.

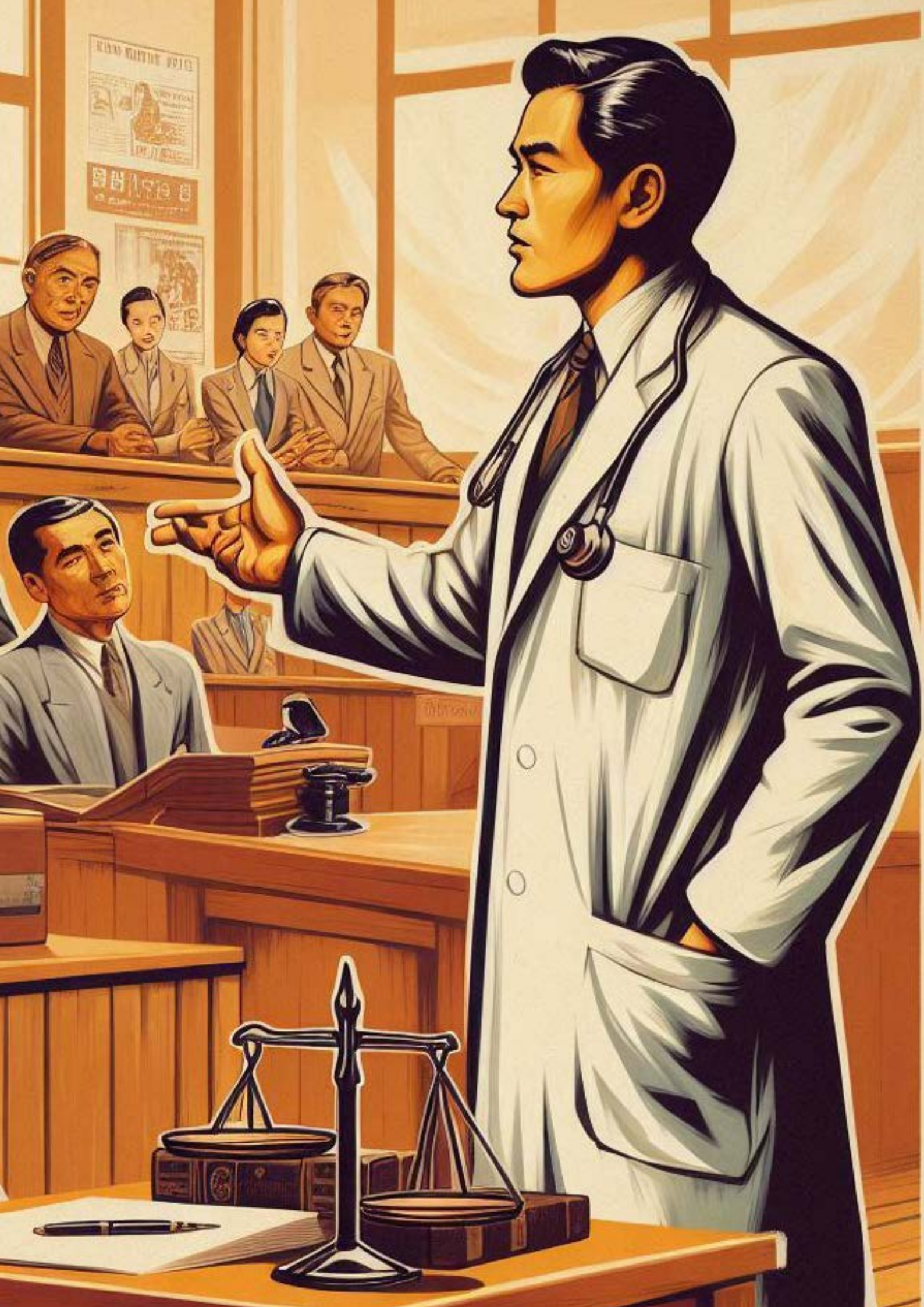
• Latex allergy, which was previously widespread, has now be- come much less prevalent due to regulations and implementation of nitrile gloves. The largest pay-out of over $5 million dollars was exceptional and not representative of the other cases of litigation.

• 12 of the 41 (29%) of pay-out cases were associated with "product liability". Product liability, as defined by torts law in USA, entails multiple components, including the product meeting the consumer's expectations, the defect in the product was present before the consumer purchased it and the injury the consumer suffered from is directly related to the product. Hair products are the most common product associated with product liability (12%).

Based on the findings of their study, the authors recommend a two-part strategy for Dermatologists to avoid such litigation:

1. Advocate to ensure improved labelling of particularly cosmeceuticals and other beauty products regarding the presence of potential haptens in various products, as well as in various workplaces.

2. Promptly performing patch testing with screeening series for any patient suspected of having contact dermatitis, to determine culprit haptens, and mitigate exposure, and initiate treatment as early as possible.



Doubtful Patch Test Reactions

Based on the article….

Allergic or Not: Final Interpretation of Doubtful Patch Test Reactions from the North American Contact Dermatitis Group, 2019–2020",

by Margot J Reader et al.,
in DERMATITIS, Vol 35, No.2, March-April 2024, pp 138-143.
https://doi.org/10.1089/derm.2023.0087

A second paper on the clinical relevance of doubtful patch test reactions is reviewed on pages 14-15 in this 19th issue of The Patch Tester. Although that second article, by Arora et al, was published almost simultaneously to this NACDG-based article, in the European-based journal CONTACT DERMATITIS, it is also based on USA clinical practices. It should therefore serve as an adjunct to this paper by Reader et al.

Doubtful patch test reactions generally do not meet criteria for positivity in patch testing and so are seldom reported – one study stating 84% of doubtful reactions as not being reported. This exclusion of data, however, may be wasting good useful diagnostic information of relevance to the clinician and the patient.

+Doubtful readings are a challenge to the Dermatologist with respect to the interpretation of the result and its clinical significance. Though doubtful reactions may have been defined as macular erythema, there is a significant degree of variation in the classification, reporting, and interpretation of doubtful results.

Doubtful results may be caused or at least influenced by several factors:

1. Variations in patch test materials (haptens and chambers), including concentrations.

2. Variations in patch test techniques, including interpretation.

3. Variations in reading times, whereby late-developing haptens (such as nickel, neomycin, corticosteroids) may only show stronger positivity after the time of the second reading, and early developers (such as fragrances) are already fading by the time of the second reading.

Few studies have been reported in the literature of the incidence and clinical significance of doubtful reactions, despite the potential usefulness of the information. Those few studies did however recommend that this information on doubtful reactions be included in the PT reports, and assess them with the same scrutiny as stronger allergic reactions in the clinical setting.

A previous survey reported that 79% of 417 previously-tested patients with doubtful reactions self-reported the relevance of their symptoms as corresponding to their doubtful results months to years

after the testing was completed. Surely then, in this study at least, the conclusion should be that doubtful results are most usually relevant, and so the information should be included in the PT report.

In order to ascertain the importance, or otherwise, of doubtful PT reactions, this study group led by Reeder analysed the NACDG data from 2019-2020 of 4,121 patch tested patients, who were tested with the NACDG-80 series. This study is therefore based tightly on formally recognised NACDG-based patch test practices in the USA.

For those readers of this journal “The Patch Tester” who are not familiar with the USA-based NACDG recommendations for patch test procedures, or their interpretation of patch test reactions, below is a very brief refresher.

1. Patch test first reading is performed after patch removal at 48 hours.
A second reading is performed between 72 and 144 hours after the initial placement, most usually 48 hours after the first reading, so 96 hours in total.

2. Reactions may be interpreted and recorded as:

- Positive - weak (+)
- Positive - strong (++)
- Positive - very strong (+++)
- Negative (-)
- Irritant (IR)
- Doubtful (+/-)

3. Doubtful reactions are typically macular erythema without induration and do not meet the threshold criterion for being labelled as “allergic/positive”.

4. Different nomenclatures are used to signify doubtful reactions: macular erythema, ?+ or +/-.

5. There is disagreement and variation in the interpretation of doubtful reactions, with many groups defining a ‘‘positive/allergic’’ reaction as only +, ++, or +++ on the second reading.

6. The North American Contact Dermatitis Group (NACDG) allows for doubtful reactions to be interpreted and reported with a final determination of ‘‘allergic/positive’’ based on the temporal pattern, appearance, known characteristics of the allergen, and/or other supportive patch test reactions, such as related substances.
The NACDG uniquely records a ‘‘final interpretation’’ at the last clinic visit (Day 4 or 5 usually).

7. Doubtful reactions can be coded as either ‘‘allergic/positive’’ or ‘‘not allergic/negative’’ at this final interpretation, based on the clinical scenario, crescendo/decrescendo pattern, and known characteristics of that particular allergen.
For example, a doubtful reaction to imidazolidinyl urea may be interpreted as “allergic/positive” if the patient has a strong reaction to formaldehyde as well as a positive reaction to a cream containing imidazolinidyl urea. Similarly, a doubtful reaction to an allergen/hapten known to peak later than others (such as nickel, neomycin, and corticosteroids) may be coded with a final interpretation of ‘‘allergic/positive’’ if the reading frame is earlier and perhaps too early for the reaction to fully develop by Day 4.
Conversely, a doubtful reaction to formaldehyde may be interpreted as “non-allergic/negative” in the setting where no other formaldehydes or formaldehyde-releasing preservatives are positive.

From the original article by Reader et al on doubtful PT reactions, many interesting points can be discerned as follows;

• 0.8% of all PT reactions were recorded as “doubtful” on the second/final reading.

• 32% (2,538) of 4,121 patch-tested patients gave at least 1 doubtful PT reaction

• Of all the 2,538 doubtful reactions recorded on the second/final reading, 46% were recorded as “allergic/positive” and 54% as “non-allergic/negative”. Of the non-allergic/negative reactions, 34% were labelled as Irritant, 13.4% were labelled as “Unknown” and 6.5% were labelled as “Negative”.

• The haptens with the highest incidence of doubtful reactions were, in order of magnitude:

o Hydroperoxides of linalool	4.5%
o Fragrance mix I (8%)	3.9%
o Cetrimonium chloride (0.5%)	3.4%
o Myroxylon pereirae resin (25%)	3.2%
o Benzisothiazolinone (0.1%)	3.0%
o Propolis (10%)	2.5%
o Iodopropinyl butylcarbamate (0.5%)	2.1%
o Propylene glycol 100%	2.0%
o Formaldehyde (2.0%)	2.0%

Followed by, at medium incidence:

- o MDBG (0.2%)
- o Oleamidopropyl dimethylamine (0.1%)
- o Benzophenone 4 (0.1%)
- o Cocamidopropyl betaine (0.1%)

• The haptens more likely to be interpreted as “non-allergic/negative” were:

o MBT (1%)	< 0.1%
o Ethylhexylglycerin (5%)	< 0.1%
o Phenoxyethanol (1%)	< 0.1%
o Polyhexamethylene biguanide (2%)	< 0.1%
o Mixed dialkyl thioureas (1.%)	< 0.1%
o Panthenol (5%)MCI/MI (0.02%)	< 0.1%

• Four allergens/haptens with doubtful reactions (MCI/MI 0.02%, MI 0.2%, nickel sulfate hexahydrate 2.5%, and neomycin sulfate 20.0%) were more likely to be interpreted as “allergic/positive”. These are among the most commonly positive allergens in patch testing in general. Positive reaction frequency rates were 18.2% for nickel sulphate hexahydrate, 13.8% for MI 0.2%, 9.0% for MCI/MI 0.02%, and 6.8% for neomycin sulphate. MCI/MI, MI, and nickel sulphate hexahydrate were also found to have a high Significance-Prevalence Index Number (SPIN Factor - which is an objective calculation that measures both prevalence and clinical significance).

• Of the doubtful reactions recorded as “allergic/positive” 84.9% had current clinical relevance, comprising 5.0% “definite”, 25.5% ”probable”, and 49.4% “possible”.

• Of the 1,315 patients with doubtful reactions, 54.4% had just 1 doubtful reaction, 23.9% had 2 doubtful reactions, and 22.7% had 3 or more doubtful reactions.

For further information, the reader is recommended to see the original article in DERMATITIS, Vol 35, No.2, March-April 2024, pp 138-143, or via https://doi.org/10.1089/derm.2023.0087.

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.

HEMA - 2-Hydroxyethyl methacrylate

Two articles in the May issue of CONTACT DERMATITIS are based on the significance of HEMA as a hapten. Based on article “Results of patch testing 2-hydroxyethyl methacrylate (HEMA) in the European baseline series: A 4-year retrospective study” BY Gizem Kocabas, et al, CONTACT DERMATITIS, Volume 90, Issue 5, May 2024, pp 466-469. https://doi.org/10.1111/cod.14488

The second article, 2-Hydroxyethyl metharylate (2-HEMA) sensitisation, a global epidemic at its peak in Spain, by Maria Elena Gatica-Ortega, et al. is reviewed on page 16 of this 19th issue of the Patch Tester.

Below is relevant background information on HEMA, derived from the Chemotechnique website at www.chemotechnique.se

HEMA, 2-hydroxyethyl methacrylate is one of the several acrylate and methacrylate compounds that constitute 22% of materials causing allergic contact dermatitis and 8% of dental products. It is known by several different names, including glycol methacrylate, beta-hydroxyethyl methacrylate, mhoromer, heme-a, 2-propenoic acid, 2-nethyl-2-hydroxyethyl ester, GMA, ethylene glycol methacrylate, 2-HEMA or just plain HEMA.

Its formula is $C_6H_{10}O_3$ with a molecular weight of 130 daltons.

It has uses as a methacrylic monomer in inks, adhesives, lacquers, dental materials, and perhaps most significantly in artificial nails.

It also usually contains the sensitising substance sorbitan sesquioleate 1% as an emulsifier.

It is found in numerous patch test hapten screening series:

S-1000	= European Baseline Series
ECB-1000	= European Comprehensive Baseline Series
SB-1000	= Spanish Baseline Series
PB-1000	= Portuguese Baseline Series
SIDAPA-1000	= Italian Baseline Series
PST-1000	= Polish Standard Series
GB-1000	= British Standard Series
ICB-1000	= International Comprehensive Baseline Series
AC-1000	= American Core Series
NAC-80	= North American 80 Comprehensive Series
NA--1000	= North American Series
ABS-1000	= Australian Baseline Series
NZBSE-1000	= New Zealand Baseline Series Extended
CB-1000	= Chinese Baseline Series

Hapten of the Quarter

MA-1000 = Methacrylate Series (Adhesives, Dental, Printing and other)
MN-1000 = Methacrylate Series (Nails)
DS-1000 = Dental Screening Series
DMS-1000 = Dental Materials – Staff
DMP-1000 = Dental Materials – Patients
IMP-1000 = Implant Series

In the past decade, HEMA has been increasingly recognised as a significant cause of allergic contact dermatitis, primarily through two sources, acrylic nails/nail polish, and dental materials. Therefore, in 2019, the ESCD added HEMA 2% in petrolatum to the European Baseline Series for routine testing. Several European-based countries have added HEMA to their own national screening series, some prior to it being added to the EBS and some afterwards. In addition, HEA has been present in the NACDG-80 screening series since 2007, so a real forerunner.

Several studies over the years and in different countries have reported a surprisingly consistent frequency of sensitisation, and a similar increasing trend.

•	USA-NACDG	2019-2020	3.2%, with a significant increase since 2009-2018
•	UK	2016-2017	1.7%
•	Italy	2016-2018	1.5%, with 2.5% for women and 0.5% for med
•	Italy	2018	1.6%, with 2.4% for women
•	Denmark	2017-2019	2.4% with women
•	Spain	2019-2020	3.7%
•	EBS	2019	2.3% in 13 countries, ranging from 0.9% in Hungary to 4.4% in Finland, 1.8% in Spain, 1.6% in Italy and 2.5% in UK.

• In the Denmark-based study, the proportion of HEMA-positive patients with a history of using UV nail polish increased from 50% in 2017 to 85% in 2018 and 100% in 2019.

• In this Amsterdam-based study, of 2,927 consecutive patients who were tested in 2019 to 2023, there was a 3.0% incidence of positivity to HEMA, with 3.9% (79 cases) in women and 1.0% (9 cases) in men.

• 49% of positive reactions were judged to be of current clinical relevance, plus a further 24% with previous clinical relevance.

• In the cohort of 64 patients with relevant clinical reactions, 28% had occupational contact with (meth)acrylate-containing products, of whom 11 (61%) were nail stylists.

• Of the 46 patients with non-occupational ACD, 67% reacted to nail cosmetics.

• The maximum strength of patch test positivity was as follows:
+ = 75% ++ = 20.5% +++ = 4.5%.

• Sources of occupational exposure for 18 patients were:

nail cosmetics, eyelash extension glues, dental materials, and industrial glues.

• Sources of non-occupational exposure for 46 patients were:
nail cosmetics, glues including eyelash extension glues, dental materials, TENS machine electrodes, hearing aids, hygiene pads, medical adhesives and ECG electrodes.

• Five patients who were sensitised by nail cosmetics went on to develop sensitisation and often more debilitating symptoms, to other sources of (meth)acrylates.

• As a consequence of the major even dominant role of nail cosmetics in causing sensitisation to HEMA, the great majority of such sensitised patients are female, in this Amsterdam study 90% and in other studies as much as 94% and 97%.

• This Amsterdam study shows that the inclusion of HEMA in the European Baseline Series was very much justified, both due to the overall frequency of sensitisation at 3.0% of all patch testing (using the EBS) and even 3.9% amongst women patients, and the high number of clinically relevant reactions at 73%.

The second article in this edition of The Patch Tester was based in Spain, and has similar findings and conclusions.

Clinical relevance of Doubtful Reactions in Patch Testing

by Puneet Arora, et al.,
CONTACT DERMATITIS, Volume 90, Issue 6, June 2024, pp 607-612.
https://doi.org/10.1111/cod.14526

Just by coincidence, a second article on the relevance of doubtful patch test reactions has been published in the second quarter of 2023. This particular article was published in the ESCD journal CONTAT DERMATITIS, though the study and the authors are USA-based. This second study is however based on the results and analysis of patch test doubtful reactions at a single clinic in USA that ran the NACDG Standard Series of 80 haptens, plus some additional haptens, including patients own materials. The commercially provided materials used were, in contrast to the other study, a mix of different manufacturers of haptens (Chemotechnique and SmartPractice "AllergEAZE") as well as a mix of different chambers (IQ Ultra and Finn Chambers). This fact does introduce a couple of extra elements of non-standardisation that may, repeat, may influence the incidence of the patch test reactions, and therefore also the results of the analysis and hence the conclusions.

One thousand five hundred and fourteen (1,514) patients were referred to the clinic in Minneapolis with suspected atopic dermatitis, and were all patch tested.

The results and the author's conclusions are as follows; but for full information, please read the original article in CONTACT DERMATITIS journal.

- 68.9% demonstrated at least one doubtful reaction, out of the minimum 80 patch tests performed on each patient.

- There were 4,453 doubtful reactions in total, of which 92.2% were unique.
By "unique" is meant a single doubtful reaction for that patient. The clinical significance of having a unique doubtful reaction compared to non-unique doubtful reactions is debatable.

- Only 3.3% were judged to be of definite clinical relevance, and 12.2% were judged to be of probable clinical relevance.

- Fragrance was the most commonly encountered source of unique, doubtful reactions of definite clinical relevance, though 64.9% of these also had a stronger reaction to another fragrance.

- Cocamidopropyl betaine was the second most commonly encountered hapten exhibiting doubtful reactions and was unique in 85.2% of cases.

- MI/MCI was the most prevalent hapten causing doubtful reactions, but was less-frequently unique (58.3%).

The authors of the research draw several conclusions from their results and observations:

• Doubtful reactions may not be as impactful to clinical decision making as has been postulated in other research publications.

• Few doubtful reactions demonstrated clinical significance - which is definitely not in concordance with the paper by Reader et all reviewed elsewhere in this issue of The Patch Tester.

• Many haptens with doubtful reactions exhibit stronger definite reactions to related haptens, and so would have been identified by the NACDG Screening Series or supplementary hapten tests.

• The significance of doubtful reactions to cocamidopropyl betaine and MI/MCI may be more significant because they were generally not in association with stronger reactions to associated haptens, so the doubtful reaction may be the only such indication.

• Interestingly, an observation noted by the authors was that although interpretation of patch test reactions on darker pigmented skin was more difficult due to the visualisation of erythema, this did not give cause to a (statistically significant) change of incidence of doubtful reactions.

• Whenever a particular allergen or personal care product is suspected to be involved in a patient's symptoms, patch testing to the patient's own product 'as-is' should be performed, in addition to the standardised hapten, especially when doubtful reactions are observed, as this may aid the determination of clinical relevance and allergen avoidance counselling.

2-Hydroxyethyl methacrylate (2-HEMA) sensitisation, a global epidemic at its peak in Spain

by Maria Elena Gatica-Ortega, et al.
CONTACT DERMATITIS, Volume 90, Issue 5, May 2024, pp 507-513.
https://doi.org/10.1111/cod.14520

As part of the claimed global epidemic of allergic contact dermatitis to acrylates and methacrylates, Spain has declared these haptens to be a prevalent health issue.

The study was based on the testing during 2019 to 2022 of 6,134 consecutive patients at 24 member clinics of the Spanish Allergic Contact Dermatitis Registry (REIDAC) with the Spanish Baseline Series that includes 2-HEMA 2% in pet.

- 265 of the 6,134 patients (4.3%) tested positive for HEMA.
- Positive reactions of current relevance accounted for 69% (184/265) of the positive reactions.
- The efficiency of testing for HEMA, calculated as the number of patch tests for HEMA that were required in order to achieve a positive result as 6,134/184 = 34.
- The variable factor “occupational” was found to be significantly associated with a greater risk for relevant positive reactions to 2-HEMA, thereby indicating the greater degree of sensitisation amongst relevant occupational workers.
- 2-HEMA 2% pet. was considered to be a highly effective marker within the Spanish/GEIDAC Baseline Series of sensitisation to (meth)acrylates.

The authors conclude by stating that the responsible authorities should implement policies guaranteeing accurate labelling of industrial, medical and consumer materials whilst ensuring the enforcement of that labelling through appropriate legal means.

This is obviously a very general and broad-sweeping recommendation, but particularly with regard to acrylates and methacrylates, this would imply the accurate labelling and promotion of public awareness of the risks of these (meth)acrylates.

Literature Review

Declining frequency of sensitisation to Fragrance Mixes I and II: IVDK-data of the years 2012-2021

by Johannes Geier, et al.
in CONTACT DERMATITIS, Volume 90, Issue 5, May 2024, pp 470-478.
https://doi.org/10.1111/cod.14493

A retrospective analysis of data from the German Information Network of Departments of dermatology (IVDK) during the decade of the years 2012 to 2021 was undertaken to determine the changes in incidence of sensitisation to Fragrance mixes I and II.

There is particular reference to the prohibition of two highly sensitising fragrance haptens atranol and chloroatranol, that are constituents in *Evernia prunastri/Oakmoss*, as well as the prohibition of hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC) in cosmetic products by the EU in 2017.

The screening of Fragrance mixes I and II is used to assess the effect of such prohibitions, though of course other factors will be involved besides the disappearance of those three substances.

The results of the analysis of the data showed that positive reactions to FM-I declined from 9.1% in 2012 to 4.6% in 2021, a halving over the 10-year period.

Similarly, positive reactions to FM-II declined from 4,7% in 2012 to 3.0% in 2021, so a reduction of approximately 50%.

Further analysis of the data from the positively reacting patients revealed that for oakmoss absolute specifically, the decline during the period was from 1.9% to 0.8%. The corresponding figures for HICC were a decline from 1.8% to 0.9%.

The authors concluded that, despite the various limitations of the study, including a possible underestimate of the overall level of sensitisation to fragrance haptens, it is clear that the EU regulations had a very significant benefit of reducing the incidence of sensitisation to these fragrance haptens.

Analysis of Preservatives and Fragrances in topical Medical Devices: The need for more stringent regulation

by Ania Stras, et al.
CONTACT DERMATITIS, Volume 90, Issue 6, June 2024, pp 594-606.
https://doi.org/10.1111/cod.14533

Medical devices comprise a broad range of primarily hardware. Classic examples are insulin sensors and pumps and their associated accessories and ancillaries. These have been the subject of several reviews by The Patch Tester in previous issues, for example the causation of contact dermatitis by isobornyl acetate in insulin pump adhesives in the very first issue of the Patch Tester e-magazine over 4 years ago.

Gels and creams used in cosmetics and skin-care are more-or-less effectively regulated by the EU concerning their ingredients, to minimise and ideally prevent sensitisation to potential haptens. However, the gels and creams that are utilised together with medical devices such as insulin sensors and pumps and other hardware, are not regulated, yet are often used on damaged skin whereas the regulated cosmetics are used on intact health skin, possessing an effective barrier to hapten penetration.

This study by Stras et al is intended to identify the presence of preservatives and fragrances in topical medical devices.

Sixty nine such medical devices available within EU countries were subjected to previously validated chromatographic analysis methods (Tandem mass spectrometry LC-MS/MS and gas chromatography (GC-MS).

The results were frankly shockingly poor, in several respects:

1. 32% of the 69 MDs did not provide comprehensive lists of ingredients including chemical compounds (such as preservatives, fragrances, etc). Users of these inadequately-labelled MDs would therefore be unaware of the presence of potentially sensitising haptens in and on those MDs. This is particularly important for those individuals who are already aware of their sensitisation (perhaps due to previous contact dermatitis symptoms with such MDs, or to positive patch test reactions).

2. 30% of the 69 MDs would not meet safety standards for cosmetic products; which are more carefully regulated as to their content of preservatives, fragrances and other potential haptens.

3. 13% of the 69 MDs contained substances that are actually prohibited as ingredients in leave-on cosmetics; thereby implying that these substances should also be prohibited for use in MDs, especially those that remain in contact with the skin.

The authors of the study concluded that there is obviously a pressing need for more stringent regulation of the labelling of medical devices to include a comprehensive list of ingredients. Also, known haptens that have been prohibited in cosmetics should have at least the same standards applied to medical devices. Thereby, improved transparency and increased regulation can mitigate at least some of the potential risks associated with the use of medical devices.

Results of Patch Testing with five Fragrance materials hitherto not tested: A dose-finding study in the clinical population

by Thanisorn Sukakul, et al.
in CONTACT DERMATITIS, Volume 90, Issue 6, June 2024, pp 566-573.
https://doi.org/10.1111/cod.14525

And now for something rather different....

Instead of clinical studies on prevalence and symptoms, this original article delves into the world of the behind-the-scenes research into potential new haptens, and the optimal concentration of those haptens to be incorporated into standardised patch test materials to be used in future studies to assess the clinical significance. Amongst the 12 investigators from the 7 different European countries was Bo Niklasson, of Chemotechnique.

The purpose of the study was to determine the optimal concentration of five fragrance materials that have hitherto not been included in any screening panels on a regular basis. These five fragrances, at these optimal concentrations in patch test materials will then be used in a surveillance study with consecutive patch tested patients over an extended period.

These five fragrance chemicals have been selected by the group “International Dialogue for the Evaluation of Allergens” (IDEA, https://ideaproject.info).

1.	Furaneol	CAS.3658-77-3
2.	Trans-2-hexenal	CAS 6728-26-3
3.	4,8-dimethyl-4,9-decadienal	CAS 71077-31-1
4.	Longifolene	CAS 475-20-7
5.	Benzaldehyde	CAS 10052-7

All five chemicals are synthetic fragrances but can be present in natural extracts and have been widely used in consumer products for almost 40 years. Four of them, with the exception of 4,8-dimethyl-4,9-decadienal, are also used as flavours in the food industry.

There is extensive background information in the article, in order to provide context on the regulatory environment around the potentially highly sensitising substances that have been and perhaps still are used in some sectors of the fragrance industry.

Fragrances are one of the most commonly encountered groups of contact allergens. Allergenic fragrance substances are usually low molecular weight chemicals, which act as ‘haptens’, which

upon binding with dermal proteins become active allergens that are recognised by the host immune system, eventually possibly leading to the signs and symptoms of allergic contact dermatitis.
Patch testing is the standard in vivo procedure to identify individual sensitising fragrance chemicals and so to diagnose fragrance contact allergy.

Fragrance mix I (FM I), II (FM II), and Myroxylon pereirae resin (balsam of Peru, BOP) are common patch test screening preparations that are found in most national and international screening series as well as various types of series.

A research project conducted in five European countries from 2008 to 2010 in a general population sample reported that the prevalence of contact allergy to FM I, FM II and BOP was 2.6%, 1.9%, and 0.7%, respectively, though the prevalence is higher in dermatitis patients reported from different continents owing to obvious patient selection due to clinical symptoms.

The EU-based Scientific Committee on Consumer and Non-Food Products (SCCNFP), states that only 24 potential allergenic fragrances need be listed on a cosmetic label, and only when the concentrations exceed the arbitrary cut-off limits of 0.001% for leave-on products and 0.01% for rinse-off products. However, it has recently been recommended to expand this list. A regulatory proposal to add additional 62 materials has been finalised, and the regulation (EC) 2023/1545 was published in the EU Official Journal on 27 July 2023, listing these additional materials.

In total, approximately 60 different fragrance ingredients with standardised or previously studied concentrations and vehicles are commercially available for patch testing. Patch testing for fragrances is most usually initiated with testing using Fragrance mix I and perhaps also Fragrance mix II. Additional fragrance ingredient preparations, such as the individual constituents of the Fragrance mixes I and II, plus the more recently revealed hydroperoxides of linalool and limonene, is useful and assumed to increase the sensitivity of diagnosing fragrance contact allergy and identifying the individual culprit chemical substances. Outside this list of approximately 60 commercially readily available fragrance allergens/haptens, when contact allergy to any other fragrance constituent is suspected, additional test preparations may be prepared on special request by specific laboratories based on knowledge from previous studies and personal experience. However, patch test concentrations and vehicles for these substances are not usually standardised, and outside advanced professional research studies, such preparation of new chemicals and their subsequent use in patch testing is indeed rare.

In this initial pilot study to the Extended Fragrance Ingredients Surveillance Study (EFISS), these five ingredients were tested in patients with suspected allergic contact dermatitis to determine a suitable patch test concentration for each, so that this optimal concentration could be used in standardised preparations and concentrations on consecutive dermatitis patients for an extended monitoring period in the main EFISS study.

Patch testing was conducted in three rounds, starting with the lowest concentrations of the five ingredients. If no late-appearing positive reactions and virtually no irritant reactions were reported in each round, then the doses were increased 50% in the subsequent round.

In this study, any positive reactions to other tested fragrance haptens in a very large panel comprising:

- Fragrance mix I plus its 8 individual constituents,
- Fragrance mix II plus its 6 individual constituents,
- BoP
- Sorbitan sesquioleate
- 12 other non-mix fragrances
- *Evernia prunastri* (oakmoss) and *Evernia furfuracea* (tree moss) were tested, both at traditional levels and at trace levels.

This is an exceptionally complex multicentre study so if greater depth of information is required then please read the original publication in CONTACT DERMATITIS.

Standardisation of several critical factors was achieved, in order to reduce the number of potential variables throughout the multi-centre study.

• An interesting anecdote is the use of a calibrated syringe, developed by one of the authors, Bo Niklasson of Chemotechnique, to extrude exactly 22 um of petrolatum per dose.

• Only one type of chamber was used throughout the multi-centre study; the Chemotechnique IQ Ultra chambers, with 64 square mm of each camber, therefore providing a standardised dose of 0.34 mg/mm2.

• All hapten preparations other than 7 made up specially were also standardised as commercially available Chemotechnique haptens.

• The raw materials of the 5 study haptens were provided by the fragrance industry and were exhaustively checked by both their manufacturers and by the study authors.

The results of the study gave the following useful points:

• A total of 373 patients were enrolled in the pilot study; 120 tested with the lowest concentrations, 104 with the medium concentrations, and 149 with the highest concentrations, in each of the four centres.

• Of all 288 patients (Zagreb patients excluded), 47 (16.3%) had a positive reaction to at least one of the test preparations. Of these patients, 36 (76.6%) were positive to the baseline fragrance allergen screens of FM I, FM II, and BOP), whereas 11 (23.4%) patients reacted positively to other fragrance haptens.

• Of the six treemoss-positive patients, two reacted positively only to the standard material, two to the material at trace levels, and the other two to both standard and trace levels of the atranol and chloroatranol (components of oak moss and tree moss). Four out of 11 patients with a positive reaction to oakmoss reacted positively only to the preparation with trace levels of atranol and chloroatranol, whereas five patients reacted positively only to the standard test preparations.

• Doubtful and Irritant reactions were exceedingly rare. Irritant reactions and one doubtful reaction were reported to two study allergens in the first round only on D3/4. However, the reactions were negative on the subsequent reading at D7.

When the concentrations of these allergens were increased in the latter two rounds, no irritant or doubtful (or positive) reactions were found in subsequent patients. This phenomenon suggests that the highest test concentrations should be safe to test in consecutive patients without causing an irritant reaction.

In addition, there was no report of any late-appearing reaction subsequent to the reading on D7, which suggests that there is only a very minor risk of the patch test preparations inducing sensitisation, even at the higher concentrations.

• There were no (zero) unequivocal allergic reactions to any of the 5 new haptens even at the highest concentrations. However, this does not indicate that these substances are safe for the general population as the number of patients in this pilot study who did not react (149) is inadequate to draw such a conclusion. Only the results of the full long-term EFISS study can confirm or refute any claims to safety.

• There were positive reactions to other common screening fragrances, with comparable prevalences to previous studies. Nevertheless, approximately one quarter of positive results would have been missed if testing only with the screening mixes. Additional patch testing with fragrance allergens other than FM I, FM II, and BOP was useful, since about one-fourth of the fragrance contact allergy patients would have been undiagnosed if the additional testing, with both the FM I/II constituents and non-mix fragrances, had not been performed. The most likely reason could be that most of the individual fragrance substances present in a fragrance mix are tested at higher concentrations individually than when part of a mix. The results of this study supported the contention that patients with a stronger reaction and/or who had more than one contact allergy to individual fragrances would react positively to the mixes, in contrast to patients with a weak positive reaction to just one ingredient. This finding suggests that further research should be done on the concentration of different constituents of fragrance mixes.

• Sorbitan sesquioleate sensitivity is a clinical problem and a complicating factor in such studies. The prevalence of sensitisation to SSO in this study was 0.8%, which could affect the interpretation of patch test readings when some test preparations such as FM I and BOP contain it as an emulsifier.

In conclusion, the results of this pilot study indicate that the five new patch test haptens are considered to be safe at the highest patch test concentrations, and therefore suitable for patch testing in consecutive dermatitis patients as part of the long-term EFISS study.

For further details on the design and results of this complex study, the reader is recommended to access the original article in CONTACT DERMATITIS.

Association between Atopic Disease and Vaccination Granulomas: A nested case-control study

by Stine Skovbo Hoffmann, et al.
in CONTACT DERMATITIS, Volume 90, Issue 4, April 2024, pp 411-419.
https://doi.org/10.1111/cod.14472

Granulomas resulting from vaccination with aluminium-adsorbed vaccines are known to occur in approximately 1% of cases. These aluminium-adsorbed vaccines can be classical Pneumococcal virus vaccines, HPV vaccines, Hep B vaccines and more.

For more information on aluminium in vaccines see the notes at the end of this review article.

Most children with such vaccine-derived aluminium granulomas also present with contact allergy to aluminium. As both contact allergy and atopic diseases are highly prevalent in children, then there may be a link between them with aluminium as a culprit or causative factor.

This study was designed to investigate the association in children between vaccination granulomas derived from aluminium-adjuvant vaccines and atopic dermatitis, asthma and rhinitis.

The study was based on 2,171 cases of Danish children born from 2009 to 2017 with vaccination granulomas, and compared with 21,710 controls regarding the factors of sex, gestational age, season of birth, and socioeconomic class. A strong 10:1 ratio to ensure validity of the result and conclusions.

All cases and the controls were vaccinated with aluminium adsorbed vaccines and then followed until their second birthday.

The study authors found a statistically significant association between the presence of vaccination granulomas and atopic dermatitis, at 2 years of age and an even stronger association at 4 years of age. There was however no statistically significant association between vaccination granulomas and asthma or rhinitis.

Additional editorial notes on aluminium as an adjuvant in vaccines.

Vaccination is one of the major contributors to the global control of infectious diseases in the human population. It has been estimated that vaccination has prevented more than 100 million cases of infectious diseases in people since the 1920s in the United States alone.

Aluminium is one of several different types of adjuvants that may be used in different vaccines. An adjuvant is an ingredient used in some but by no means all vaccines that helps create a stronger immune response in the recipient of the vaccine. Some vaccines that are made from weakened or killed bacteria or viruses contain naturally occurring adjuvants which create a stronger protective immune response. However, most vaccines developed nowadays include just small components such as the proteins of the bacterium or virus, rather than the entire bacterium or virus. Compared to non-adjuvanted vaccines, adjuvanted vaccines can however cause more local reactions such as erythema, oedema, and pain at the injection site, as well as more systemic reactions such as fever, chills, and body aches.

Aluminium is one of the most common metals found in nature and is present in air, food, and water. Previous scientific research has shown the amount of aluminium exposure in people who follow the recommended vaccine schedule is low and it is not readily absorbed by the body.

Aluminium is a ubiquitous element that is released naturally into the environment via volcanic activity and the breakdown of rocks on the earth's surface. Exposure of the general population to aluminium occurs primarily through the consumption of food, antacids, and buffered analgesics. Exposure to aluminium in the general population can also occur through vaccination, since vaccines often contain aluminium salts (frequently aluminium hydroxide or aluminium phosphate) as adjuvants.

Even though aluminium is regularly ingested in food and drinks containing aluminium throughout a lifetime, only a small amount of aluminium enters into the blood stream from digestion, the rest is remaining unabsorbed and comes out in faeces. Most of the aluminium that does enter the blood circulation is quickly processed and removed by the kidneys, in urine. The small amount that remains absorbed into the tissues is mainly stored in skeletal bones, with some stored in the lungs and brain.

Approximately 95% of an aluminium load becomes bound to transferrin and albumin intravascularly and is then eliminated renally. In healthy subjects, only 0.3% of orally administered aluminium is absorbed via the gastrointestinal tract, and the kidneys effectively eliminate aluminium from the human body. Only when the GI barrier is bypassed, such as by intravenous infusion or in the presence of advanced renal dysfunction, does aluminium have the potential to accumulate. As an example, with intravenously infused aluminium, 40% is retained in adults and up to 75% is retained in neonates.

The signs and symptoms of aluminium toxicity are usually nonspecific. Typical presentations in chronic toxicity may include proximal muscle weakness, bone pain, multiple nonhealing fractures, acute or subacute alteration in mental status, and premature osteoporosis.

Aluminium salts, such as aluminium hydroxide, aluminium phosphate, and aluminium potassium sulphate have been used safely in vaccines for more than 70 years. Aluminium salts were initially used in the 1930s, 1940s, and 1950s with diphtheria and tetanus vaccines after it was found they strengthened the body's immune response to these vaccines.

The widespread use of aluminium adjuvants is due to their excellent safety profile, which has been established through the use of hundreds of millions of doses in humans over many years and many countries. In addition, they are inexpensive, readily available, and are well known and generally ac-

cepted by regulatory agencies. Moreover, they offer a very flexible platform, to which many vaccine components can be adsorbed, enabling the preparation of liquid formulations, which typically have a long shelf life under refrigerated conditions. Nevertheless, despite their extensive use, they are perceived as relatively 'weak' vaccine adjuvants, as well as the not so rare research publications highlighting the adverse effects of using aluminium adjuvants, including the formation of granulomas at the injection site, and the possible association with atopic dermatitis or asthma in such recipients of aluminium-conjugated vaccines. Hence, there have been many attempts to improve their performance, which typically involves co-delivery of immune potentiators, including Toll-like receptor (TLR) agonists. This approach has allowed for the development of improved aluminium-based adjuvants for inclusion in licensed vaccines against HPV, HBV, and COVID-19, with others likely to follow.

These newer adjuvants have been developed to target specific components of the body's immune response, so that protection against disease is not only stronger but also persists for longer.

To give an idea of the scale of the administration of aluminium to infants through aluminium-adjuvant-based vaccines, the aluminium contained in vaccines is similar to that found in a litre of infant formula. While infants receive about 4.4 milligrams of aluminium in the first six months of life from vaccines, they receive more than that in their diet. Breast-fed infants ingest about 7 milligrams, formula-fed infants ingest about 38 milligrams, and infants who are fed soy formula ingest almost 117 milligrams of aluminium during the first six months of life. Of course, injection is not the same as ingestion, but this comparison gives an idea of the scale of the matter.

An observational study published in September 2022 on "Association Between Aluminium Exposure From Vaccines Before Age 24 Months and Persistent Asthma at Age 24 to 59 Months" identified a possible association between exposure to aluminium from vaccines and later development of persistent asthma in a cohort of children who received care at healthcare organisations participating in the Vaccine Safety Datalink. So both this USA-based study and this newer Denmark-based study warrant further investigation into this potential safety issue.

For more information on aluminium exposure due to aluminium-adjuvant vaccines, see the research on aluminum exposure and vaccines. (https://pubmed.ncbi.nlm.nih.gov/22001122/)

Also, see the USA FDA's web page on common ingredients in U.S. licensed vaccines, and the following articles on the topic of aluminium vaccine adjuvants:

1. ncbi.nlm.nih.gov/pmc/articles/PMC10383759/
2. chop.edu/centers-programs/vaccine-education-center/vaccine-ingredients/aluminum
3. nature.com/articles/s41541-018-0089-x
4. immune.org.nz/factsheets/aluminium-in-vaccines
5. emedicine.medscape.com/article/165315-overview?form=fpf

Vaccines that are known to include aluminium as an adjuvant include the following;
Note this list is not complete or exhaustive.
Anthrax, DT, DTaP (Daptacel), DTaP (Infanrix), DTaP-HepB-IPV (Pediarix), DTaP-IPV (Kinrix), DTaP-IPV (Quadracel), DTaP –IPV/Hib (Pentacel), DTaP-IPV-Hib-HepB (VAXELIS), HepA (Havrix), HepA (Vaqta), HepB (Engerix-B), HepB (PREHEVBRIO), HepB (Recombivax), HepA/HepB (Twinrix), HIB (PedvaxHIB), HPV (Gardasil 9), Japanese encephalitis (Ixiaro), MenB (Bexsero, Trumen-

ba), Pneumococcal (Prevnar 13, Prevnar 20, VAXNEUVANCE), Td (Tenivac), Td (Mass Biologics), Td (no trade name), Tdap (Adacel), Tdap (Boostrix), Tick-Borne Encephalitis (TICOVAC)

Other adjuvants are as follows:

AS01B
AS01B is an adjuvant suspension used with the antigen component of Shingrix vaccine. Shingrix is the recombinant zoster vaccine recommended for persons aged 50 years or older. AS01B is made up of monophosphoryl lipid A (MPL), an immune-boosting substance isolated from the surface of bacteria, and QS-21, a natural compound extracted from the Chilean soapbark tree (*Quillaja saponaria molina*). In pre-licensure clinical trials in USA, AS01B was associated with local and systemic reactions, but the overall safety profile was reassuring.
AS01B is also a component of vaccines currently being tested in clinical trials, including malaria and HIV vaccines. To date, these trials have included over 15,000 people.

AS04
Beginning in 2009, monophosphoryl lipid A (MPL) was used in one U.S. vaccine (Cervarix®) for HPV infections; however, the vaccine is no longer available in the United States due to low market demand. This immune-boosting substance was isolated from the surface of bacteria.

CpG 1018
CpG 1018 is a recently developed adjuvant used in Heplisav-B vaccine. It is made up of cytosine phosphoguanine (CpG) motifs, which is a synthetic form of DNA that mimics bacterial and viral genetic material. When CpG 1018is included in a vaccine, it increases the body's immune response.
In USA pre-licensure clinical trials, adverse events after Heplisav-B were comparable to those observed after another U.S.-licensed, non-adjuvanted hepatitis B vaccine.

MatrixMTM
MatrixM adjuvant is made from saponins derived from the soapbark tree (*Quillaja saponaria*), along with cholesterol and phospholipids. It is currently used in the Novavax COVID-19 vaccine.

MF59
MF59 is the adjuvant contained in Fluad quadrivalent (an influenza vaccine licensed and recommended for adults aged 65 or older). MF59 is an oil-in-water emulsion composed of squalene, which is a naturally occurring oil found in many plant and animal cells, including humans. MF59, used in flu vaccines in Europe since 1997 and in the United States since 2016, has been given to millions of people and has an excellent safety record.

No Adjuvant
Chickenpox, cholera, COVID-19 (includes mRNA Pfizer-BioNTech, mRNA Moderna and adenoviral Johnson & Johnson/Janssen), dengue, Ebola, Hib (ActHIB, HIBERIX), measles, mumps & rubella (MMR), meningococcal (Menactra, Menveo, MenQuadfi), polio (IPOL), rabies, rotavirus, seasonal influenza (except Fluad and Fluad quadrivalent), smallpox and monkeypox (ACAM2000, JYNNEOS), Typhoid, yellow fever, zoster live (Zostavax).

Patch Testing with Nickel, Cobalt, and Chromium in Patients with Suspected Allergic Contact Dermatitis

by Jonathan Silverberg, et al.
in DERMATITIS, Vol 35, No. 2, March-April 2024, pp 152-159.
https://doi.org/10.1089/derm.2023.0139

This study based on 43,522 patients presenting with allergic contact dermatitis at a single major hospital in USA tested with the NACDG Series, over 17 years to 2018. The patients were tested for the incidence of sensitisation, as indicated by positive patch test results, to nickel, cobalt and chromium. Although the results are unsurprising and largely in line with previous studies, there is also the addition of new information and data on simultaneous co-sensitisation to these three metals.

The major points of interest from the study are as follows:

- 18.0% were sensitised to nickel sulphate hexahydrate, 7.3% to cobalt chloride hexahydrate, and 3.0% to potassium dichromate.
- In comparison, a recent study from 13 European countries reported: 24.0% were sensitised to nickel sulphate hexahydrate, 4.9% to cobalt chloride hexahydrate, and 3.2% to potassium dichromate.
- A Polish study of 1,200 subjects reported:
  17.3% were sensitised to nickel sulphate hexahydrate, 9.8% to cobalt chloride hexahydrate, 7.7% to potassium dichromate.
- An Iranian study of 313 subjects reported:
  20% were sensitised to nickel sulphate hexahydrate, 8% to cobalt chloride hexahydrate, and 6.2% to potassium dichromate.
- A systematic review of European and USA-based studies reported:
  11.4% were sensitised to nickel sulphate hexahydrate, 2.7% to cobalt chloride hexahydrate, and 1.8% to potassium dichromate.
- 13.0% reacted only to nickel, 2.2% reacted only to cobalt,1.5% reacted only to chromium, 4.1% reacted to both nickel and cobalt, 0.51% reacted to chromium and cobalt, 0.50% reacted to chromium and nickel, 0.42% reacted to nickel and chromium and cobalt.
- 77.7% tested negative to all three metals.
- 87.9% had no currently relevant reaction to any of the three metals.

- Regarding clinical relevance of positive reactions;

  7.5% had currently relevant reactions only to nickel (3.1% definite relevance, 33.0% probable relevance and 63.9% possible relevance).

  1.0% had currently relevant reactions only to chromium:
  (5.6% definite relevance, 31.9% probable relevance and 62.5% possible relevance,

  0.9% had currently relevant reactions only to cobalt (2.3% definite relevance, 15.9% probable relevance and 81.8% possible relevance).

In total, clinical relevance was found in approximately half of patients with PT reactions to one or more of these three metals, so it must be concluded that PT reactions to metals are not always relevant to the patient's suspected contact dermatitis.

- The prevalence of PT positivity and currently relevant reactions against nickel remained stable throughout the 17-year period to 2018. However, the prevalence decreased significantly throughout the period for chromium and cobalt. Currently relevant reactions to chromium but not cobalt also significantly decreased. However, a systematic review of European and USA-based studies reported a similar stability with nickel and decrease with cobalt and chromium, though a Sweden-based study reported an increase in nickel and cobalt allergy whilst a Japan-based study reported a decrease.

- Regarding the sources of the sensitisations, among the patients with a known source of their metal sensitisation, the source varied with the metal sensitivity in those patients who were sensitised to more than one of the three metals. The most commonly identified source of nickel in patients with 1 or 2 metal sensitivities were the classical jewellery, belts and food products. Though in those patients who were sensitised to all three metals then tools became an additional source of sensitisation. Cobalt sensitisation was also most commonly associated with jewellery, but also cement and watches. Sources of chromium in those patients with 1 to 3 sensitisations were most usually footwear and cement.

- Previous studies have shown that subjects with allergy to nickel are often co-sensitised to cobalt, and also to chromium but less frequently. This study reported 4.1% of patients co-sensitised with nickel and cobalt and solitary cobalt at just 2.2%. This may suggest that there is concurrent presence of both these metals in many products, which may lead to co-sensitisation. Conversely, it has been suggested that nickel potentiates sensitisation to cobalt, which may explain the concurrent sensitivities, but the immunopathogenesis of such concurrent sensitisation remains elusive.

- Concurrent respiratory allergies: in summary there is a significant association between sensitisation to more than one of these three metals and asthma, which is say the authors a new phenomenon. Anther study reported elevated s-IgE levels in multiple-metal sensitisation, and of course such elevated s-IgE is indicative of type I allergy, which may include asthma. Previous studies have shown an association between nickel allergy and asthma, though not for cobalt or chromium, which suggests that subjects with a history of asthma may have an increased susceptibility to sensitisation in general rather than to individual metal allergens (or

rather haptens). This study reported no significant association between metal allergy and hay fever / rhinitis. Nor did this study find any association between multiple-metal sensitisation and atopic dermatitis, which is in contrast to a previous Germany-based study which did report such an association.

- The source of cobalt sensitisation has hitherto been rather vaguely defined. In this study, the reports were of jewellery, belts, and cement, though the source did vary according to co-reacting metal haptens in subjects who were multiple sensitised. Multiple sensitisations to cobalt plus chromium was most frequently as a result of exposure to cement, footwear and watches. Cement is a major culprit of both cobalt and chromium sensitisation, being the second most significant sensitiser for construction workers.

- The source of chromium sensitisation varied with the co-reacting metal. Those subjects with solitary chromium sensitisation and chromium-cobalt sensitisation had cement, concrete, mortar, gloves and footwear as a source, rather than jewellery. Chromium plus nickel-sensitised subjects encountered chromium primarily in footwear and jewellery, suggesting that jewellery may contain both metals. Those subjects with triple sensitisation to all three metals encountered chromium in cement, gloves, jewellery, footwear, leather jackets and coats..

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

2024 EAACI

In this nineteenth issue of “The Patch Tester” we are taking a look at the recently finished congress of the European Academy of Allergy and Clinical Immunology, that was held in Valencia Spain on May 31st to June 3rd 2024.

Chemotechnique was present as an exhibitor in the trade exhibition.

In this picture at the Chemotechnique exhibition booth at EAACI were Helena Friman, Vanja Skrkar, (Jessica Mückenheim), and Steve Lee. Also present in the most intensive first day were Bo Niklasson and David Alsheimer-Niklasson.

At times the exhibition stand was so busy that we were all simultaneously engaged in discussions and presentations with visiting clinicians.

EAACI is nominally for allergy specialists from European countries; however, over the many years it has been running an annual congress somewhere in Europe, it has become the *de facto* major

allergy congress for much of the world, including Australia/New Zealand, and South Africa, as well as some clinician visitors from USA. Just because this particular meeting was held in Valencia, there were many delegates also from Latin America. There were also many delegates from emerging nations in the Near East and Far East.

It is truly a global event.

In our own exhibition stand we encountered a lot of interest not just from Allergy Specialists but also some ENT specialists and researchers.

The EAACI congress exhibition hall is also perhaps the world's most intensive trade exhibition, possibly exceeding the major USA-based allergy congress AAAAI (https://annualmeeting.aaaai.org/), as well as even the World Allergy Congress (https://www.worldallergy.org/wao-meetings/wac-2024).

If your company is a global player in the allergy world, then you just have to be at EAACI and be seen.

We were certainly well satisfied with the exposure and the interest that we received from visiting delegates; it was so much more than we expected.

Although we had brought with us from Sweden a large consignment of materials such as syringes, patches, brochures, booklets, prints of The Patch Tester e-mag #18, and business cards.... we had to start rationing them already the second day, and by the end of the third day and the closure of the exhibition, we were totally empty.

There was simply no time available to enjoy the sights and sounds of Valencia, a beautiful city bathed in warm sunshine in early June.

Next year the EAACI congress and trade exhibition is being held in Glasgow, Scotland, on June 14th to 16th 2025. A greater contrast to Valencia is hard to imagine, but we are not there for the Spanish cerveza, or the Scottish whisky, we are there to meet with our established clients and new clients from around the world.

Contact Dermatitis / Patch Testing

4th – 7th September 2024
ESCD 2024
Dresden, Germany
https://escd.org/meetings-courses/

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/

National

2nd – 4th July 2024
British Association of Dermatologists 2024
Manchester, UK
https://badannualmeeting.co.uk/

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