the Patch Tester

Contact Dermatitis | Haptens | Patch Testing

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THE 2022 ESCD EDITION

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

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CHEMOTECHNIQUE DIAGNOSTICS

Chemotechnique cosmeceuticals

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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 twelfth issue comprises forty-six 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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CONTACT

If you would like to contact Chemotechnique about any aspect of The Patch Tester, or any other topic of mutual interest, then please write to us by clicking the “Contact” box on the front cover, or here.

ACKNOWLEDGEMENTS

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David Alsheimer-Niklasson & Steve Lee

What’s New in Patch Testing?

Chemotechnique representatives David Alsheimer-Niklasson, Helena Friman, Fredrik Irwe and Bo Niklasson

ESCD Congress Reportage

On June 8th to 10th 2022, the ESCD held its annual congress in Amsterdam Netherlands. This is the first live event for ESCD since the COVID pandemic and in fact is one of the first live events amongst many medical specialities.

One major concession to COVID, or a development (depending on how you look at it), has been the availability online of videos of most of the congress presentations. Therefore, Dermatologists who could not participate personally for whatever reason (including a persistent caution due to the still-remaining COVID infections) could still benefit from the presentations at the congress.

Just as COVID has accelerated several other trends and changes in society, so medical education has now also irrevocably changed due to the accelerated adoption of online consultations and online professional learning/education.

It is interesting to note that some national and regional medical societies are now starting to offer online e-meetings and training workshops and sessions and consultations amongst colleagues. An example is the Update meeting of the Caribbean Dermatology Association, a first for them.
See https://mailchi.mp/caribderm/cda-2020-updates-in-dermatology-pre-registration-now-open-14185871?e=0a4fa1e0d1

What's New in Patch Testing?

ESCD seems to have taken the online proceedings a step further by substituting the traditional publication in print of the congress proceedings. However, that could perhaps be construed as a step too far as there is still much to be gained from a printed proceedings where it is easy and so much faster to eye-scan printed texts or to computer-scan pdf documents than it is to ear-scan audio-visual presentations!!

For this 12th edition of The Patch Tester, we have chosen three major themes for presentation, and have then supplemented those theme presentations with a relevant paper from the last 3 months (July + August + September) of the printed journals DERMATITIS and CONTACT DERMATITIS.

The three themes are:

- Medical Devices
- Metals
- Fragrances

For further information on these three topics please see the relevant sections of the ESCD On Demand webpages, at, respectively:

Medical Devices: https://escd2022.com/wednesday-ondemand/#fs1a
Metals: https://escd2022.com/wednesday-ondemand/#fs2a
Fragrance: https://escd2022.com/thursday-ondemand/#edu3a

Of course, you'll need the login password, but as an ESCD member that is readily available to you.

The ESCD 2022 Congress Posters, all 52 of them, are also available for viewing, at https://escd2022.com/posters/, (accessible without any password) including several Posters on the three topics above.

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.

6 What's New at Chemotechnique

Chemotechnique Post-COVID

The COVID pandemic really kicked off its great restrictions on personal freedoms and travel restrictions and workplace restrictions in Europe in approximately February 2020. The healthcare services were not only also suffering enormously from the same restrictions as the rest of the population but were also overwhelmed with the management and care of the numerous COVID cases. Dermatology was suddenly forgotten, or thrust so far back down the list of medical priorities that it reached vanishing point, both in state hospital care and even in private practice. Part of the problem was that dermatological examinations essentially require face-to-face consultations to enable visual and perhaps also palpable examination of the dermatological problem. Patch testing is simply impossible to do remotely, though PT results can if necessary be photographed and emailed through to the Dermatologist for evaluation.

Dermatology clinics closed.
Patch Test clinics closed.
Routine Patch Testing largely ceased.
Consumption of patch test haptens and chambers dwindled to a fraction of normal usage.

We at Chemotechnique were fortunate that in Sweden where we are based, there was a much lighter touch from government on restrictions to travel and in the workplace, compared to the rest of Europe and indeed the world. Nevertheless, because consumption of patch test products worldwide was greatly reduced then our business operations were correspondingly suddenly and drastically reduced. We continued to service incoming orders and we continued to manufacture according to the reduced level of consumption. Despite this scaling-back of some activities, we continued with many of our marketing activities, including the compilation and publication of The Patch Tester e-magazine, which has continued unabated throughout the past 3 years. Of course, our distributors throughout the world were almost all also adversely affected by the COVID restrictions in their own countries, which would have restricted them, including their own marketing and sales promotion activities.

The global situation was all looking rather grim, on a grand scale.

As a consequence of the pandemic, Chemotechnique's business declined approx. 15% from full-year 2019 to full-year 2020. Whilst a year-on-year reduction is a first such event for Chemotechnique, a 15% reduction is indeed not as much as would have been expected due to the enormous practical restrictions and difficulties for Patients, Dermatologists, international Distributors, and the Manufacturer.

However, the corner has been well and truly turned and the trend is again strongly upwards.
We are very happy to report that in full-year 2021 the patch test business returned with a vengeance, so that the pre-COVID levels of 2019 were exceeded in 2021, and have continued to develop and expand ever since throughout 2022.

So "What's New at Chemotechnique" is that we are back at full throttle!!
And we trust that you are too!!

Hydroperoxides of Limonene and Linalool

Allergic contact dermatitis (ACD) to fragrances is common, affecting 1.1%–2.6% of the general adult population in Europe. Moreover, some studies report a prevalence that can reach up to 15% in patients with a history of dermatitis.

Many fragrance materials used today belong to the chemical group of terpenes and of these, limonene (citrus scent) and linalool (lavender scent) are among the most common fragrance terpenes used in everyday products. They are frequently found in multiple household items (personal hygiene and cosmetic products) as well as products that come into contact with the skin daily such as essential oils, natural products, and aromatherapy products.

Limonene and linalool are pre-haptens, forming hydroperoxides (Lim-OOHs, Lin-OOHs) upon oxidation, and then inducing frequent positive patch test reactions in patients with dermatitis. However, If the compounds limonene and linalool are patch tested with not-deliberately-oxidised ("pure") form, positive patch test reactions are rarely found. Conversely, the hydroperoxides are frequent causes of positive patch test reactions in patients in multiple studies when using standardised patch test materials for oxidised limonene and oxidised linalool that have been recently developed and made available commercially.

Limonene hydroperoxide

Synonyms: Carvene, (+)-4-Isopropenyl-1-Methylcyclohexene, Optical Isomer of Dipentene, (+)-R-Limonene, (R)-1-Methyl-4-(1-Methylethyenyl) Cyclohexene, D-(+)-Limonene.

Uses: Limonene is found in cosmetics, fine fragrances and hygiene products as well as in household and industrial products. Limonene is one of the most commonly found fragrance ingredients in consumer products presently available. Limonene is a naturally occurring terpene, present in large amounts in various citrus fruits. Limonene auto-oxidises on air exposure at room temperature, forming hydroperoxides. Compared to pure unoxidised limonene, the hydroperoxides of oxidized limonene have shown to be far more allergenic. The hapten preparation contains 0.2% or 0.3% oxidised limonene. The concentration of the active haptens in the preparation is measured from the added amount of the hydroperoxides of d-limonene.

Lim-OOH is manufactured by Chemotechnique in 2 different concentrations:

Lim-OOH >> H-032A as 0.3% in petrolatum, with a Safety Data Sheet
Lim-OOH >> H-032B as 0.2% in petrolatum, with a Safety Data Sheet

Lim-OOH as H-032B (0.2% concentration in petrolatum) is found in the following screening series:

1. ECB European Comprehensive Baseline Series
2. F Fragrance Series
3. PST Polish Baseline Series
4. GB British Baseline Series
5. AC American Core Series

Lim-OOH as H-032A (0.3% concentration in petrolatum) is found in the following screening series:

1. B Bakery
2. O Oil & Cooling Fluid
3. ECB European Comprehensive Baseline Series
4. NA North American
5. ICB International Comprehensive Baseline Series
6. ABS Australian Baseline Series
7. BS Belgian Baseline Series
8. F Fragrance Series
9. NAE North American Series
10. NAC North American Comprehensive Series
11. CB Chinese Baseline Series
12. GB British Baseline Series
13. NZBS New Zealand Baseline Series
14. NZBSE New Zealand Baseline Series Extended

So both concentrations (0.2% and 0.3%) of Limonene hydroperoxide hapten preparations are found in the following screening series:

1. ECB European Comprehensive Baseline Series
2. F Fragrance Series
3. GB British Baseline Series

D-Limonene

Synonyms: (+)-4-Isopropenyl-1-Methylcyclohexene; (+)-R-Limonene; Citrene; D-(+)-Limonene (+)-p-menth-1,8-diene; Carvene; Optical Isomer of Dipentene; Dipentene; (R)-1-Methyl-4-(1-Methylethyenyl); Cyclohexene.

Uses: Limonene is a hydrocarbon, classified as a cyclic terpene. It is a colourless liquid at room temperatures with an extremely strong smell of oranges. It takes its name from the lemon, as the rind of the lemon, like other citrus fruits, contains considerable amounts of this chemical compound, which is responsible for much of their smell. Limonene is a chiral molecule, and as is common with such forms, biological sources produce one enantiomer: the principal industrial source, citrus fruit, contains D-limonene ((+)-limonene), which is the (R)-enantiomer (CAS number 5989-27-5, EINECS number 227-813-5). Racemic limonene is known as dipentene.

D-Limonene is manufactured by Chemotechnique as L-006C, as 10.0% in petrolatum.
The only screening series in which D-Limonene is to be found is the Fragrance Series.
There is a Safety Data Sheet for D-Limonene.

Note that none of the Limonene-based haptens are included in the TRUE Test® product.

Linalool hydroperoxide

Synonyms: Linalool

Uses: Linalool is found in fine fragrances, cosmetics, and hygiene products as well as in household and industrial products. Linalool is among the most commonly found fragrance ingredients in consumer products presently available. Linalool is a naturally occurring terpene, present in large amounts in various plants, for example in lavender, rosewood, bergamot and jasmine. Linalool auto-oxidises on air exposure at room temperature forming hydroperoxides. Compared to pure unoxidised linalool, the hydroperoxides of oxidised linalool have shown to be far more allergenic. The Chemotechnique preparation contains oxidised linalool. The concentration of the active haptens in the preparation is measured from the added amount of the hydroperoxides of linalool. The hydroperoxides of linalool is also available for testing in a lower concentration (H-031B). Using this lower concentration will decrease the risk of obtaining false positive test results.

Lin-OOH is manufactured by Chemotechnique in 2 different concentrations:

Lin-OOH >> H-031A as 1.0% in petrolatum, with a Safety Data Sheet
Lin-OOH >> H-032B as 0.5% in petrolatum, with a Safety Data Sheet

Note that Linalool hydroperoxide hapten preparations for patch testing are available only from Chemotechnique of Sweden; not from any other patch test hapten manufacturer.

Lin-OOH as H-031A (10.0% concentration in petrolatum) is found in the following screening series:

1. GB British Baseline Series
2. NA North American series
3. ECB European Comprehensive Baseline Series
4. ICB International Comprehensive Baseline Series
5. SB Spanish Baseline Series
6. F Fragrance Series
7. ABS Australian Baseline Series
8. BS Belgian Baseline Series
9. NAE North American Extended Series
10. NAC North American Comprehensive Series
11. CB Chinese Baseline Series
12. NZBS New Zealand Baseline Series
13. NZBSE New Zealand Baseline Series Extended

Lin-OOH as H-031B (0.5% concentration in petrolatum) is found in the following screening series:

1. F Fragrance Series

So both concentrations of Linalool hydroperoxide hapten preparations are found in the following screening series:

1 F Fragrance Series

Linalool

Synonyms: Linalool, synthetic, ( )-linalool, (+-)-Linalool, (1)-3,7-Dimethyl-1,6-octadien-3-ol, (R)-3,7-Dimethyl-1,6-octadien-3-ol, (S)-Linalol, .beta.-Linalool, 0-01-00-00462 (Beilstein Handbook Reference), 1, 6-Octadien-3-ol, 3,7-dimethyl-, (-)-, 1,6-Octadien-3-ol, 3,7-dimethyl-, 1,6-OCTADIEN-3-OL, 3,7-DIMETHYL-, (-)-, 1,6-Octadien-3-ol, 3,7-dimethyl-, (3R)-, 11024-20-7, 126-91-0, 2,6-Dimethyl-2, 7-octadiene-6-ol, 2,6-Dimethyl-2,7-octadien-6-ol, 2,6-Dimethyl-2,7-octadiene-6-ol, 2,6-Dimethylocta-2,7-dien-6-ol, 2,7-Octadien-6-ol, 2,6-dimethyl-, 22564-99-4, 3,7-Dimethyl-1, 6-octadien-3-ol, 3,7-Dimethyl-1,6-octadien-3-ol, 3,7-Dimethylocta-1,6-dien-3-ol, 78-70-6, AI3-00942, AIDS-032328, AIDS032328, allo-Ocimenol, beta-Linalool, BRN 1721488, C03985, Caswell No. 526A, CCRIS 3726, CCRIS 6557, CHEBI:17580, EINECS 201-134-4, EINECS 204-811-2, EINECS 245-083-6, EPA Pesticide Chemical Code 128838, FEMA No. 2635, FEMA Number 2635, HSDB 645, L-Linalool, Linalol, Linalool, Linalool (natural), Linalyl alcohol, LINOLOOL (D), LS-1752, NSC 3789, NSC3789, p-Linalool. It has other names such as â-linalool, linalyl alcohol, linaloyl oxide, p-linalool, allo-ocimenol and 2,6-dimethyl-2,7-octadien-6-ol.

Uses: Linalool is a naturally occurring terpene alcohol chemical found in many flowers and spice plants with many commercial applications, the majority of which are based on its pleasant scent (floral, with a touch of spiciness). Is a main constituent of oils of rosewood, Ho, lavender, lavandin, clary sage, bergamot, petitgrain; minor of neroli, tangerine, and jasmine.
Linalool is manufactured by Chemotechnique as L-005B, as 10.0% in petrolatum.
The only screening series in which Linalool is to be found is the Fragrance Series.
There is a Safety Data Sheet for Linalool.

Note that none of the Linalool-based haptens are included in the TRUE Test® product.

In Summary, Chemotechnique are the go-to manufacturer for these Limonene and Linalool-based patch test haptens, offering the most comprehensive range of these haptens.

Haptens from Chemotechnique

Art no	Name	Conc.	Veh.
H-032A	Hydroperoxides of Limonene	0.3%	pet
H-032B	Hydroperoxides of Limonene	0.2%	pet
L-006C	D-Limonene	10.0%	pet
H-031A	Hydroperoxides of Linalool	1.0%	pet
H-031B	Hydroperoxides of Linalool	0.5%	pet
L-005B	LINALOOL	10.0%	pet

In-vivo diagnostic test allergens in Europe: A call to action and proposal for recovery plan – An EAACI Position paper

By Ludger Klimek et al.
In ALLERGY, 2020; Issue 75, pp 2161-2169.
See https://doi.org/10.1111/all.14329 .

EAACI is the European Allergy and Clinical Immunology professional medical society for Allergy Specialists. They compile and publish numerous Position Papers on topics of importance, and as such exceeds the current regulatory climate of importance for practicing specialists. This Position Paper boasts as authors no less than 26 absolutely leading-edge Allergy Specialists from throughout Europe.

You may be asking what does EAACI and Allergy have to do with Dermatology and Dermatologists…… well besides the obvious overlap of clinical conditions such as allergic dermatitis (the clue is in the name), this Position Paper seeks to encompass not only the Skin Prick Test diagnostic solutions used to diagnose Type I allergy, but also the patch test allergens/haptens used to diagnose type IV allergy, through patch testing. However, no further reference is made to the epicutaneous patch test (EPT) except regarding the number of registrations of SPT and EPT allergens at the PEI regulatory authority (Paul Ehrlich Institute) in Germany. There is no reference to Dermatologists or ESCD or any other association of Dermatologists, which is remarkable since a closing statement of the paper is that “Allergologists, manufacturers and authorities should join forces to make sure that relevant diagnostics stay in the EU markets to ensure a sustainable comprehensive service for the diagnosis and treatment of allergic diseases”.

So, now it would appear to be a good time for the Dermatologists of Europe to make their collective voice heard and either to reclaim their territory (patch testing and patch test products) or to collaborate with EAACI and the exact same medical product regulatory authorities to ensure that patch test diagnostics also remain available to Dermatologists in the EU, and beyond.

You are recommended to read the original article in ALLERGY or downloaded from Wiley online library.

Below are a handful of the more important points (for Dermatologists!) raised in the original article, with our editor’s personal comments.

“Diagnostic allergens are defined as medicinal products in the EU. Marketing authorisation by national authorities is necessary; however, diagnostic allergens are not homogeneously regulated in different EU member states”.

Editor’s Comment*: Some medical product regulatory authorities such as the TGA of Australia do distinguish between invasive SPT allergen solutions and epicutaneous non-invasive patch test allergens/haptens; theoretically requiring full registration of the former but no registration for the latter.*

However, in reality, the TGA acknowledge the safety and efficacy of SPT allergen solutions and their clinical need and the cost impositions for registration, and so enables easy access of SPT solutions for all Australian Allergists. The Australasian Society of Clinical Immunology and Allergy has lobbied government and the regulatory authority to achieve that eminently sensible and pragmatic situation. The European dermatology society might learn from such effective lobbying, and the European medical product regulatory authorities would seem to need a big dose of such Australian pragmatism.

"…the National Allergy Societies in Europe report that diagnoses rely on skin tests as first option in almost 2/3 of all types of allergic diseases and in 90% with regard to respiratory allergies".
***Editor's Comment**: For the diagnosis of Type I allergy there are alternative excellent in vitro tests that can and are used instead of SPT. A typical Allergy clinic will have 20 to 40 different SPT allergen solutions out of the circa 200 manufactured by different manufacturers. In contrast, there are over 500 different SPT allergens available in the global standard in vitro test, though a laboratory will stock perhaps 40 to 100 such allergens. There is also a new diagnostic test called "ALEX" (www.macro-arraydx.com) that measures allergen specific IgE to no less than 295 individual allergens or allergen components in a single small venous or capillary blood sample. That is therefore a true allergen screening test for inhalant and ingestant and other Type I allergens. Imagine if there existed a simple blood test that identified and quantified 295 different patch test haptens for Dermatologists!! However, in reality, Dermatologists do not have the luxury of any alternative in vitro tests if patch tests were to become unavailable for any reason.*

"Regardless of this broad acceptance of skin tests, the quantity of commercially available skin test DAs has been tremendously reduced in European countries since 2004".
***Editor's Comment**: The number of patch test allergens/haptens has conversely not decreased in the past two decades, because one or the other or both of the two global manufacturers of patch test haptens/allergens have added new substances that have become recognised from prevalence and other studies as significant new causes of allergic dermatitis. Examples are hydroperoxides of limonene, and carmine, et cetera. Despite this increase in the number of different patch test haptens, there are the same regulatory and cost pressures on these manufacturers as there are on the manufacturers of skin prick test solutions, which is exacerbated by the smaller number of practitioners and patients of patch testing compared to skin prick testing.*

"For example, in the German Paul-Ehrlich-Institute (PEI) database, a total of 1014 marketing authorizations (~52% of available products) for test allergens (744 biological Type I, 270 epicutaneous Type IV) have been lost from beginning 2010 until 05/2019. At the time given (status May 2019), there are 918 (547 biological Type I, 371 epicutaneous Type IV) licensed/marketable test allergens that are allowed to be distributed in Germany; however, it is not known, to which extent these are actually available on the market as some are not required to obtain official batch release by PEI".
***Editor's Comment**: The number of patch test allergens/haptens that are registered in a country is NOT the same as the number of allergens (whether EPT haptens/allergens or SPT allergens) that are produced by the manufacturer. Due to the cost and to the documentation required, a manufacturer and its local national distributor may decide to apply for registration of only a limited number of diagnostic allergens for a particular national market. Germany is the largest allergy market in Europe, so every manufacturer of SPT allergens is present and with their largest possible portfolio of clinically relevant SPT allergens registered. A smaller market would motivate fewer manufacturers and their distributors to register a wide portfolio. Note that the number of DAs quoted includes all the different commercial brands, so similarly the number of DA registrations that have been lost (allowed*

to lapse) indicates the number from all manufacturers combined, not the loss of particular allergens such as individual pollens or foods. Note that in most cases it costs the manufacturer (or their local distributor) significant funds merely to maintain an existing registration/marketing approval for an individual DA. So if the sales are not adequate to warrant the continued registration of a particular allergen then the registration will be allowed to expire and the DA is then no longer able to be sold in that market. In this case of Germany, just because there have been numerous DAs removed from the PEI register, that does not necessarily mean that the manufacturer has ceased to manufacture such DA's; it means the manufacturers have chosen to not renew those registrations in Germany.

"While some member states have largely implemented the need for marketing authorization in DAs, others largely make exceptions (according to Art. 5) or allow long transition periods.
***Editor's Comment**: Critically important is the fact that different countries apply the nominally EU-wide rules with more-or-less stringency. Scandinavia and Germany are the most "strict", whilst Spain, Italy and Greece are still in varying degrees of catch-up mode. It Is not just a case of strictness; in some countries there is apparently a lack of competency and capacity in the regulatory authorities to manage the ever-increasing demands for documentation that they themselves have imposed.*

"This reduction may be due to the fact that the costs for biological standardization, and clinical documentation, and initiation and maintenance of DA-authorizations far exceed their related revenues, forcing manufacturers to significantly limit their allergen portfolios, taking out of the market rarely used DAs for economic reasons. Allergen manufacturers argue that offering a comprehensive panel of DAs may be economically disastrous, since most of the costs are fixed and identical for frequently and for rarely used DAs, making the latter unequivocally more expensive".
***Editor's Comment**: The same pressures exist for the manufacturers of patch test haptens/allergens as for the manufacturers of skin prick test solutions. Chemotechnique partially accommodate these different cost pressures for different volumes of haptens/allergens by having a 4-level tier of prices, which also partially reflects the differing costs of the raw materials that go into the final product.*
One major difference between the patch test manufacturers and the skin prick test manufacturers is that the SPT manufacturers have a portfolio of products where the SPT solutions are actually the most minor product group, with the allergen immunotherapy vaccines being the main product groups where the manufacturers have far greater volume (value) of sales and far greater unit profitability. The SPT solutions are merely an appetiser for the Allergy Specialist to prescribe the allergen immunotherapy vaccines from the same manufacturer. Patch test manufacturers conversely have no such main course; they have to stand or fall on the financial proceeds of their patch test products alone. This is especially true for Chemotechnique. Perhaps that is one reason why there are only two such global EPT manufacturers, whereas there are a dozen or more global SPT manufacturers.

Costs are a dominant factor in the process of product registration and Marketing Authorisation. "A DA (diagnostic allergen) can obtain marketing authorization via different routes, including procedures concerning only single EU states or procedures resulting in authorizations in several Member States at once……. Fees applicable in such procedures may also be problematic. In a MRP/DCP, national fees for each involved member state vary from ca. € 712 to € 55.000 in different EU states…….These fees rapidly add up to enormous sums if a wide portfolio of different DAs is registered, thereby strongly limiting companies' commitment to bring DAs to the market…….. The entire approval documentation must permanently be kept up to date in every member state in which the DA is authorised, inducing costs (primarily for personnel) in the range of a six-figure Euro sum per year for a SPT portfolio ……. Moreover, Periodic Safety Update Reports (PSUR)

have to be submitted to the national authorities every 6 months during the first 2 years after approval for a DA, every 12 months in years 3 and 4 of the approval, and every 3 years after that. ….. Depending on the complexity and amount of data, personnel costs of creating a PSUR can be calculated with ca. €10.000…….. clinical trials are needed to demonstrate safety, sensitivity and specificity of the DA. Such studies are of particular importance for allergologists and patients; however, they are time-consuming (planning, implementation and evaluation take up to 2 years) and in a representative setting, cost of approx. €1.5 million has been calculated for a single DA.
***Editor's Comment**: So when the Dermatologist holds a single vial of 8 ml of for example Fragrance mix I, or a 5ml syringe of for example Compositae mix, and thinks that the cost of €30 is a lot of money, then they should perhaps consider the fact of the enormous costs to the manufacturer of complying with medical regulations, and the fact that 150 to 200 tests can be obtained from that vial/syringe.*

"If no changes will be implemented, allergen manufacturers may further streamline their portfolios and delete remaining DAs, so that many rare DAs may no longer be available leading to a dramatic deterioration in allergy diagnosis".
***Editor's Comment**: Fortunately for Dermatologists, this reduction has not yet been implemented by the two global manufacturers of patch test haptens/allergens, though the warning has been sounded by the manufacturers of SPT diagnostic allergens.*

Fortunately, the authors of the paper went on to make a series of recommendations that should improve the situation for *in vivo* allergy testing with diagnostic allergens:

- Simplification of Authorisation for DAs
- Reduce the need for clinical documentation
- Regulation of special types of DAs
  Further reduced documentation requirements particularly regarding rare DAs.
- Homologous Groups principle
  Use one representative allergen from a closely-related group for documentation of safety and efficacy.
- Pharmacovigilance reporting
  Reduce the demands for PSUR reports, including use of Homologous Groups principle.
- Fees
  Fee reduction, especially for rarer DAs.
- Reimbursement
  EU countries are encouraged to review and amend reimbursements for DAs in accordance with the socio-economic importance of the DAs.

***Editor's Comment**: Strange though that no mention was made of the opportunity for an EU- wide registration for DAs. Perhaps the authors of the article recognised that 100% harmonisation between all EU countries on this very complex topic will not be achievable in their career life-time!!*

As the Chinese philosopher Lao Tzu said "The journey of 1,000 miles begins with one step" ….. but the EU regulation of Diagnostic Allergens is already well down that path, and their regulation of Medical Devices has almost reached the goal…..

For further information, the reader is encouraged to read the original paper at https://doi.org/10.1111/all.14329

Legislation on Medical Devices: What's in it (and what's not)?

By Vera Mahler, Paul Ehrlich Institute, Germany.
ESCD Congress 2022: Wednesday, Round 1, Blue Room, 14:50 – 15:10.
https://escd2022.com/wednesday-ondemand/#fs1a.

The following is a loose transcription of the original audio-visual presentation, enhanced by inclusion of information shown in the slides of the original audio-visual presentation, though with every effort made by the editor to retain the original purpose, intent and meaning of the original presentation.

The reader is of course encouraged to listen to the original audio-visual presentation at https://escd2022.com/wednesday-ondemand/#fs1a

In 2017, the new medical devices regulation was entered into force, though with a very long transitional period so that the regulation was first intended to be applied from 26 May 2020, but that was postponed due to the COVID pandemic to 26 May 2021. The second regulation, concerning In Vitro Diagnostics has already been applied since 26th May 2022.

This new regulation has 175 pages compared to the 43 pages of the previous directive on Medical Devices. So there is a much bigger volume now. The changes were that the governance structure and coordination was strengthened, and there are now stricter requirements for the oversight of the national Notified Bodies. All these medical devices are not authorised by a national competent authority as medical products. Instead, these national Notified Bodies assessed and confirmed conformity. However, they operated rather independently, possibly liberally, and without much oversight. Now with the new regulations, and new accreditation, there are stricter requirements and oversight of these national Notified Bodies.

The increase of pre- and post-market scrutiny especially of high-risk medical devices is in the new regulation. There are new requirements for transparency and traceability of medical devices, as well as new processes for clinical investigations, vigilance and post-market surveillance.

Importantly, there is a new database to be set up by the European Commission, called the EUDAMED. This should include information on the manufacturer, product conformity, assessment of side effects, and clinical trials data. This should be an open database which is also accessible to normal customers.

There are also new and increased responsibilities for medicines regulatory authorities.

The key changes with the new regulations are essentially as follows:

1. Stricter *ex ante* control for high-risk devices via new pre-market scrutiny mechanism with the involvement of a pool of experts at the EU level. Therefore, the national Notified Bodies are no longer so independent.
2. Reinforcement of the criteria for the designation and oversight of national Notified Bodies.
3. Inclusion of certain aesthetic medical devices also under these medical personal device regulations.
4. Improved transparency through establishment of a comprehensive EU database with a unique device identification.
5. Introduction of an implant card for the patient.
6. Reinforcement of the rules for clinical evidence.
7. Strengthening post marketing surveillance requirements.
8. Improved coordination mechanisms between EU countries in the field of vigilance and market surveillance.

It is important to note that the last certificates issued according to the previous directives expire in May 2024. By then, everything needs to be notified to and be assessed by the newly certified Notified Bodies.

The new MDR (Medical Devices Regulation) applicable since 26 May 2021 introduces new or revised responsibilities for the EMA (European Medicines Authority) and national competent authorities for:

1. Medicines with an integral device, such as pre-filled syringes and pre-filled inhalers.
2. Medical Devices containing an ancillary medicinal substance, such as drug-eluting stents and bone cement containing an antibiotic, etc.
3. Medical devices made from substances that are absorbed by the human body to achieve their intended purpose.
4. Borderline products for which there is uncertainty over which regulatory framework applies.

Common borderline products are between medicinal products, medical devices, cosmetics, biocidal products, herbal medicines and food supplements. For these the competent authorities have to be contacted and be involved.

In Germany, the national competent authority in charge for Medical Devices is not the Paul Ehrlich Institute, but the sister Federal Institute for Drugs and Medical Devices; abbreviated to BfArM.

There is also in Germany the Federal Institute for Vaccines and Bio-Medicines.

It was her personal hope as a dermatologist, that with a switch from the previous Medical Device Directive to the incoming Medical Device Regulation, that any gaps in the enforced provision of ingredient information could be closed. This would have been a significant improvement that would have facilitated allergy diagnosis and prevention.

But admittedly, that was not the case; even with the new MDR, there are still gaps in the information that must be provided by manufacturers.

So what is not in the new MDR?

1. There is no article in the new MDR regulations that requires that information has to be provided concerning a complete list of ingredients is to be indicated on the packaging or even online; that is nowhere to be found in all the 175 pages.
2. There is no article that explicitly states requirements for labelling of ingredients classified as hazard H317 (Skin sensitising) or as H334 (Airways sensitising) according to the CLP regulation.
3. There is also no article that clearly states an obligation for the manufacturer to disclose all necessary information to manage individuals with an adverse reaction.

However, although these wished-for statements do not appear as articles, there are various points throughout the 175-page document that refer to these topics, which may well be useful for the future and for the transition period. For example; there is in the Annex 1 Chapter II (Requirements regarding Design and Manufacture) a statement 10.4.5 (Labelling) “Where devices ….contain substances that are carcinogenic or mutagenic or toxic to reproduction or have endocrine-disrupting properties ….in a concentration above 0.1% w/w, the presence of those substances shall be labelled on the device itself and/or on the packaging of each unit, or, where appropriate, on the sales packaging, with the list of such substances”.

There is nothing mentioned concerning contact allergens or sensitisers.

There is more information on what information needs to be included, in the Instruction for Use in Annex I 23.4 (Information in the Instructions for Use). This states that the instructions for use shall

contain all of the following particulars:

- Any residual risks
- Contraindications
- Undesirable side-effects
- Warnings
- Precautions
- Measures to be taken and limitations of the use regarding the device
- Information to be conveyed to the patient.

The information shall cover where appropriate warnings, precautions and limitations related to the medicinal substance or biological materials that are incorporated in the Medical Device.

This is the most important sentence because it is related to materials incorporated to the device that contain or consists of CMR substances that are endocrine disrupting, or that could result in sensitisation or an allergic reaction by the patient or user.

The summary of safety and clinical focus should be written in a way that it's clear to the intended user.

Also useful are post-marketing surveillance systems where the manufacturer needs to maintain relevant data such as quality performance data.

In addition, the safety of the device throughout the entire lifetime needs to be recorded and analysed. This is useful because in all the cases Dr Mahler had personally experienced, when contacting the manufacturers, they have always claimed that this is the very first such case and nobody else has ever had any problem with that specific product.

Therefore, it is really important that this register is fed with the cases so nobody can say "oh this is a single case not worth any further notice".

During her time at PEI, she learned a little bit about the European Commission's role and also how European Commission works. The EU European Commission has a virtual monopoly on the introduction of legislation and also putting legislation into a legislative process. The Commission also has considerable influence as an agenda-setter.

The European Commission is widely collecting information and opinion on topics. All stakeholders are heard and unfortunately, the industry of representatives is always a little bit more progressive, more present and more active than the regulators are, or the scientific societies.

Also, she could say from her own experience that the employees at the European Commission are highly motivated to step in for consumer's rights and care.

The scientific and medical organisations may submit position papers to the European Commission to make their point and to set the scene on record. These position papers are the way to communicate with the lawmakers. Sending a single angry letter does not work. Instead, medical practitioners need to bring colleagues together who share their opinion and think in this opinion on a scientific level.

Last time the ESCD met in Milan, there was a position paper written by Ann Herman and colleagues entitled "Position statement: The need for EU legislation to require disclosure and labelling of the composition of medical devices". This was supported by the ESCD, EECDRG, EADV Contact Dermatitis Task Force and EAACI.

This document was forwarded to the European Commission, and this has ultimately resulted in the Directorate General for Health and Food Safety becoming very much aware of and acting in accordance with our own wishes for improved safety of medical devices.

To quote: "Therefore the applicable legal framework provides the basis to evaluate, and to prevent as much as possible, and to inform about the potential risks related to chemical composition and the ingredients of medical devices in contact with the human body. Manufacturers shall comply with the requirements ensuring that the device and their constituent materials and particles are safe and effective, with a high level of protection of health and safety of patients and users, taking into account the general acknowledged state of the art".

So the manufacturers need to comply with the regulations and they need to give the information so we can test; and this is something to be quoted maybe when appropriate.

The conclusion of the Director, Anna-Eva Ampelas, is "with respect to the effective and harmonised implementation and enforcement of this legal requirements, the role of national competent authorities of the EU member states is crucial, as well as the active and responsible contribution of all interested parties, in particular manufacturers and other economic operators, notified bodies, patients and users".

So, whereas the regulation is rather fuzzy and not very clear, now the implementation process is happening, and this is the time where it's an important tool to raise awareness.
Now it's the time to do some lobbying, also from the sides of the scientific societies, and the patient organisations.

Dr Mahler's recommendation now is that we should feed this surveillance database, so it is clear that it's not single cases, but there is a whole group of people who are affected by the problem.

Editor's Note: A very interesting question was subsequently presented by a member of the audience who asked whether participation in the database was obligatory or voluntary. Prof. Mahler replied that participation is voluntary but that is still work in progress as the designers of the database encourage networking between the different countries. She also stated that this database should be linked to the Medical Products Database, to which patients also had access.

The reader is encouraged to see the original ESCD 2022 presentation at
https://escd2022.com/wednesday-ondemand/#fs1a.

Quantification of Preservatives in Tattoo and Permanent Make-up Inks in the frame of the new requirements under the REACH Regulation

By Marco Famele, et al.
In CONTACT DERMATITIS, Volume 87, Issue 3, September 2022, pp 233-240.
See https://doi.org/10.1111/cod.14105 .

According to the REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) regulations, tattoo and permanent make-up (PMU) inks placed on the European Union market after January 4, 2022, shall not contain methylisothiazolinone, benzisothiazolinone (BIT), octylisothiazolinone (OIT), or other skin sensitisers in concentrations of 10 mg/kg or higher and phenoxyethanol (PE) or other eye irritants or damaging substances in concentrations of 100 mg/kg or higher. In addition, preservatives and other substances enlisted in Annex II to Cosmetic Product Regulation shall not be present in concentrations of 0.5 mg/kg or higher. As a consequence, preservatives classified within skin sensitisers categories 1, 1A, and 1B such as MI, benzisothiazolinone (BIT) (CAS No. 2634-33-5), octylisothiazolinone (OIT) (CAS No. 26530-20-1) shall not be present in inks in concentration ≥10 mg/kg. Preservatives classified within skin corrosive categories 1, 1A, 1B, or 1C or skin irritant category 2, or as serious eye damage category 1 or eye irritant category 2, such as phenoxyethanol (PE) and *o*-phenylphenol (*o*-PP) shall not be present in inks in concentration ≥100 mg/kg. Preservatives enlisted in Annex II to CPR such as isopropylparaben, isobutylparaben, pentylparaben, and benzylparaben shall not be present in concentrations ≥0.5 mg/kg.

Over 4,000 substances are covered by the REACH regulations.

There is also a great deal of overlap with other regulations. According to the opinions of ECHA Committee for Risk Assessment (RAC) and Committee for Socio-economic Analysis (SEAC), preservatives as part of the tattoo ink mixture are also regulated under the EU Biocidal Products Regulation (BPR) No. 528/2012 and fall under the authorisation regime of this Regulation. These uncertainties about REACH and BPR joint applications in matter of preservative uses in inks remain unresolved.

Interestingly, according to the current knowledge, no biocidal product containing active substances approved for PT-06 (product type-6; preservatives for in-can preservation) has been authorised for its use in tattoo/PMU inks, although preservatives have been added to inks.

Classification, labelling and packaging (CLP) regulations are also greatly involved in this issue of inks and preservatives used in Tattoos and PMUs. The CLP section 2.8 of Annex II, state that in order to be compliant, mixtures that contain sensitising substances above the CLE (concentration

limit for elicitation) must have special labelling requirements to protect already sensitised individuals. Therefore, the hazard statement on the label “Contains [name of sensitising substance]. May produce an allergic reaction” shall be mandatory and apply to inks.

There are two groups of substances that are of interest:

1. Inks / colourants
2. Preservatives

Preservatives are often added to tattoo and permanent make-up (PMU) ink formulations in concentrations up to 1.5% by weight to prevent microbiological contamination after opening of the containers.

Note that among the investigated preservatives only MCI/MI and o-PP have been approved as PT-06 preservatives to date.

Inks or colourants mostly remain close to the area of injection, but preservatives and other soluble components of the mixture are expected to be subjected to a systemic distribution within hours or days after the tattoo or PMU is injected. Therefore, skin and other organs are exposed to the effects of such soluble substances until their excretion by one route or another.

Instant or delayed allergic reactions and, to a lesser extent, acute contact dermatitis and inflammatory reactions, represent common acute adverse effects. About 37% of tattoo-related adverse effects in individuals with severe symptoms or complications seen in clinics are expected to be of an allergic nature and predominantly associated with a reaction to a pigment, implying that reactions to the soluble components such as the preservatives is of lesser importance.

However, the rate of allergic reactions due to soluble components of the inks is currently thought to be underestimated due to at least three factors:

1. Limitations in the patch test methodology due to the commercial non-availability of some ink components and their sub-products.

2. The lack of information on ink labels on the ingredients in the inks.

3. There is an apparent reduction in the number of individuals with mild symptoms who visit clinics, for any of several different reasons.

One greatly confounding factor in the topic of inks and PMU colourants is the fact that neither ISO (International Organization for Standardisation) nor EN (European Standards) standard test methods are currently available for the analysis of tattoo and PMU inks. Therefore, analytical laboratories have to establish their own test procedures, and gain the necessary experience with those analytical methods so that stakeholders are able to check the compliance with the new restriction. So, it is essential that reliable analytical methods are developed and validated for the wide number of substances covered by REACH regulations, thereby standardising on the measurement procedures.

The study aimed to quantify 14 preservatives in 99 tattoo and 39 PMU inks from the Italian market, and presented a comparison with concentration limits set by the REACH restriction. 138 inks from

Italy were analysed to estimate the concentrations of 14 different preservatives, and compared them with the concentration limits established by the restrictions stated in the regulations.

A total of 138 inks (99 tattoo and 39 PMU inks) from the Italian market were selected among the most popular brands and colours in order to take into account the most representative samples. Products were purchased at different professional vendors from 2020 to 2021 (with expiry dates: 2021-2028).

The preservatives of interest were as follows:

- Methylisothiazolinone (MI)
- Methylisothiazolinone + Methylchloroisothiazolinone (MI + MCI)
- Benzisothiazolinone (BIT)
- Octylisothiazolinone (OIT)
- Methylparaben (MetP)
- Ethylparaben (EtP)
- Isopropylparaben, propylparaben
- Isobutylparaben, butylparaben
- Pentylparaben
- Benzylparaben
- Phenoxyethanol (PE)
- *O*-phenylphenol *(o*-PP).

Preservative haptens from Chemotechnique

Art no	Name
M-035B	Methylisothiazolinone (MI)
C-009C	Methylisothiazolinone + Methylchloroisothiazolinone (MI+MCI)
B-003	Benzisothiazolinone (BIT)
O-004	Octolisothiazolinone (OIT)
Mx-03	Methylparaben (MetP) (part of Paraben Mix Mx-03A and Mx-03C)
E-010	Ethylparaben (EtP)
P-020	Isopropylparaben, propylparaben
Mx-03	Isobutylparaben, butylparaben (part of Paraben Mix Mx-03A and Mx-03C)
-	Pentylparaben
-	Benzylparaben
P-025	Phenoxyethanol (PE)
P-010	O-phenylphenol (o-PP).

In the study it was found that mislabelling or incomplete labelling of samples was frequent. Twelve inks were labelled as containing PE; MetP, EtP, BIT, and other isothiazolinones were declared in none of the tested sample labels, although they were detected.

Analysis showed that 24.0%, 15.2% and 1.5% of the overall samples contained BIT, PE and OIT, respectively, at concentrations exceeding REACH concentration limits. They were therefore in breach

of REACH regulations despite more than half a year after the implementation of those regulations in Italy.

The number of non-compliant tattoo inks (49.5%) is significantly greater than that of the PMU inks (17.9%).

In conclusion, approximately 40% of the samples would be non-compliant with the restriction for the presence of preservatives above the permitted level.

In particular, MCI/MI, OIT, and BIT were found to exceed the CLE (concentration limits for elicitation) up to about 16-, 12- and 8-fold, respectively.

The most frequently detected preservatives were PE (38.3%), MI (25.5%), MCI (23.4%), and BIT (17.0%) in black inks and BIT (50.6%), PE (6.6%), and MI (5.5%) in coloured inks.

The highly frequent detection of BIT in the tested inks (54/138, 39.1%) could be alarming, because it is a skin sensitiser in animal models with potency similar to MI.

It was interesting to note the differences between inks sourced from different countries. BIT was never detected at concentrations over the limit of detection in any of the Italian inks, whereas MetP, EtP, and OIT were found only in these samples. BIT was detected only in inks manufactured in the United States with a rate of non-compliance of 36.7% (33/90). PE was present in both Italian and US inks with rates of non-compliance of 34.6% (9/26) and 13.3% (12/90), respectively. None of the preservatives of interest was found in inks manufactured in Germany.

There are no REACH concentration limits for MetP and EtP because they are not subjected to harmonised classification under CLP.

Reactions to parabens are quite uncommon and they remain one of the least sensitising preservatives available. Nevertheless, the absence of classification for a substance does not necessarily indicate that it is not hazardous but rather, in some cases, it might indicate an absence of data.

Manufacturers should focus their attention on the replacement of PE and BIT, because in the investigated samples they have been found up to about 70- and 40-fold exceeding REACH concentration limits, respectively.

For further information, the reader is encouraged to read the original paper at:
https://doi.org/10.1111/cod.14105.

Update on Metal Implant Allergy

By Peter Thomas, Munich, Germany
In ESCD Congress 2022; Wednesday, Round 2, Red Room, 17:30 – 17:50
https://escd2022.com/wednesday-ondemand/#fs2a

The following is a loose transcription of the original audio-visual presentation, enhanced by inclusion of information shown in the slides of the original audio-visual presentation, though with every effort made by the editor to retain the original purpose, intent and meaning of the original presentation.

The reader is of course encouraged to listen to the original audio-visual presentation at https://escd2022.com/wednesday-ondemand/#fs2a

Dr Thomas concentrated on orthopaedic and surgery implants.

The main points of the presentation are as follows:

1. What is normal?
2. Neglected / new allergens
3. Exposure scenario
4. Diagnostics
5. Revision with “hypoallergenic” materials
6. Outlook

There will be a consensus paper based on a recent international meeting on metal implant allergy, and specially on diagnostics; and hopefully that will be published sometime this year.

We heard there are so many implants, and it is almost normal that I guess every one of you more or less will have an implant. And then it’s also normal that we have metals in the implant. Some years ago, it was found that the cobalt level was increasing a lot if you had a hip arthroplasty, especially metal on metal. In UK and the US were a little bit different in their points of view, but for pre-implant knee arthroplasty patients in 2020, they have more or less one microgram per litre of cobalt in the blood should be still normal.

There was a study of 60 patients of whom 24 patients were followed up over 18 years after a hip arthroplasty and they were frozen samples of the serum. The levels of IL-6 were elevated initially, but then declined. Then to the surprise of the investigators, after approximately five years there was this peak of interleukin eight (IL-8). At the same time, IL-1 Beta increased slowly. TNF alpha went up. These were patients however, who had a very long-lasting arthroplasty implant of 18 years. We believe that after all those years, there was some kind of remodelling of the bone. It was not just a case of the implant sitting there and doing nothing. But there were for example, Osteoprotegerin and Plasma RANK Ligand seen to be rising, but somehow they could antagonise themselves.

What is the message? The normal situation might be that the body is dealing with the implant for many years, which we don’t understand really very well why did these patients have the good luck to retain their implant for 18 years. The study started with 60 patients. However, the authors do not say what happened to the other 42 patients who lost their implants. Pity, that would have been very interesting.

As an Allergologist, we have to question if there is allergy to components. Never forget that there are many different components if you just talk of a dental implant or if you talk about the knee implant. You have the different metallic parts and the bone cement for example.

You have this let’s say plastic in-liner but never forget some have heavy stainless steel marker so we can see it on the X ray. And the same is true for the dental implant.

What about benzoyl peroxide (BPO)?
This is a very mysterious substance; some people find contact allergy to it, some people don’t.
And nobody so far could really answer the question…..is there any BPO after you have cemented the arthroplasty implant?
This paper was published one year ago and it provides two important items of information.
There is a certain ratio between BPO and the counterpart DmpT.
You see that it is showing different molar ratios depending on the different brands of bone cement.
When you mix the bone cement in the laboratory and then try to find out is there’s still BPO you see there’s some bone cements which still contains a substantial part of BPO. In these bone cements, there’s a different ratio between BPO and DmpT. The message is if you ever have the very delicate case of a BPO-allergic patient and the orthopaedic surgeon asks you what to do, then tell him please use a bone cement that has a very favourable ratio between BPO and the DmpT….that is if you have to use cement anymore.

I was amazed by the data on iron and iron sensitisation.
This perfectly fits to what we did in a recent study, just published. What did we do? We looked at the patients in our ambulatory implant group, and to our surprise, we found about 5.5% of the patients with the problems reacting to iron - this was iron sulphate in the patch test. Ten out of 183 patients reacted to iron pre-implant, so there was a 5.5% prevalence of sensitivity to iron sulphate. 8 out of 183 reactions to iron sulphate after the implant were late reactions only. That means we could have completely overlooked the reaction if we had read the patch test result only until Day-3.

This was an astonishing high frequency of iron allergy in knee arthroplasty, yet there is no almost no iron in the knee implant. So we wondered what does this mean?

We had since 2019 introduced iron and aluminium reagents into our patch test metal series. We found direct reactivity to aluminium and clearly a lot to nickel. Bruze and Sigmund published a nice paper just this year on aluminium and they say aluminium might be an interesting new upcoming allergen because it’s not only in the transplants, and it’s not only in hyposensitisation or specific immunotherapy injections, but it is also contained in implants. And so far almost nobody has checked if there is any reaction to aluminium in the implants.

We have many years ago observed a patient who had specific immunotherapy reaction to aluminium. Maybe some of you have the same experience. The patient reacted strongly also to the patch test with aluminium salt. And then I asked my colleague to have a look at the aluminium reactivity in our patient data. Again, we found not so much sensitivity to aluminium but roughly 1% aluminium reactivity. That might be something interesting in the future.

Now let’s come back to the question …. Why did we find rather many iron-sensitised people in the knee arthroplasty implant group, whereas they don’t actually have iron in the knee implant.
If you’re doing knee arthroplasty, the surgeon has to prepare the bones, and you need literally a saw, a really strong saw blade and you need the blocks so you know where you make the cut.

Years ago, it was already published that there are roughly one to two milligram of metal particles which were generated during surgery, and although there's jet water lavage somehow many of these particles remain.

And there's this publication that came up just two months ago that resolves several questions.

Question one: people say is it really a good idea to have a hypoallergenic or nickel-avoiding arthroplasty implant for the nickel allergic patients. Why did they say that? - because they found that even when you had a titanium implant that is completely free of nickel, cobalt and chromium then the patient still had a lot of cobalt or chromium or nickel in the knee – so where does it come from?

Before the surgery there were very low levels of nickel and/or chromium and/or cobalt indeed in the knee, but after implantation of even a titanium implant (containing none of the other metals) there was found a lot of chromium underneath a lot of nickel in the knee. And a bit more cobalt. Why?

I tell you now the authors came back to the story. They found a very simple answer. The cutting blade of the bone saw was made of stainless steel, and this is about two thirds iron, 10 to 15% nickel and a lot of chromium, but no cobalt.

So now I know why we found such a lot of iron-sensitised individuals in the knee arthroplasty implant patients. If you need the hypoallergenic implant you can say to the orthopaedic surgeon to clean the implant site as best as he can so that there are no metal particles that remain in the knee. Otherwise, your patients will not do so very well even having a hypoallergenic implant.

PEEK polyether ketone is a thermoplastic polymer frequently used in medical devices. There may be a cross reactivity with the epoxy resins, as they are based on similar chemistry. So far nobody has really checked if people with a potential PEEK intolerance might have also epoxy resin allergy and *vice versa*. We will have a look at such a question this year.

This year we will start the phase three part of an international study on a panel of metal allergens. We are very much looking forward to when we might get new validated metal-based patch test preparations. So maybe in one or two years we hopefully will have a lot of extra good, metal allergen patch test preparations.

The utility of late readings: some years ago, we found out that some people reacted to gentamicin in the bone cement, and they did it especially after a longer period of five to six days. We found this significant number of reactions, and if we compared the Day-6 and the Day-3 reactivity, we had long and strong gain of positive reactivity if we did a late reading. I really recommend you do a late reading if you have a suspicion of allergic reactions. We did the reading for any other materials as well. The increase for chromate was 50% more detected, for cobalt 20% more, and even for nickel, allergy almost always showed more detection of positive results if you take the time to also test later. We did not invent this idea. Many other authors did that before; so this was just for us very interesting.

If any one of you is interested to learn about peri-implant histology, they came up with a completely new international classification scheme; that's really wonderful. And it describes the scenario around the implant.

This is a representative paper on patients who had this strong reactivity around the implant; you can see a lot of lymphocytes, even eosinophils. The patients all had enormous symptom relief when they were switched to a hypoallergenic implant; for example, around ceramic or titanium-based implants.

What about the gentamicin allergy we found? Had this any importance? Yes! Orthopaedic surgeons are very clever. They say I do a second surgery only if I must. That's why these people with the gentamycin allergy did not undergo revision surgery with gentamicin-free material because they did not have so many problems. That means their score was not dramatic. But this other group of patients got the revision surgery because they had strong pain and effusions; and they did profit in a significant way from omitting gentamycin from the implant.

This patient here did not react at all – and you want to know why this person is not reacting. This person has a so called arthrofibrosis This is a very strong reaction that makes a fibrotic tissue around the knee and basically it does not react to any kind of treatment.

Performance of a surface coded implant: There's a new registry that is a very good idea in Europe to have the follow up studies. The existing Australian registry is one of the very few that already has data. Only in this five-year period when this special type of surface-coated ceramic implant was introduced, it already had a quite different performance with regard to revision rate. It will be very interesting in the future to see which type of implant might have very good performance data. I might speculate that in about 10 years from starting to input the registry data, we will know that we had the chance to compare two groups of patients who had the knee implant uncoated and the same manufacturer, and the same same implant that was ceramic surface coated.

We were extremely surprised when we compared the circulating cytokine levels with the background cytokine levels. We thought that there must be a mistake in the analyses. However, you'll remember the strange peak five years after insertion of the implant. But it was interesting because there was this difference of IL-8, IL-6 similarly, and those who had the uncoated implant those patients had fortunately, it seems some more regulatory mechanisms. They had higher levels of IL-10. In fact, both groups did perfectly well.

There are similar studies on this performance of implants, human cytokine response and what happens in the blood, respectively, in the peri-implant tissue. There seems to be some marker cytokines like interferon gamma that are very high in the blood, and they are preceding the future problem. If there is no counter regulation, (and this is not a large number of patients in the study) I was really amazed. There are so many other data in the study, but look at that. If you look to these four cytokines, there seems to be clear-cut information. Which of the cytokine scenario might be favourable, and which might be really bad prognosis for implant survival? And I think many other researchers have shown the mediators, but I think with the help of several investigators we might know a little more what happens around the implant and what enables the body to keep the implant as long as possible.

I really don't know if there is some genetic background as well, (such as drug allergy or hay fever), or whatever, but would be interested to learn more about that.

Some researchers from the health group have published one of the very many concepts on pathophysiology and they thought it might be the debris will activate the innate immune system. We have, let's say an imbalance, and then they speculated we can just use anti IL 17; maybe also plugged interferon gamma and IL1 and we can then abolish the transition to the allergic response. I am not so sure if this approach is really so simple to solve the problem.

My wishes for the future would be it would be wonderful if we could learn:
1. Which cytokine and cellular network helps first survival of the implant.
2. What triggers metal implant allergy.
3. Genetics.
4. Aspects of long survival of the implant.
5. Toxic effects.

The reader is encouraged to view the original ESCD 2022 presentation at:
https://escd2022.com/wednesday-ondemand/#fs2a

Nickel and Cobalt Release from Beauty Tools: A field study in the German Cosmetics Trade

By Cara Symanzik, et al.
In CONTACT DERMATITIS, Volume 87, Issue 2, August 2022, pp 162-169.
See https://doi.org/10.1111/cod.14107 .

In the European Union, the utilisation of nickel in metallic objects is regulated by the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) regulation.

Until now, the use of cobalt in metallic objects is not subject to any legal regulation.

Both nickel and cobalt have steadily appeared among the most common contact allergens in recent decades. Current data from the Information Network of Departments of Dermatology (IVDK) show that the current sensitisation prevalence of nickel and cobalt amounts to 14.7% and 5.2%, respectively.

This field study is thought to be the first that investigates nickel and cobalt release from a wide range of beauty tools that are used in the cosmetics trade.

Nickel and cobalt release from occupationally used tools of different professional areas has been evidenced within a variety of studies conducted in the EU. For example, in the hairdressing trade, nickel and cobalt release was found in two currently conducted studies in which “sectioning clips”, tail combs, tweezers, hair clips, crochet hooks, and straight razors have been identified as nickel and/or cobalt releasing. Nickel release from scissors, which are the main working tool of hairdressers, has also been previously identified.

People other than hairdressers also work in beauty salons; for example beauticians, aestheticians, cosmeticians, and so on. In Germany alone, there are approximately 22,800 beauty salons, with a total of approximately 54,000 workers, mostly in small enterprises.

These other workers are all subjected to a high occupational skin strain, which is comparable to the skin strain of hairdressers. In the cosmetics trade, the skin strain results mainly from a high amount of wet work conducted while performing various beauty treatments such as facial treatments or massages. Skin contact with detergents as well as other cosmetic chemicals is prevalent and relevant.

This exposure to sensitising chemicals leads to an impairment of the epidermal barrier function, concomitant with the induction of a pro-inflammatory skin milieu, thereby facilitating the penetration of, and sensitisation to, harmful substances. The risk of developing occupational allergic contact dermatitis of the hands is thus elevated.

A previous study on Croatian beauticians showed that protective gloves might commonly not be worn as recommended in the cosmetics trade. Therefore, it must be assumed that a high proportion of daily tasks of beauticians might be carried out without deploying proper skin-protection measures.

The authors of the study screened a broad selection of the tools used in average German beauty salons to test for the release of nickel and cobalt, in order to identify the potentially relevant sources of exposure to these notorious sensitising chemicals.

The results of the study were as follows:

- 99 metal tools and 209 tools with metallic parts were tested, total 308 tools.
- Tests used were Chemo Nickel Test™ and Chemo Cobalt Test™.
  (see the Chemotechnique Advertorial on a subsequent page for further information).
- 67 of 308 tools (21.8%) no manufacturer could be noted; the remaining 241 tools were produced by 41 different manufacturers.
- 143 of 308 beauty tools (46.4%) released Nickel according to the Chemo Nickel Test.
- 18 of 308 beauty tools (5.8%) released Cobalt according to the Chemo Cobalt Test.
- 16 of 18 (88.9%) Cobalt-releasing tools also released Nickel.
- 8 of 308 (2.6%) beauty tools showed an inconclusive result with Chemo Nickel Test, with all giving a black colour.
- 17 of 308 (5.5%) beauty tools showed an inconclusive result with the Chemo Cobalt Test, with 14/308 (82.4%) showing a green colour and 3/18 (17.6%) an orange colour.
- Repeated testing after 2 weeks of 31 (10%) randomly selected tools showed 100% reproducibility.

In this study, the investigators have shown that people working in beauty salons are exposed to a wide range of beauty tools releasing nickel and/or cobalt at allergologically relevant levels. Clinical “relevance” is assumed, as the sensitivity of the spot tests is such that the detected release is likely to elicit allergic contact dermatitis with sufficient (be it repeated, short-term) contact, and in the case of nickel release, likely exceeding regulatory threshold levels. Even a short (and repetitive) contact with nickel and/or cobalt ions can be harmful—especially in already sensitised individuals.

Literature Review

This release of sensitising ions applies for a wide range of metal tools (e.g., nail clippers, corner pliers, tweezers, cuticle scissors, and cuticle removers/pushers) and tools with metallic parts (e.g., foundation brushes, eyeshadow applicators, contour brushes, lip brushes, eyeliner brushes, mask brushes, eyeshadow brushes, eyebrow brushes, nail art brushes, highlighter brushes, eyebrow spoolies, concealer brushes, and blusher brushes).

The tested metal tools are sold nationally throughout Germany, and nickel and cobalt release was identified in all the visited beauty salons spanning two German federal states, so the findings of this study are likely to be representative for Germany. Further, since many of the evaluated metal tools are marketed all over the EU, our study findings might be applicable to other European countries. Certainly, the results of this first such study should encourage further such investigations in the cosmetics trade of other countries.

Of all the metal tools and metal-containing tools that were the subject of this field study, the identification of tweezers as especially problematic has confirmed previous findings from the hairdressing trade also now in the cosmetics trade. Results of previous studies have shown that tweezers releasing nickel and cobalt in allergologically relevant amounts (detection limits being 0.5 µg nickel/cm^2/week for nickel and 8.3 ppm for cobalt) are used in the hairdressing trade. Tweezers should thus be in the focus of dermatologists who are searching for occupational relevance in the case of nickel and/or cobalt allergy in employees in the beauty industry. Furthermore, this particular item should be included in educating nickel and/or cobalt allergic patients, especially in terms of adequate allergen avoidance.

Logically, self-screening with the DMG test (Chemo Nickel Test) of all metallic items with potential skin contact is an important part of secondary prevention for every nickel-allergic patient (and beautician and salon colleagues).

This shows that beauty tools that are supposed to comply with the current EU nickel regulation[1] may nonetheless be considered relevant sources of nickel exposure.

In conclusion, the authors of the study stated that according to the findings of this field study, employees working in beauty salons are not adequately protected from nickel and/or cobalt emission from beauty tools. Setting threshold limits for the use of cobalt, in addition to stringent compliance with the REACH nickel regulation, appears appropriate.

For the dermatologist and occupational health physicians when confronted with a nickel or cobalt allergic beauty salon employee, they may initiate comprehensive testing of occupationally used beauty tools for nickel or cobalt release. In this context, not only metal tools but also tools with metallic parts should be considered.

For the primary prevention of occupational dermatoses in the cosmetics trade, general preventive advice, as, for example, wearing gloves while handling beauty tools, should be integrated into health education programs in order to prevent hand eczema in employees working in beauty salons.

For further information, the reader is encouraged to read the original paper at:
https://doi.org/10.1111/cod.14107

How to Test for Fragrance Allergy – Are the current Baseline Markers Useful?

By John McFadden, UK.
In ESCD Congress 2022; Thursday, Round 3, Blue Room, 11:35 – 11:55.
https://escd2022.com/thursday-ondemand/#edu3a

The following is a loose transcription of the original audio-visual presentation, enhanced by inclusion of information shown in the slides of the original audio-visual presentation, though with every effort made by the editor to retain the original purpose, intent and meaning of the original presentation.

The reader is of course encouraged to listen to the original audio-visual presentation at https://escd2022.com/thursday-ondemand/#edu3a

Here are some of the points I'm going to cover:

- Have a low threshold for patch testing for fragrance allergy.
- Patch test with both mixes and the individual fragrances. That's the optimal.
- Patch test patient's own products and in some circumstances even ROAT testing.
- The 7-Day reading is optimal.
- The Essential Oil playbook.
- Determining clinical relevance, which can be very difficult.
- Sources of exposure, the roots of exposure to clinical manifestations.
- And finally, should we consider missed allergen in some circumstances?

So the first thing is to have a low threshold for patch testing. Now a lot of general dermatologists will, or not now maybe, actually say isn't a diagnosis of allergic contact dermatitis obvious from the clinical history? No, in our clinic, maximum 25% of people who are patch test positive to fragrance will actually say I've got a problem with fragrance. So it's not obvious from the history. Most people would think that hair dye contact dermatitis should be obvious from the history, but it is in fact just 50%, so that too is not obvious.

Examination is very important when you are patch testing the fragrance, both pre- and post-patch testing, and I always tell the trainees to split your examination into local i.e. where the presentation is, but also distal signs of CD. And that's important for fragrance. So, save if they come with periorbital dermatitis, look at the rest of the patient for distal signs of contact dermatitis. Now we have the benefit of temporal or photographic records too. Often the patient will take photographs of when there's a bad flare and that will give you priceless information.

This is our data concerning the benefit of testing both mixes and individual fragrances.
St Johns Clinic, Guys Hospital, London; 2016:

- 189 patients are testing positive to individual fragrances only.
- 40 patients are testing positive to mixes only.
- 130 patients are testing positive to both mixes and individual fragrances.

You can see from this VEN diagram quite clearly, it's optimal to test with both mixes and individual fragrances. We test for all 26 individual fragrances. Can everyone do that? I don't know. But we do. And it's very helpful.

Limonene and Linalool are now in the European Baseline Series.
When we add the limonene and linalool into the testing program, the results change to the following:

- 181 patients are testing positive to individual fragrances only.
- 39 patients are testing positive to mixes only.
- 139 patients are testing positive to both mixes and individual fragrances.

Adding Limonene and Linalool to the test panel of individual fragrances increases the sensitivity of the testing by about 10%. Again, testing with both individual and mix fragrances is still obviously the optimal testing system.

We don't know why some individuals are positive to mixes but not to the individual component fragrances, and conversely some patients test positive to individual fragrances but not to the mix that contains those positive fragrances. This anomaly when mixes are positive but individual fragrances are negative could be due to increased innate/danger signalling. Also, when individual fragrances are positive, but mixes are negative could be due to the higher concentration of the individual fragrance compared to the concentration in a mix. Or is there some other reason?

If someone comes up positive to one or two unrelated individual fragrances, we tend to tell them the sensitivity is probably specific to those one or two fragrances. But if they come up testing positive to three or more unrelated fragrances, they may well have a generalised PARFUM problem, and we advise those people with three or more unrelated fragrance sensitivities to really try and avoid PARFUM on their ingredient labels, as they may well have a generalised fragrance allergy problem.

Now a few extra tricks to increase sensitivity: this is something I discovered before promoting the so-called IFRA Transparency List. Maybe I should have been aware of that before, but it's freely available on the website. The 2022 IFRA Transparency List includes 3,224 fragrance ingredients, used for odour or malodour coverage. There are also 395 functional ingredients that are used to support the functionality and/or durability of a fragrance compound.

Of these, 26 fragrance agents are required to be individually I.N.C.I. labelled, and the rest included under the term "PARFUM".

We at St John's Clinic test for the 26 individual fragrance chemicals, which is just 0.03% of the 3,224 fragrance ingredients. They are supposed to be the most allergenic but still, it is a very low proportion.
There may also be some other fragrance allergens out there that we're not testing for.

Therefore, it's worth testing for the patient's own products. There's a question about the sensitivity because we don't know what concentration they're at in the product, and it is probably not at the optimal concentration for patch testing.

If you've got a high index of suspicion, then you may even want to go further and do a 14 Day ROAT. I know our Scandinavian colleagues are doing ROATs for either limonene and/or linalool, and I'm looking forward very much to see those results as to how the patch tests compare to ROATs.

Another trick is to do Day-7 patch test readings as well as the Day-3 reading; which seems to be optimal for fragrance patch testing. In a very interesting study by van Amerongen in 2019, where they increased the sensitivity by some margin. Fragrance mix I on Day-7 reading goes up 15%. For Fragrance mix II it goes up 13%. So that's really worth thinking about.

Essential oils can increase your sensitivity for perfume too. This is one paper by Geier et all in 2022, where they patch tested (aimed testing) 10,930 patients for 12 Essential Oils, of whom 908 (8.3%) reacted to at least one Essential Oil. Six of these EO elicited more than 1% positive patch test reactions: yland ylang oil 3.9%, lemongrass oil 2.6%, jasmin absolute 1.8%, sandalwood oil 1.8%, clove oil 1.6% and neroli oil 1.1%. Concomitant reactions amongst EO or to EO and fragrances were frequent.

Perhaps even more interestingly was this study and it was a joint study between the NACDG of USA and IVDK of Europe (see, if America and Europe get together they are very productive). What they found was 18% reacted to at least one fragrance mix or essential oil but look at 1.4% reacted to one or more essential oils but none of the three fragrance mixes. So it's a clear sign that you use this essential oil trick or playbook to increase your sensitivity of testing for fragrances.

The Americans also found that testing for Tea tree oil was useful. The Europeans found Ylang ylang, Sandalwood and Jasmine are useful essential oils to add to your fragrance screen. We do that at St John's when we're suspicious.

Determining clinical relevance to positive patch tests: usually what I say to trainees is when you do the pre-patch test history, have a wide screen. Focus on sources of exposure, routes of exposure, a careful examination (local, distal, temporal, photographic). You ask about lots of things and when you get the positive patch tests that's the time to focus down. So if someone comes up positive to perfume, for example, I say to focus down on that allergen. The problem with perfume it's very difficult to focus down on perfume and I'll show you why.

You think of sources of routes of exposure and clinical manifestations.
Sources of exposure are numerous, so you can see how widespread the possibilities of exposure and dermatitis can be.

<u>Exposure colour code:</u>

- Clothing, jewellery/ornamentation – red
- Use of appliances – orange
- Personal Care Products, cosmetics – light blue
- Medicaments and procedures – green
- Agents in the domestic environment – dark blue
- Agents in the work environment / occupational exposure – yellow
- Sports / leisure / travel – purple
- Others – grey.

<u>Routes of Exposure</u>

- Direct contact
- Airborne
- Hand to face/neck/chest
- Mucosal
- Systemic
- By proxy.

If you look at something like hair dye, you've got very limited routes of exposure. But with fragrance, these are the six routes of exposure, and they tick all those boxes. The one I'd like to point out there is By proxy. If someone comes and they've got no rhyme or reason to the dermatitis, and often the dermatitis is asymmetrical, that's when we start thinking about By proxy, and there's various clinical manifestations.

<u>Clinical manifestations</u>

- Direct exposure
- Exacerbating endogenous eczema
- By proxy
- Airborne
- Systemic CD
- Pustular
- Granulomatous cheilitis
- Contact urticaria
- Oral CD

The point here is the examination may be helpful. For example, if it's airborne, you think possibly it's a full width of the eyelids upper and perhaps less to lower, and spreading to the malar region. Seborrheic, you may think there's something in the scalp, the eyebrows, and the glabella. But remember, allergic contact dermatitis such as perfume can present as an exacerbation of an endogenous eczema, so it could present as your severe eczema getting worse. And then they look distally; look at the neck, at the axillae, and the wrist. If there is a secondary spread such as from one axilla vault to the other axilla vault, then the secondary spread can also be a clue. Therefore, a local secondary spread can be a clue to allergic contact dermatitis being operative. So it's a bit of a challenge and you have got to work very hard at it to conclude on clinical relevance, particularly when it comes to fragrance, because there's so many sources of exposure and there's so many routes of exposure and there's so many ways it can manifest clinically.

Let's consider a missed allergen. Remember, we're not testing for all fragrance chemicals used. You think of airborne; you think of fragrance resins, preservatives, plants. Now if you suspect a missed airborne allergen, what we sometimes do is - we know we're not testing for all fragrance allergens - so we sometimes ask them a trial period without exposure to PARFUM or if you're in toiletries, household products or freshly scented candles, diffusers, etc; just to see if there is any improvement.

So how to test the fragrance or are the current baseline markers useful? Yes!
But do the current baseline markers ensure exclusion of contact allergy to fragrance? No!

The IFRA Code of Practice is the global fragrance industry's commitment to ensuring best practice in our industry and the safe use of fragrance ingredients and mixtures.

Are we safely using fragrance ingredients and make ingredients. Well, I'll leave that question open. But I'll refer to the late great Thomas Diepgen et al who published in 2016 when testing 12,377 adult European normal population, and found positive patch tests to Fragrance mix I in 1.8% and to Fragrance mix II in 1.9% of the screened population. Obviously, some of these overlap. That was without methods just outlined to increase the detection of allergy to fragrance. So approximately 2% of the European adult population have contact allergy to fragrance.

So that's something we all have to work at, and the industry has to work at, and we have to work in

diagnosing fragrance allergy correctly.

In summary, my suggestions are:
1. Have a low threshold for patch testing for fragrance.
2. Patch test optimally with both mixes and individual fragrances.
3. Patch test or even ROAT the patient's own products.
4. Day seven reading adds to the sensitivity.
5. Remember the essential oil playbook.
6. Determining clinical relevance, you have to consider:
- the sources of exposure,
- the routes of exposure,
- the clinical manifestations.
7. Consider missed allergen to a fragrance.

<u>Answers to Questions:</u>

1. A: I would suggest it's optimal to test for both the mixes and the individuals. I've given up saying what we should or shouldn't test for; instead I say this is optimal. Now what's practical? I would recommend testing for individuals and mixes, but what's practical for people? I don't know. But there's clear evidence that this increases the sensitivity, and it's not just from our group. There are other groups, and the Scandinavians that have shown this too.

2. *Q: When you see this patient's own product, you think only ROAT*.
Certainly, I would patch test patients own materials, but the problem is we don't know if the concentration is optimal, and it would appear that 14-Day ROATs can be more sensitive.

3. *Q: I just want to add something and that's when you're patch testing with the fragrances independently from the baseline series, or additional series, and the patient's own products. It's enormously important not to get false negative reactions when applying the patch test preparations and their own products directly in contact with the patient's back*.

4. *Q: I have a comment to this because unlike the 26 fragrances we are testing or you're testing, the value of patch testing with the essential oils is quite limited because unlike these 26 fragrances the EO are not required to be labelled. I will just utter a plea here at this point, that finally 10 years after the 2012 opinion, perhaps we can move forward with calling for the extended labelling in this fragrance business of also the essential oils*.
A: That's a very good point to emphasise that essential oils *per se* are not part of the fragrance mix screen but they add something to the fragrance mix screen.

5. *Q: Just a quick question about the Day-7 readings: Do you do that routinely at your centre? Or is it only for people with highest level of suspicion?*
A: We're moving to Day-7 readings, and we've already started when we suspect something like that.

6. A: I think one other common thought might come up in the questions is actually an ingredient labelling. If we want to optimise a patch, that's when we really need to know what's in all of it. You know, my approach to labelling….. is the ingredient list the whole ingredient list and nothing but the ingredient list. I know we have all got the internet, so there's no excuse now not to put the information online.

7. *Q: How many fragrances do you test routinely?*
A: I test with the whole 26 individual fragrance ingredients from Chemotechnique. I test at the 2% and not the 1% and from benzyl alcohol we test at 10% and not 1%. We push up to the maximum concentrations available commercially.

8. *Q: What series do you use?*
A: We use the Chemotechnique Series of Fragrances, and as I have just mentioned, we often add in sandalwood, jasmine and ylang ylang.

9. *Q: I do have a suggestion for testing sesquioleate. Do you test for it routinely?*
A: We at St John's have been testing for sorbitan sesquioleate for more than 30 years. That's because there's a paper showing that someone was found to be positive to Fragrance mix I which has Sorbitan sequioleate as a base, but in fact he was reacting to the Sorbitan sesquioleate that was in his Dermovate cream.

10. *Q: Could you just finally comment on how frequent you see frequently fragrance allergy among your patients? I mean, is this every day? How often do you see it?*
A: We haven't done prevalence studies recently but it's really quite high now with testing for Limonene and Linalool, its over 10% now, so it is very common.

Fragrance Mixes from Chemotechnique

Art no	Name	Conc.	Veh
Mx-07	Fragrance Mix I	8.0%	pet
	CINNAMYL ALCOHOL	1.0%	pet
	CINNAMAL	1.0%	pet
	HYDROXYCITRONELLAL	1.0%	pet
	AMYL CINNAMAL	1.0%	pet
	GERANIOL	1.0%	pet
	EUGENOL	1.0%	pet
	ISOEUGENOL	1.0%	pet
	Oakmoss absolute	1.0%	pet
Mx-25	Fragrance Mix II	14.0%	pet
	Hexyl cinnamic aldehyde	5.0%	pet
	HYDROXYISOHEXYL 3-CYCLOHEXENE CARBOXALDEHYDE	2.5%	pet
	FARNESOL	2.5%	pet
	COUMARIN	2.5%	pet
	CITRAL	1.0%	pet
	CITRONELLOL	0.5%	pet

Fragrance Series F-1000 from Chemotechnique

1.	Art no	Name	Conc.	Veh.
2.	C-014	Cinnamal	1.0%	Pet.
3.	C-013	Cinnamyl alcohol	2.0%	Pet.
4.	A-014	Amyl cinnamal	2.0%	Pet.
5.	E-016	Eugenol	2.0%	Pet.
6.	I-002	Isoeugenol	2.0%	Pet.
7.	G-001	Geraniol	2.0%	Pet.
8.	O-001	Oakmoss absolute	2.0%	Pet.
9.	H-008	HYDROXYCITRONELLAL	2.0%	Pet.
10.	N-006	Narcissus poeticus absolute	2.0%	Pet.
11.	M-021	Musk xylene	1.0%	Pet.
12.	M-028	MEHYL ANTHRANILATE	5.0%	Pet.
13.	M-019	Musk moskene	1.0%	Pet.
14.	S-005	SORBITAN SESQUIOLATE	20.0%	Pet.
15.	J-001	Jasmine synthetic	2.0%	Pet.
16.	B-010B	BENZYL SALICYLATE	10.0%	Pet.
17.	B-008B	BENZYL ALCOHOL	10.0%	Sof.
18.	V-001	VANILLIN	10.0%	Pet.
19.	L-001	Lavender absolute	2.0%	Pet.
20.	C-002	Cananga oil	2.0%	Pet.
21.	R-003	Rose absolute	2.0%	Pet.
22.	Y-001	Ylang ylang oil	2.0%	Pet.
23.	G-002	Geranium oil	2.0%	Pet.
24.	J-002	Jasmine absolute	2.0%	Pet.
25.	S-009	Sandalwood oil	2.0%	Pet.
26.	L-003	Lyral	5.0%	Pet.
27.	C-036	CITRAL	2.0%	Pet.
28.	F-004	FARNESOL	5.0%	Pet.
29.	C-037	CITRONELLOL	1.0%	Pet.
30.	H-025	Hexyl cinnamic aldehyde	10.0%	Pet.
31.	C-038	COUMARIN	5.0%	Pet.
32.	A-036	Amyl cinnamyl alcohol	5.0%	Pet.
33.	A-037	Anise alcohol	10.0%	Sof.
34.	B-038	BENZYL BENZOATE	10.0%	Pet.
35.	B-039	ENZYL CINNAMATE	10.0%	Pet.
36.	B-040	BUTYL PHENYL METHYLPROPIONAL	10.0%	Pet.
37.	E-026	Treemoss absolute	1.0%	Pet.
38.	I-017	Alpha Isomethylionone	10.0%	Pet.
39.	L-006C	D-Limonene	10.0%	Pet.
40.	L-005B	LINALOOL	10.0%	Pet.
41.	M-034	Methyl-2-octynoate	0.2%	Pet.
42.	M-033	Majanthole	5.0%	Pet.
43.	H-031A	Hydroperoxides of Linalool	1.0%	Pet.
44.	H-032A	Hydroperoxides of Limonene	0.3%	Pet.
45.	H-031B	Hydroperoxides of Linalool	0.5%	Pet.
46.	H-032B	Hydroperoxides of Limonene	0.2%	Pet.
47.	S-008	Styrax	2.0%	Pet.

***Editors Comment**: In Dr McFadden's presentation he referred to 26 haptens in the Chemotechnique Fragrance Series. This Series now comprises 46 haptens including several Essential Oils.*

The reader is encouraged to view the original ESCD 2022 presentation at:
https://escd2022.com/thursday-ondemand/#edu3a

Limonene and Linalool hydroperoxides review: Pros and Cons for routine Patch Testing

By Isabel A Ogueta, et al.
In CONTACT DERMATITIS, 2022, Volume 87, Issue 1, March 2022, pp 1-12.
See https://doi.org/10.1111/cod.14064 **.**

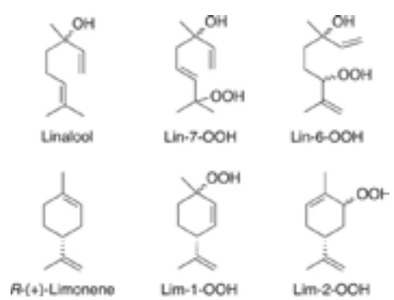
This review by Ogueta et al evaluates current patch testing with Lim-OOHs and Lin-OOHs by asking whether hydroperoxide patch testing is warranted, and examining the difficulties or challenges related to reading and interpreting hydroperoxide patch test results with currently available material, and assessing their relevance.

Clinically, an association between a positive clinical history and a strong patch test reaction has been described, but problems with doubtful/irritant reactions have also been reported.

Exposure to oxidation products, such as limonene hydroperoxides (Lim-OOHs) and linalool hydroperoxides (Lin-OOHs), remains largely elusive, as there are several factors that contribute to the difficult situation regarding sensitisation to these substances.

1. There has been debate about the patch test concentrations required to obtain a reliable result when testing oxidised limonene and linalool, so without invoking a high percentage of Doubtful or Irritant Reactions that would falsely elevate apparent positivity rates.
2. Although limonene and linalool are found in many consumer products, it is often difficult to identify if these oxidised terpenes are the culprit ingredients causing ACD.
3. It is not easy to confirm the clinical relevance of these hydroperoxides as these products when patch tested "as is" often induce no reactions (false negatives).
4. The problem is exacerbated by the fact that analyses of commercial products rarely detect or allow quantification of hydroperoxides in those products.

Despite these difficulties, it has been shown in repeated open application test (ROAT) studies that both Lim-OOH/Lin-OOH can cause ACD in sensitised patients.



The chemical structures of Limonene and Linalool, and their corresponding hydroperoxides.

Literature Review

One possible hypothesis of Lim-OOHs and Lin-OOHs sensitisation is that there is repeated exposure to the respective hapten/allergen from many sources, and even low concentrations of oxidised terpenes in each product can induce cumulative exposure capable of generating ACD in previously sensitised individuals.

The original article by Ogueta et al delves into the depths of the radical bio-chemical mechanisms by which Lim-OOH and Lin-OOH may cause the usual allergic contact dermatitis features. For further details please read the original article. Suffice to say here that substances that are low-molecular-weight compounds (haptens) are coming into direct physical contact with the skin but do not stimulate an immune response *per se.* However, after reacting with cutaneous proteins to form stable hapten-protein conjugates, they become immunogenic, and are then presented to and processed by the immune system. They are then called allergens.

The best-known mechanism for hapten-protein interaction is the formation of covalent bonds by two-electron mechanisms. Indeed, very often the allergen is an electrophile and reacts with nucleophilic side chains of amino acids from skin proteins such as cysteine and lysine. However, organic hydroperoxides (R-OOHs) do not fit this model and one-electron radical-mediated mechanisms are suspected to be involved.

The investigators concluded that considering the high frequency of relevant positive reactions, the incorporation of Lim-OOHs 0.3% and Lin-OOHs 1% in the baseline series may be justified.

However, it is still early days in the investigation of this hot topic, since exposure, sensitisation, and elicitation limits of Lim-OOHs and Lin-OOHs in the products still need to be better determined. This is all the more reason for the inclusion of these two haptens in various standard series, to determine the frequency and severity of sensitisation in consecutively screened patients, and to test which is the optimal concentration of the substance in order to invoke the maximum number of true positive reactions with the minimum number of false positive reactions due to irritant effects.

For further information, the reader is encouraged to read the original paper at:
https://doi.org/10.1111/cod.14064

Haptens from Chemotechnique

Art no	Name	Conc.	Veh.
H-032A	Hydroperoxides of Limonene	0.3%	pet
H-032B	Hydroperoxides of Limonene	0.2%	pet
L-006C	D-Limonene	10.0%	pet
H-031A	Hydroperoxides of Linalool	1.0%	pet
H-031B	Hydroperoxides of Linalool	0.5%	pet
L-005B	LINALOOL	10.0%	pet

Website Review

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

CAMP
Contact Allergen Management Program

In this twelfth issue of “The Patch Tester” we are taking a look at the website called CAMP. This is a service provided by the USA-based American Contact Dermatitis Society, at https://www.contactderm.org/patient-support/camp-access

The American Contact Dermatitis Society created the **C**ontact **A**llergen **M**anagement **P**rogram (CAMP) as a web-based resource designed to help patients manage their allergic contact dermatitis and find personal care products that are free of the ingredients that are causing their allergic reactions and so are safe for them to use.

It is intended for use by USA-based patients who are consulting USA-based Dermatologists who are members of the ACDS.

Each list generated is personalised for the patient. The list is not exhaustive, but is an excellent starting point for patients to find products that will relieve their allergic reactions.

The products included have been uploaded by CAMP administrators using publicly available information or voluntarily provided by manufacturers of personal care products who are committed patient safety. Product ingredient information is imported into CAMP from several different sources and reviewed on a continual basis.

The CAMP database is accessed by patients at http://www.acdscamp.org/

***Editors Comment**: As the optimal treatment for any contact dermatitis is avoidance of the sensitising allergen or hapten, once the offending substances have been identified (including by patch testing) then the patient should try their utmost to avoid the offending substances. CAMP is essentially a database of American personal care products where the ingredients and constituents are listed, and the patient can input information on their own allergen/hapten sensitivities, and the CAMP program will create a list of suitable products that are free from the offending allergens/haptens. This service thereby facilitates for the patient (and the Dermatologist!) the avoidance of problem allergens/haptens by a sensitised patient. As this is a USA-based service, listing American products, and requiring the use of codes that can only be provided by ACDS-member Dermatologists, it is only intended for use in USA. It Is not known if there are any other comparable comprehensive databases or even comprehensive lists of “free-from” personal-care products available in other countries or languages.*

How CAMP Works

- Following patch testing, your physician determines you are allergic to certain allergens.
- Using CAMP, a personalised safelist is generated by your ACDS physician which identifies products that are free of your known allergens or ingredients that are closely related to your allergen.
- Allergen search codes will be given to you as the patient. These are unique codes tied to your specific allergens, as identified by your ACDS physician. Allergen search codes are required to utilise CAMP.
- Click here to access CAMP and input your allergen search codes when requested. View your personalised safe list which contains a list of products that are safe for you to use.

The Personalised Safe List

The products illustrated on the list are safe for you to use!
Be sure to use the *exact* products as listed on your safe list.
Products which are the same brand and have a *similar* name as a product on the list may not be safe for you to use if it is not on the list.
Although ACDS strive to keep the information up to date, manufacturers may change their ingredient lists causing product information to become outdated. In addition, a retailer may carry an older version of the product, causing the ingredient list to be different from the information on this list. For this reason, you should review the ingredients listed on a product prior to use, and always confirm it does not contain any of your allergens.

Editors Comment*: *The CAMPS database is occasionally the subject of researcher’s published clinical papers on the prevalence of the various potentially offending allergens/haptens, (i.e., an epidemiological tool), based on the premise that the number of enquiries into the CAMP database for a particular allergen/hapten is in direct correlation to the number of times that allergen/hapten has been identified by positive patch tests. ’

For example:

American Contact Dermatitis Society Contact Allergy Management Program: An Epidemiologic Tool to Determine Relative Prevalence of Contact Allergens,
by Andrew Scheman et al, in DERMATITIS, 27(1):9-10, Jan/Feb 2016.
See: doi:10.1097/DER.0000000000000151

American Contact Dermatitis Society Contact Allergy Management Program: An Epidemiologic Tool to Quantify Ingredient Usage,
by Andrew Scheman et al, in DERMATITIS, 27(1):11-13, Jan/Feb 2016.
See: doi:10.1097/DER.0000000000000152

Contact Dermatitis / Patch Testing

16th March 2023
34th Annual Meeting ACDS 2023
New Orleans, USA
https://www.contactderm.org/events/acds-annual-meeting

ESCD 2024
To be announced

Dermatology - International

16th March 2023
34th Annual Meeting ACDS 2023
New Orleans, USA
https://www.contactderm.org/events/acds-annual-meeting

3rd – 4th October 2022
27th World Congress and Expo on Dermatology
Perth, Australia
dermatologyexpo@asia-meetings.com

6th – 7th October 2022
42nd Cours de GERDA
Antwerp, Belgium
www.gerda2022.com

1st – 2nd March 2023
7th International Congress on Dermatology
Berlin, Germany
lifescience@Worldcongressforum.com

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

27th – 28th July 2023
23rd European Dermatology Congress
Paris, France
eurodermatology@europeanmeets.com

The webpage at www.waset.org/dermatology-conferences-in-2022 is one potentially very useful source of information of Dermatology congresses in 2022.

WASWT is the World Academy of Science, Engineering and Technology. Their webpage states numerous dermatology-related congresses and conferences for 2022.

In this current era of ever-changing health and travel restrictions due to the ongoing COVID-19 pandemic, the organisation of conferences and congresses, including of course dermatology congresses, is in a state of evolution and flux. Always check with the official website for the latest information on any congress of interest.

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