What’s new in contact dermatitis?

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A personal view … on articles recently published, and on ESCD congress’ communications (Sept. 2010) (only first authors mentioned)
Non-animal sensitization alternatives

• No validated battery of assays available yet
• Advances in the field based upon the level of knowledge on the mechanism of sensitization/ACD
  – skin penetration
  – haptenation (binding to skin proteins)
  – epidermal inflammation (release of epidermal pro-inflammatory signals)
  – dendritic cell activation and migration
  – T-cell proliferation
“The fate of fluorescent allergens (isothiocyanates) through the skin…” (looking skin deep)

- Using two-photon microscopy for:
  - visualizing the distribution of allergens, as well as the processes occurring in the skin (Simonsson, Ericson)
  - visualizing the penetration of a contact allergen encapsulated in lipid vesicles (ethosomes) enhancing its allergenic effect (LLNA) (Simonsson)
  - identifying specific hapten-labelled proteins in draining lymph node cells after topical application (Jonsson)
Non-animal sensitization alternatives: progress

- ‘in silico’ (mechanistic chemistry domain classification)
- ‘in chemico’ (binding to peptides)*
- ‘in vitro’ (cellular assays) (some pre-validated at ECVAM, COLIPA research funds)
Non-animal sensitization alternatives: progress

• ‘in chemico’ (binding to peptides)

  e.g. Direct Peptide Reactivity Assay (DPRA)
  
  – mass spectrometry to investigate reactivity towards peptides/proteins (*Aleksic*)
  
  – mixtures of chemicals can be studied (*Lang*)
  
  – detection and discrimination of skin (cysteine) vs. respiratory (lysine) sensitizers (*Lepoittevin*)
  
  – adaptation to all categories of molecules using micro-emulsions (*Mecke*)
  
  – prediction of sensitizing potential of pro- and pre- haptens using micro-emulsions + enzymatic or chemical oxidation steps (*Merckel*)
Contact allergy and atopy

Controversial!

• Higher or lower frequency in atopic children?
• More (papulopustular) reactions to metals in atopics, but often irritant!

• Application of protein-containing emollient cosmetics in atopic children?

- Do we have to recommend not using oat-containing emollients in children with atopic dermatitis?
Allergy, 2008, 63, 781 (Goujon-Henry et al.)
- Sensitizing oat extracts in cosmetic creams: is there an alternative?
CD 2010, 63, 169 (Vansina et al.)
In atopic children with persistent eczema: contact allergy may be the cause!

Nickel in toys, sesame oil in topical treatment
ACD from calcineurin inhibitors (also in children!)

- Allergens in Protopic® and Elidel®
  - tacrolimus and pimecrolimus
  - excipient: oleyl alcohol (*Andersen et al. CD2006, 55, 354*)
  - Elidel +, placebo -:
    - active component not available for testing*
    - compound allergy?**
    - Bioavailability insufficient in alcohol or petrolatum?

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*Allergic contact dermatitis to pimecrolimus. CD 2007, 56, 43 (Saitta)
**Allergic contact dermatitis to Elidel® cream itself? CD 2010, 63, 171 (Neczyporenko)
Metals: nickel

- can directly stimulate Toll-like receptor 4
  (= member of the family of receptors that act as gatekeepers of innate immunity, the body's first line of defence against pathogens)

- this represents the 'danger' signal releasing TNF IL-1 IL-6 IL-18 and IL-23, promoting inflammation, and T-cell recruitment (Schmidt et al. Nature Immunology 2010, 11, 814).
Metals: nickel

• Nickel (EU regulations 2001)

  * e.g. Cellular phone addiction and allergic contact dermatitis to nickel. CD 2007, 57, 130 (Livideanu et al.)
  Also EU regulation!

  *dimethylglyoxime test

  * DMG-test = highly specific, modestly sensitive. Identification of metallic items that caused nickel dermatitis in Danish patients. CD 2010, 63, 151 (Thyssen et al)

- Strength of patch test reactivity to Ni and Co decreased; 1+ and 2+ reactions with equal frequency (33-yr. retrospective patch-test study). CD 2010, 63, 102 (Thyssen et al.)
- Nickel coins (Ledic Drvar) cause reactions in cashiers, sales assistants, and caterers (Gawkrodger)
Metals: nickel

*Children's clothing fasteners as a potential source of exposure to releasable nickel ions. CD 2009, 60, 100 (Heim et al.)*

*Children's toys as potential sources of nickel exposure. Dermatitis 2009, 20, 349 (Hsu et al.)*

*DMG +*

- Measurement of nickel, cobalt and chromium in toy make-up by atomic absorption spectroscopy. *Acta Derm Venereol* 2009, 89, 30 (Corazza et al.)
Metals: cobalt

• SPOT test

  – based on *disodium-1-nitroso-2-naphthol-3,6-disulfonate*, able to identify cobalt at approximately 8 ppm, a limit close to the elicitation threshold concentration in cobalt-allergic patients *(Thyssen et al. CD 2010, 63, 63)*

  – only a minority of inexpensive jewellery purchased in Denmark released cobalt: apparently, nickel was not replaced by cobalt following the regulatory intervention on nickel exposure *(Thyssen et al. CD 2010, 63, 70.)*
However, palladium...

- Nickel and palladium: cross-react

Ni- sulfate and Pd-chloride
tested simultaneously in 744 subjects (K.U.Leuven)

Ni pos: 302
Pd pos: 176
Pd neg: 135
Ni neg: 9*
Pd pos: 167
Ni pos: 167

- Pd often + in Swiss study, with sodium tetrachloropalladate better than PdCl₂?
  Also many reactions to manganese, but tests with optimal salts, concentrations and vehicles need to be addressed (Scherer)

- *Validity of self-reported nickel allergy is low (Josefson)
Metals: palladium

- Major sources: orthodontic appliances, jewelry, ...
- Clinical expression of contact allergy may be granulomatous

Patch test: Granuloma

Treatment = excision

- Granuloma possibly induced by palladium after ear piercing. Dermatitis 2008, 19, 26 (Thijs et al.)
- Allergic granuloma due to palladium following ear piercing. CD 2006, 55, 338 (Goossens et al.)
- Granulomatous contact dermatitis to palladium. CD 2006, 55, 42 (Gonçalo et al.)
- Persistent granulomatous contact dermatitis due to palladium body-piercing ornaments. CD 1999, 40, 111 (Jappe et al.)
Metals: aluminium

- Main source: vaccines or hyposensitisation therapy
- Long-lasting, pruritic, excoriated, subcutaneous nodules in 1% of vaccinated, mostly atopic, children (long persistence of Al in skin)
- ¾ of 250 children examined (with + PT and nodules) lost contact allergy to Al when tested 5 yrs. later (very few still nodules) (Lidholm G)
- Contact allergy may be revealed by testing with Finn chambers
- Test with Al-chloride hexahydrate may be false – (Siemund)

Finn

- There is an association between contact allergy to aluminium and persistent subcutaneous nodules in children undergoing hyposensitization therapy. CD 2009, 60, 41 (Netterlid et al.)
Cosmetics: fragrances

Baby, 1 yr. old

Fragrance-mix I

Ingredients:
Aqua, Glycerin, Methyl Gluceth-10, Imidazolidinyl Urea, PPG-26 Buteth-26, PEG-40 Hydrogenated Castor Oil, Tetrasodium EDTA, Chlorhexidine Digluconate, Citric Acid, Bisabolol, Methylisothiazolinone, Methylchloroisothiazolinone, Parfum, Alpha Isomethyl Ionone, Amyl Cinnamal, Benzyl Benzoate, Benzyl Salicylate, Butylphenyl Methylpropional, Cinnamyl Alcohol, Citronellol, Coumarin, Eugenol, Hexyl Cinnamal, Isoeugenol, Linalool.
Cosmetics: fragrances

Fragrance-mix II: important screening agent

1) Lyral* 2.5% : most important allergen
2) Citral 1%
3) Farnesol 2.5%
4) Coumarin 2.5%
5) Citronellol 0.51%
6) Alpha-hexyl cinnamic aldehyde 5%
   - *Hydroxyisohexyl 3-Cyclohexenecarboxaldehyde

- Need to test Lyral next to FMII in baseline series? (Heras et al.)
- All lyral- positive patients also react to FMII (Carvalho et al.)
- BUT negative reactions to HICC 2.5 % in the mix, while + to 5 % pet (Peter Frosch)
Essential oils

Labelling

“Rosa centifolia”

“Body lotion “fragrance-free”

INCI: International Nomenclature of Cosmetic Ingredients

Nardelli et al. Rosa centifolia in an non-scented body lotion as a cause of allergic contact dermatitis. CD 2009; 61,306
Essential oils as a source of skin allergy* (allergenic oxidation products)

* variability in composition (Karlberg): test with essential oils used by the patient to avoid false – (Poreaux)
- ** oxidized terpenes = allergens (Rozas)
- also in topical pharmaceutical products (among other fragrances) (Nardelli)

Melaleuca alternifolia (tea tree) oil**
“Compositae” contact allergy: related to fragrances...

presence of (oxidized) terpenes!

-Colophonium and compositae mix as markers of fragrance allergy: cross-reactivity between fragrance terpenes, colophonium and compositae plant extracts. CD 2005, 53, 285 (Paulsen et al.)

•Topical formulations containing parthenolide-depleted feverfew extracts may elicit positive patch tests in feverfew-allergic persons, the reactivity being lost over time (Paulsen et al. CD 2010, 63, 146)
Contact dermatitis from plants:

**Sesquiterpene lactones (and primine):**

→ **Airborne**... release of contact allergens from plants (*Christensen L*)

→ **Chronic actinic dermatitis**: the role of the alpha-methylene-gamma-butyrolactone group (photoadducts with thymidine) (*Kost et al.*)
Cosmetics: preservatives

Baby, 1 yr. old

Parabens are rare causes of cosmetic contact dermatitis
Parabens

- = esters of para-hydroxybenzoic acid: methyl, ethyl, propyl, butyl, … that metabolise in the skin

- present in numerous natural products (fruits, vegetables, …) and in human body (co-enzyme Q10 precursor)

- used in food (methyl and ethyl)

- concentration authorised in cosmetics: 0.4 % for ester (salt), 0.8 % for mix
Parabens

• Many cosmetic companies label ‘paraben-free’ (mainly because of oestrogenic effects in animal species), but this is a consumer and political issue; unfortunately, scientific data in humans are lacking!

• Any effect of parabens in consumer products likely to be insignificant

• Methyl- and ethylparaben: not any doubt about safety

• Propyl- and butylparaben: under investigation, but still allowed in cosmetics, …except in cosmetics < 3yrs. in Denmark

• What about pharmaceutical products???

- The paraben controversy for dummies (Sasseville)
Cosmetics: preservatives

- Baby wipes! ACD underdiagnosed in diaper and hand dermatitis?

- Methylchloro- and methylisothiazolinone (most frequent allergens)
- Formaldehyde releasers: imidazolidinyl-, diazolidinyl-urea, sodium hydroxymethylglycinate, dmdm hydantoin, …
MI actually …replacing MCI/MI

MCI/MI 100 ppm

Use concentration max. 100 ppm

Use concentration: max. 15 ppm

MI is a weaker sensitizer than MCI, but equally sensitizing because of higher use concentrations?

• patients allergic to MCI/MI often react to MI, however, often false – to the latter!

• methylisothiazolinone: sensitizer in its own!!! (16 new cases during the last year)

-MI in a deodorant (Amaro)

-Prevalence and cause of methylisothiazolinone contact allergy. CD 2010, 63, 164-167 (Lundov et al.): cosmetics and paints!
MI in paints, glues…
- causing airborne dermatitis in patients previously sensitized through cosmetics

Wipes: primary cause
Hair-care products: primary cause
Formaldehyde releasers:

- imidazolidinyl-, diazolidinyl-urea, bromonitro propanediol, sodium hydroxymethylglycinate*, dmdm hydantoin, Quat15 (frequency in USA > EU)


- Reactivity of formaldehyde releasers toward amino acids through breakdown products, other than released formaldehyde (Kireche et al.)
Formaldehyde releasers

• ... in cosmetics, and household, and industrial products

• derivatives of morpholine, oxazolidine, hexahydroxytriazine in metalworking fluids ...
  (de Groot et al. CD 2010,63,pp. XXX; Dastychova)

• ...and in gloves!

Hexahydrotriethyl-triazine in nitrile gloves
Occupational allergic contact dermatitis from biocides in gloves

Formaldehyde 1%: sometimes false-negative

- However, also other biocides potentially present: e.g. cetylpyridinium chloride in powder-free gloves (Hansson)

Table 2. Formaldehyde content (µg) in reusable protective gloves with flocked lining (inside and outside)

<table>
<thead>
<tr>
<th>Glove</th>
<th>Inside dig III</th>
<th>Outside dig III</th>
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<tbody>
<tr>
<td>Sempersoft</td>
<td>60</td>
<td>5</td>
</tr>
<tr>
<td>Supasoft S20B</td>
<td>40</td>
<td>5</td>
</tr>
<tr>
<td>Tegera 8180</td>
<td>10</td>
<td>2.5</td>
</tr>
<tr>
<td>Tegera 8170</td>
<td>10</td>
<td>2.5</td>
</tr>
<tr>
<td>Swehand Combex</td>
<td>30</td>
<td>2.5</td>
</tr>
<tr>
<td>Extra</td>
<td>20</td>
<td>2</td>
</tr>
</tbody>
</table>

-Formaldehyde in reusable protective gloves. CD 2006; 54: 268 (Pontén)
Cosmetics: sunscreen agents as contact allergens

Girl, 3.5 yrs

Octocrylene is a moderate sensitizer (LLNA) and its reactivity towards lysine is a likely reason for octocrylene’s ability to cause contact allergy*


Cosmetics: sunscreen agents as photo-allergens

photo-ACD

photo-patch tests

+ UVA
Sunscreen agents as photo-allergens

- Photocontact allergy to dibenzoylmethanes caused by arylglyoxals formed upon photodegradation, and
- Allergenic potential cannot be lowered by changing para substituents (Karlsson et al.)

→ Importance of studying photodegradation products, also for potential cross-sensitivity
Sunscreens as photo-allergens

+ UVA

NSAID

ketoprofen

• similar immunogenic complexes found between ketoprofen, benzofenone and octocrylene (Karlsson et al.)
* 89% of photo-allergic ketoprofen patients also reacting to cinnamic alcohol (Marmgren et al.)
Other cosmetic ingredients

- Vit K₁ oxide (García-Gavín)
- Cetearyl isononanoate* (Ito),
  but also other isononanoates**
- Ascorbyl tetra-isopalmitate ***
- Tetrahydroxypropyl- ethylenediamine (5 cases)****

*Allergic contact dermatitis from cetearyl isononanoate. CD 2003, 48, 343 (Le Coz)
** New cosmetic allergens: isononyl isononanoate and trioxyl phosphate. CD 2008, 53, 320 (Goossens et al.)
*** Allergic contact dermatitis from ascorbyl tetraisopalmitate. CD 2011, 64, 241 (Swinnen & Goossens)
****Contact sensitivity to tetrahydroxypropyl ethylenediamine in a sunscreen, without cross-sensitivity to ethylenediamine CD 2000, 43, 121 M.E. Kirkup et al.
PPD-containing hair dyes* and temporary tattoos

Reactivity to a 30-minutes’ patch-test… (Coenraads PJ)

- Hair dyes = main sensitization source for PPD (EU max. 2%) (Wong T)
- but more p-toluene diamine (TDA) (EU max. 4%) and other dyes used nowadays (Yazar)
- Several possible potent sensitizers formed during oxidation (Young)
- Alopecia universalis: rare complication of ACD from PPD? (Campbell)
Disperse dyes

• **EU Legislation:**
  - Restriction on certain dyes 43 (REACH) 6/2007
  - RAPEX: rapid information exchange between member states and Commission
  - Ecolabel since 1992 (limits/forbids...) *(LecoZ)*

• Also in textiles imported from China *(Chen)*
Disperse-dyes dermatitis

- Disperse-dye mix (8 disperse dyes): good indicator
- Disperse orange 1 and yellow 3 most frequent
- Cross-reactions with PPD (PPD-mix)
- Significant association with PPD, increasing age, and childhood eczema
- Test preparations contain impurities and lower amounts of dyes than stated on the label
- Tests with thin-layer paper chromatograms

*(Morgardt-Ryberg, Zimerson, Malinauskiene et al.)*
Drugs’ hypersensitivity

• Value of patch testing in fixed drug eruptions (Andrade et al.)

• Value of patch testing in DRESS and AGEP (Barbaud et al.)

• Also consider the excipients (and possible contaminants)! (Bircher)
  – Immediate-type: mannitol, polysorbate, carboxymethyl cellulose, soya, macrogols, povidone, benzoates, sulfites, patent blue V, …
  – Delayed-type: metacresol, mannitol, lanolins, sulfites, parabens, …
Corticosteroids (CSs)

- Alpha-ketoaldehydes responsible for skin sensitization
- CSs that are methylated at position C16 are less allergenic than those not methylated (Baeck)
- Oxidated methylated compounds did not form stable adducts with arginine, contrarily to non-methylated CS (Debeuckelaere)
- Molecular modelling (dendrogram) (Baeck)
  - 2 different types of CS allergic patients
    - to specific CS structure
    - to all CSs
- ID tests: detect additional cases, but important skin atrophy, particularly with potent CS suspensions (Soria)
Occupational allergic contact dermatitis from ‘drugs’

- **Pharmaceutical industry**: particularly airborne (also from intermediates), e.g. omeprazole, lansoprazole, ranitidine*, simvastatin, flutamide, opiates, antibiotics, … but patch testing may cause systemic symptoms *(Heras)*

- **Health-care workers** and those who take care of family members, e.g. ranitidine* and pyridoxine HCl *(Córdoba)*, apomorphine *(García-Gavín)*, budesonide aerosols*, …

*Patients with airborne sensitization/contact dermatitis from budesonide-containing aerosols “by proxy”. CD 2009, 61,1 (Baeck et al.)*
Occupational allergic contact dermatitis from tetrazepam in nurses
Occupational dermatitis

- **Resins**: aliphatic polyisocyanates in polyurethane paints (*Pesonen*) and isocyanates (and epoxies) in jewellery (*Lee*)

- **Resins** (acrylates) and **preservatives** (MCI/MI) in printing industry (*Ogden*)

- **Amines** (ethylenediamine) in concrete and cement workers (*Pontén*)

- **Preservatives and surfactants** in skin-care products, in particular, in ice-hockey players (*Erikson*)
Occupational dermatitis: prevention and treatment (gloves)

- Barrier alteration (irritation) higher after humidity exposure (wet work) than by occlusive effect from gloves (*Fartasch*)

- **Nitrile** gloves efficient in occupational acrylate allergy in beauticians (*Waton*)

* Rubber additives!  [http://www.gisbau.de/service/sonstiges/allergene/liste.html](http://www.gisbau.de/service/sonstiges/allergene/liste.html)
Persistent “Post-occupational” (?) dermatitis

• Syn.: post-traumatic eczema, post-contact chronic eczema, autoeczematization, … following particularly irritant, but also allergic contact dermatitis (epoxy, hairdressing chemicals, …)
• duration of disease important
• M > F, atopy not significant (*Nixon et al.*)
• Clinical aspect: very often nummular eczema
• Not limited to ‘occupational’ (nickel objects , joint replacement, burns, …)
• Mechanisms: T Cells reactive to keratinocyte antigens?* Abnormal immune recognition of autologous skin antigens?** …

* Fehr et al (J Am CD 2000,11,145)
** Gonzalez-Amaro (JAAD. 1993, 28,56)
Diagnostic patch testing

- Weak positive patch tests may be as relevant as strong positives (Hervella)

- Improvement/ additional tests
  - Encapsulating potential contact allergens in ethosomes may increase the challenge response as compared with the same concentrations in an ethanol/water base without ethosomes (Madsen et al. CD 2010, 63, 209). Risk of false- with other vehicles!
  - Standardized tape stripping*: detects the presence of ACD if false-negative patch test result - facilitates the penetration of test substances, but also enhances skin immunoreactivity to the test substances by inducing the expression of keratinocyte-derived ‘alarmin’ and cytokine mRNAs (Dickel et al. CD 2010, 63, 215)
  - Testing with thin-layer chromatograms (Gunasti et al.)

* e.g. beta-blockers in ophtalmology
Diagnostic patch testing

- Do not preload chambers with acrylates (freeze them) (Isaksson)

- TRUE® test vs. Trolab® (Finn chamber®) testing of FMI (n= 5006)
  - No conclusion about the best preparation
  - Finn chamber: false + ↔ True test: false –
  - Weak + with FMI Trolab: need evaluation for relevance!
  - When only + FMI TRUE test: relevant allergies may be missed (Mortz et al.)
Multiple sensitivities

- Susceptibility and reactivity in polysensitized individuals following controlled induction (compared to monosensitized and healthy controls):
  - no difference in the sensitization ratio
  - stronger trend in the strength of elicitation, and
  - lowered elicitation threshold (increased reactivity)
  - environmental exposure: most important factor in developing contact allergy
  - evidence of polysensitization as a phenotype for inherent, increased reactivity

Bangsgaard et al. CD 2010, 63, 10
Contact allergy

you can only find what you are looking for...

PATCH and photopatch and ROAT...
www.escd2012.com
11th congress of ESCD
June 13-16, 2012
Malmö, Sweden