The usefulness of clinical data and the concept of clinical relevance

Jeanne Duus Johansen
National Allergy Research Centre
Department of Dermato-allergology
Copenhagen University Hospital Gentofte
Denmark

NATIONAL ALLERGY RESEARCH CENTRE

Environmental: Preventable

Dose-response

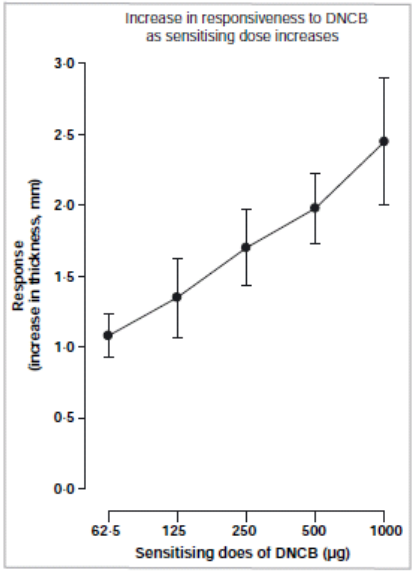
Thresholds in induction and elicitation

More get sensitized:

- Higher doses
- Repeated doses

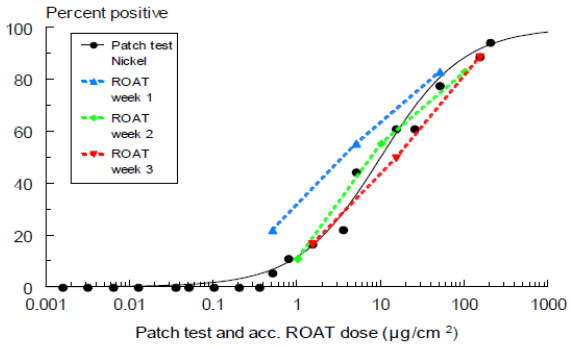
-More elicit a reaction with:

- Higher doses
- Repeated doses



P. Paramasivan,* C. Lai,* C. Pickard,* M. Ardern-Jones,* E. Healy* and P.S. Friedmann*

Journal Compilation © 2009 British Association of Dermatologists • British Journal of Dermatology 2010 162, pp594–597



Fischer LA et al. Contact Dermatitis 2009

NATIONAL ALLERGY RESEARCH CENTRE

Prevention

Information

Ingredient labelling

Cosmetics:
Secondary prevention

Limitations in use

Regulations

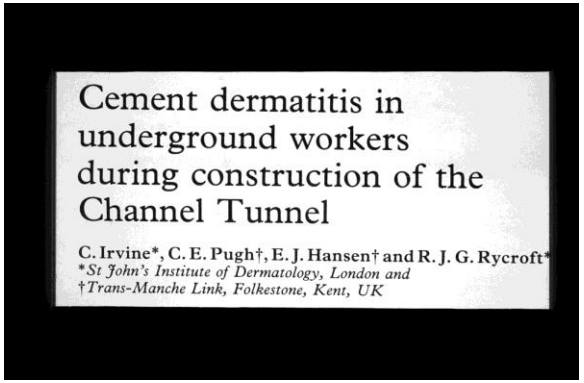
Cosmetics:
Primary and secondary prevention

Ban

Regulations

A practical example:
Prevention of chromium allergy (cement)

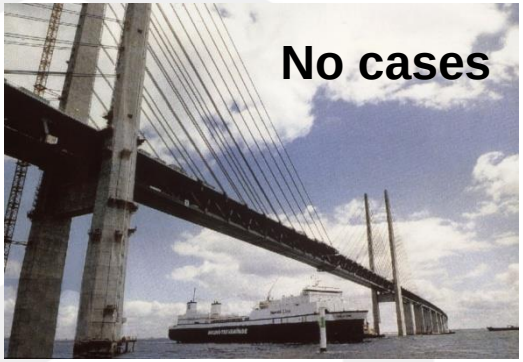
CrVI in cement: severe problems


Cement dermatitis in underground workers during construction of the Channel Tunnel

C. Irvine*, C. E. Pugh†, E. J. Hansen† and R. J. G. Rycroft*
*St John's Institute of Dermatology, London and
†Trans-Manche Link, Folkestone, Kent, UK

Scandinavian regulation (1981)
Reduction of CrVI to CrIII

17% of construction workers got CrVI allergy



EU-law: 2005

NATIONAL ALLERGY RESEARCH CENTRE

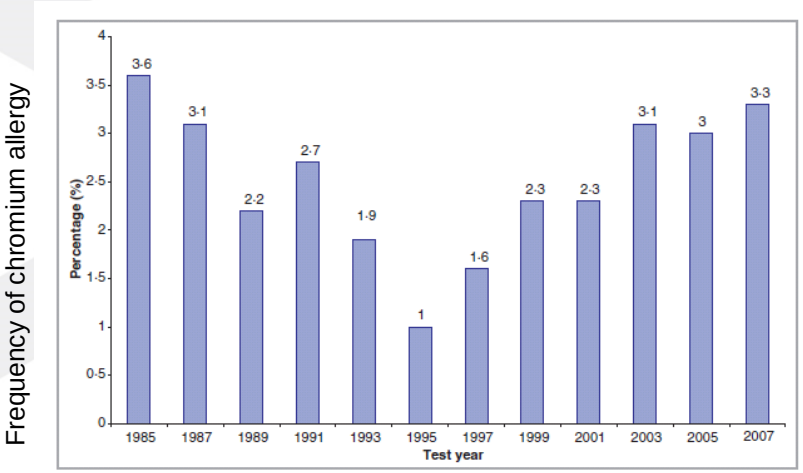
Chromium allergy and leather

CONTACT DERMATITIS AND ALLERGY BJD British Journal of Dermatology

The prevalence of chromium allergy in Denmark is currently increasing as a result of leather exposure

J.P. Thyssen, P. Jensen, B.C. Carlsen, K. Engkilde, T. Menné and J.D. Johansen

Department of Dermato-Allergology, National Allergy Research Centre, Gentofte Hospital, University of Copenhagen, Hellerup, Denmark



Construction workers Women with shoe eczema

Leather is tanned with Cr(III)

-may be released from leather
-may be converted to Cr(VI)

-**Increasing trend among women with feet dermatitis**

Investigation of 18 pair of shoes: 44% released CrVI

NATIONAL ALLERGY RESEARCH CENTRE

Hansen MB et al. Contact Dermatitis 2003

Geier J et al. Dermatol Beruf Umwelt 2000

REACH

Threshold for restriction:

3 mg/kg (0.0003%) CrVI in the total dry weight of the leather.

Based on elicitation dose-response studies (patch tests).

The threshold is expected to be 80 % effective in reducing the occurrence of new chromium VI-related allergic dermatitis cases due to chromium VI in leather articles.

The effectiveness of the restriction on the number of cases of chromium allergy **can be determined by monitoring cases** of chromium VI-related allergic dermatitis

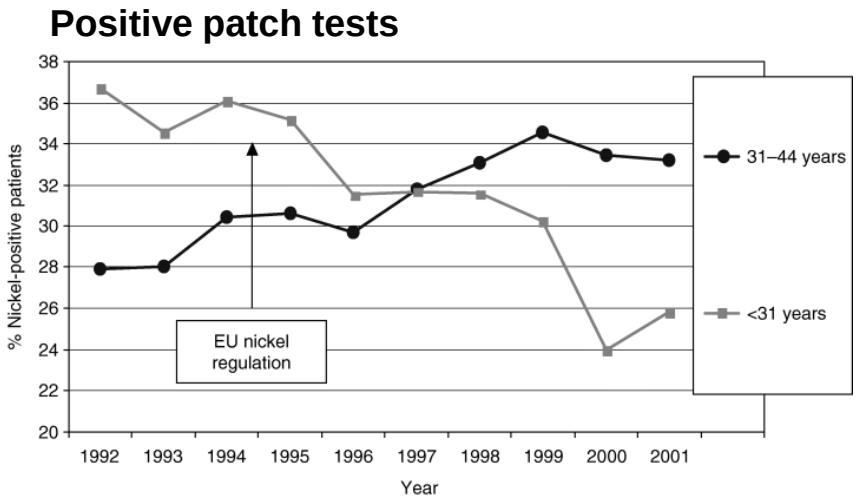
American authorities (EPA) has set very low limits to the presence of CrVI in wood to prevent chromium allergy to occur.

EU nickel regulation: based on clinical data

The European Directive restricting the use of Nickel
THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
DIRECTIVE 94/27/EC
of 30 June 1994

Products which comes in prolonged contact with skin e.g. buttons, watches, jewellery :
Nickel release <0.5 µg/cm2/week
Lower for piercing jewellery (2004)

Decrease in nickel allergy in young eczema patients



Schnuch, A. et al. Contact Dermatitis 2003

Reduction in new cases estimated value
in DK: 1.3 billon Euro/20 years

Dimethyl fumarate: cause of shoe allergy

Contact Dermatitis 2009: 61: 249–260
Printed in Singapore. All rights reserved

CONTACT DERMATITIS

Shoe contact dermatitis from dimethyl fumarate: clinical manifestations, patch test results, chemical analysis, and source of exposure

Ana Giménez-Arnau[1], Juan Francisco Silvestre[2], Pedro Mercader[3], Jesus De la Cuadra[4], Isabel Ballester[2], Fernando Gallardo[1], Ramón M. Pujol[1], Erik Zimerson[5] and Magnus Bruze[5]

[1]Department of Dermatology, Hospital del Mar IMAS, Universitat Autònoma, Barcelona, Spain, [2]Department of Dermatology, Hospital General Universitario, Alicante, Spain, [3]Department of Dermatology, Hospital General Universitario Morales Meseguer, Murcia, Spain, [4]Department of Dermatology, Hospital General Universitario, Valencia, Spain, and [5]Department of Occupational and Environmental Dermatology, Malmö University Hospital, Malmö, Sweden

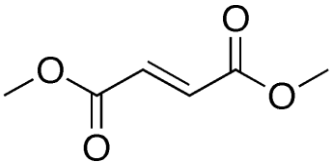
Fig.3 a.

A Summary of shoe allergic contact dermatitis caused by dimethyl fumarate in Spain

Juan Francisco Silvestre[1], Fernando Toledo[1], Pedro Mercader[2] and Ana María Giménez-Arnau[3], on behalf of the Spanish Research Group of Allergic Contact Dermatitis due to Dimethyl Fumarate in Spain

[1]Dermatology Department, Hospital General Universitario de Alicante, 03010 Alicante, Spain, [2]Dermatology Department, Hospital General Universitario Morales Meseguer, 30008 Murcia, Spain, and [3]Dermatology Department, Hospital del Mar, 08003 Barcelona, Spain.

Fungicide: dimethyl fumarate



EU Directive: From March 09 not allowed to import products treated with DMF.

NATIONAL ALLERGY RESEARCH CENTRE

Contact allergy – allergic contact dermatitis

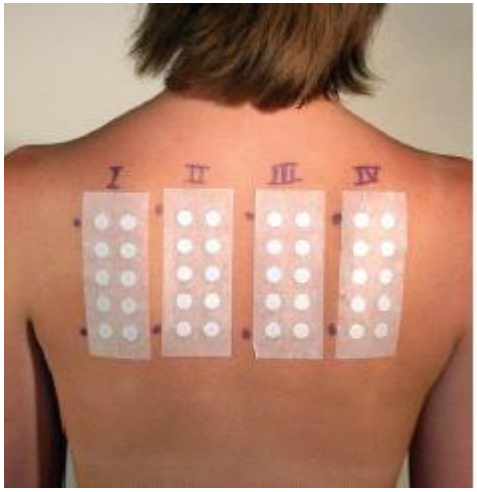
- Contact allergy
  - Altered immune status induced by a specific substance, demonstrated by a positive patch test.
  - Defines the population at risk

- Allergic Contact Dermatitis
  - Exposure to the substance causes/have caused clinical symptoms (disease)
    - Unknown
    - Yes, previously
    - Yes, currently
    - Yes, tomorrow

Diagnosis of fragrance allergy (baseline series)

FM I since 1980 (Larsen W, 1977):

Evernia prunastri (Oak moss abs.)
Isoeugenol
Cinnamal
Cinnamyl alcohol
Eugenol
Hydroxycitronellal
Geraniol
alfa-amyl cinnamal

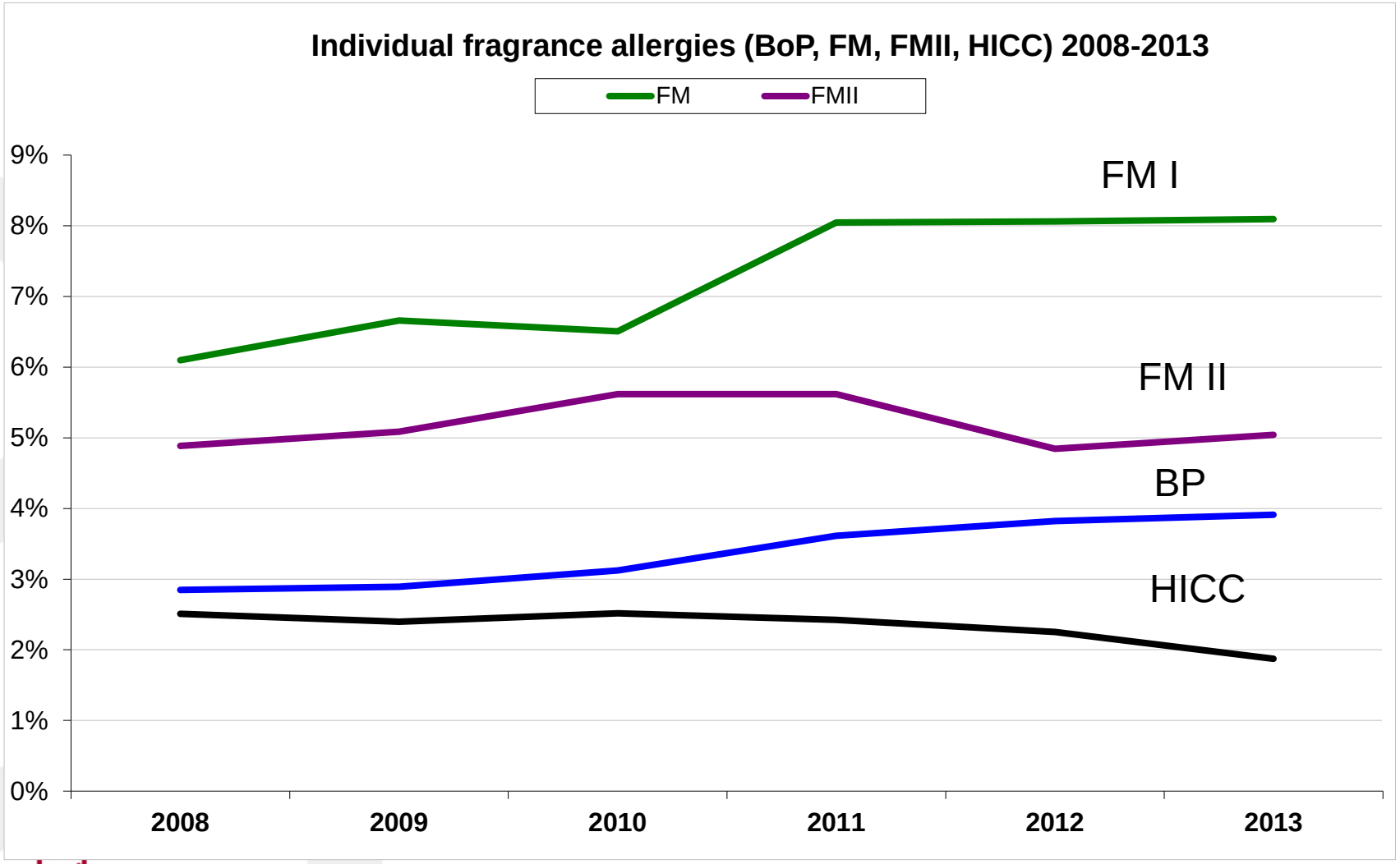


FM II since 2005 (Frosch PF, 2005):

Hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC)
Citral
Farnesol
Citronellol
Hexyl cinnamal
Coumarin

Balsam of Peru (INCI: myroxylon pereirae): **Since 1939**

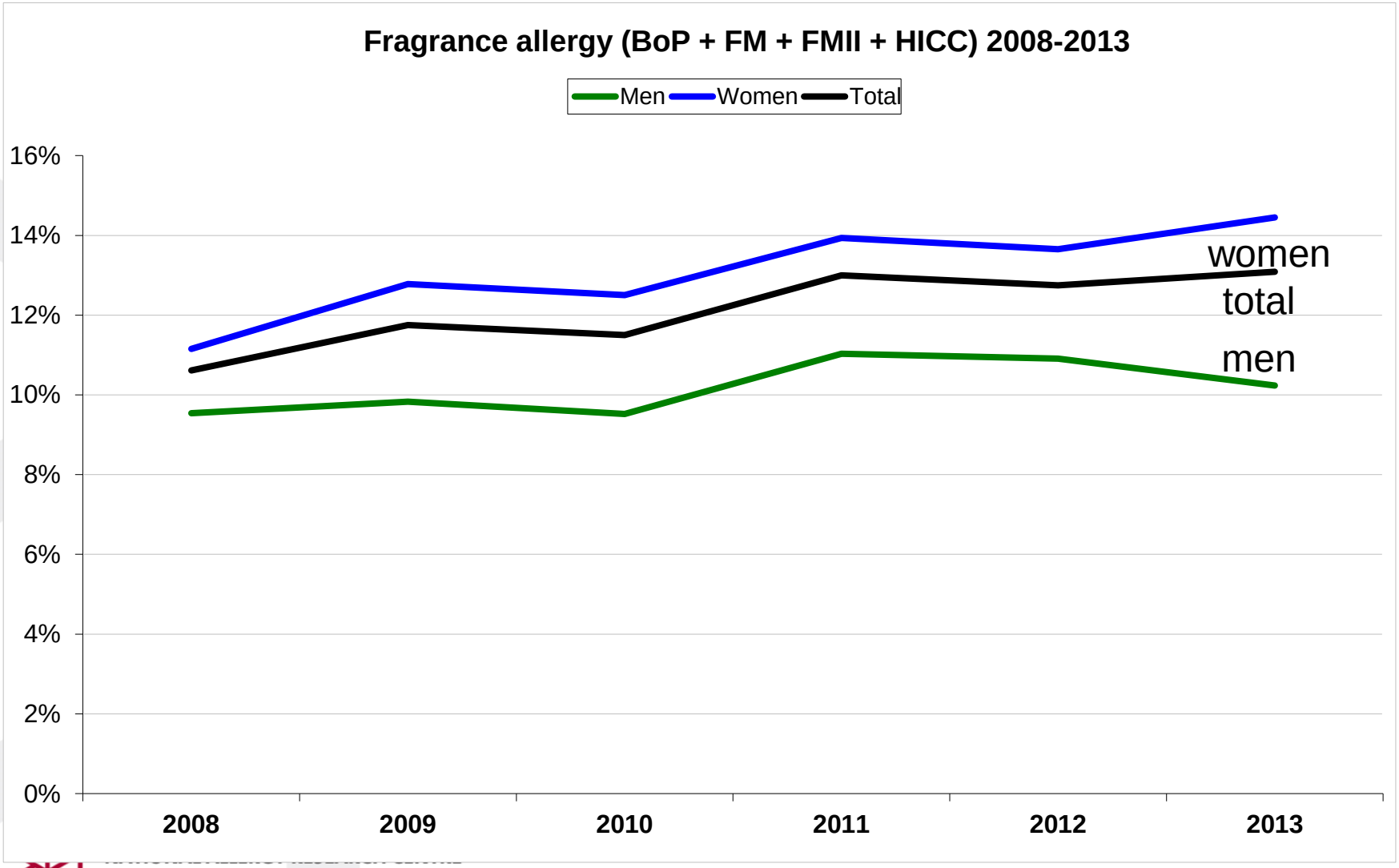
Markers of fragrance contact allergy



NATIONAL ALLERGY RESEARCH CENTRE

Danish Contact Dermatitis Group 2014, n= 28.930 patients

Fragrance contact allergy: In total



Danish Contact Dermatitis Group 2014, n=28.930 patients

Clinical relevance

1. **History of the patient (rashes)**

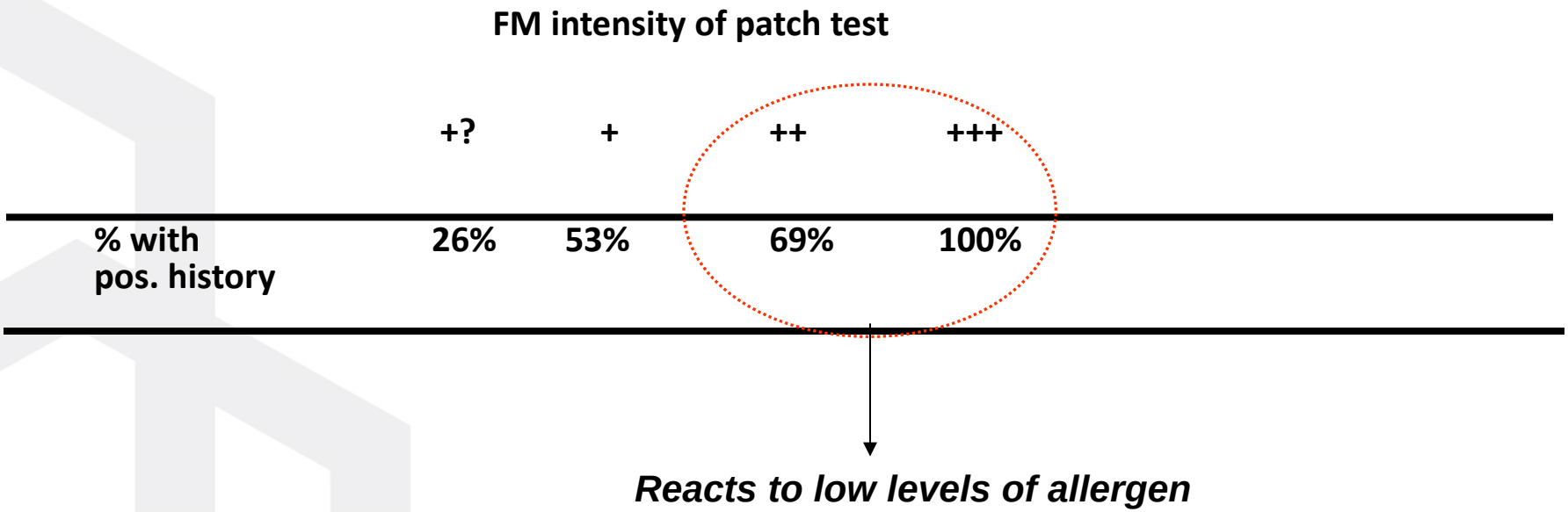
2. **Re-exposures**

- Patch testing with own products
- Use testing with a suspected product

3. **Exposure analysis**

- General knowledge (doctor)
- Ingredient labeling
- MSDS
- Chemical analysis

History of the patient



NATIONAL ALLERGY RESEARCH CENTRE

Frosch PJ et al. Contact Derm 1995:32;
Johansen JD et al. Acta Derm Venereol 1997:77

CONTACT DERMATITIS AND ALLERGY

BJD British Journal of Dermatology

The prevalence and morbidity of sensitization to fragrance mix I in the general population

J.P. Thyssen, A. Linneberg,* T. Menné,† N.H. Nielsen‡ and J.D. Johansen

General population

N=3460

Year 2006

Patch test (FM I)

Questionnaire

Dermatitis to cosmetic products (past 12 months):

Patch test pos FMI: 3.5 (2.0 -6.2)

Dermatitis to cosmetics lead to medical consultations

Patch test pos FM I: 3.4 (1.8 -6.2)

(Adjusted for age, sex and AD)

Use tests: Repeated Open Application

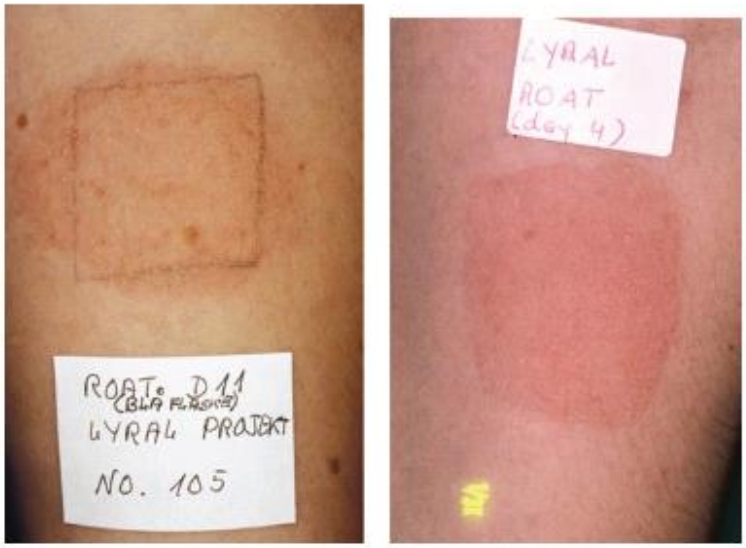


Fig. 5. Positive use tests to repeated applications of Lyral® in ethanol.

Repeated exposures

- Smaller concentrations needed for elicitation than for patch testing

Recommended:

- 14 days two applications per day

Johansen JD, Frosch PJ, Svedman C, Andersen KE, Bruze M, Pirker C, Menné T. Contact Dermatitis 2003:48:310-316

Factors of importance: Region and previous eczema

Sensitivity depends on region

Axilla > arm

Face=neck> arm

Upper back > lower back

Johansen et al, Contact Dermatitis
Zacharia C. ESCD 2004
Hannuksela, Am J Contact Derm.

Previous allergic eczema

Experimental nickel contact eczema.

Challenge later - after
- 8 months
- 4 months
- 1 months

Significantly higher reactivity at previous allergic eczema sites

Hindsén M et al. Contact Dermatitis 1997:37

Cocktail of allergens

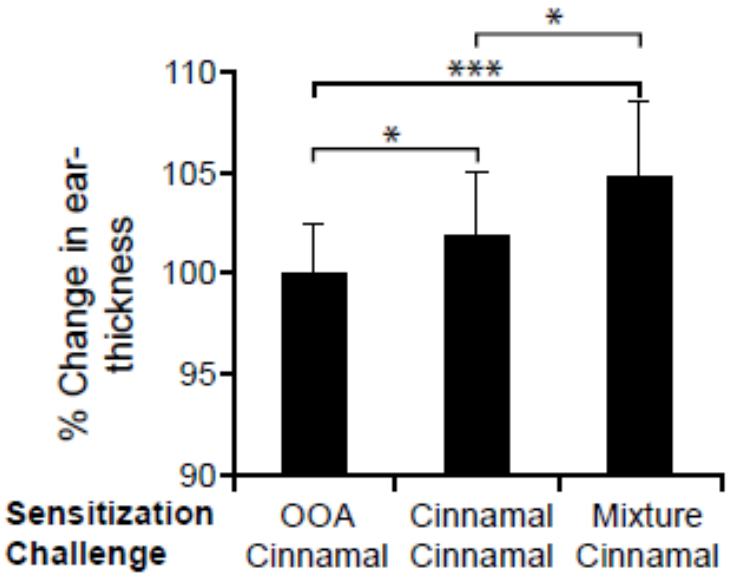
Reflects normal exposure:

Womens perfume: mean 12 allergens

In animal experiments:

Enhance induction

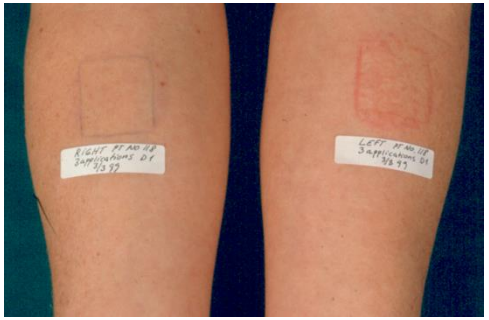
Enhance elicitation



Buckley DA.Br J Dermatol. 2007 Aug;157(2):295-300.

Bonefeld C et al. Contact Dermatitis

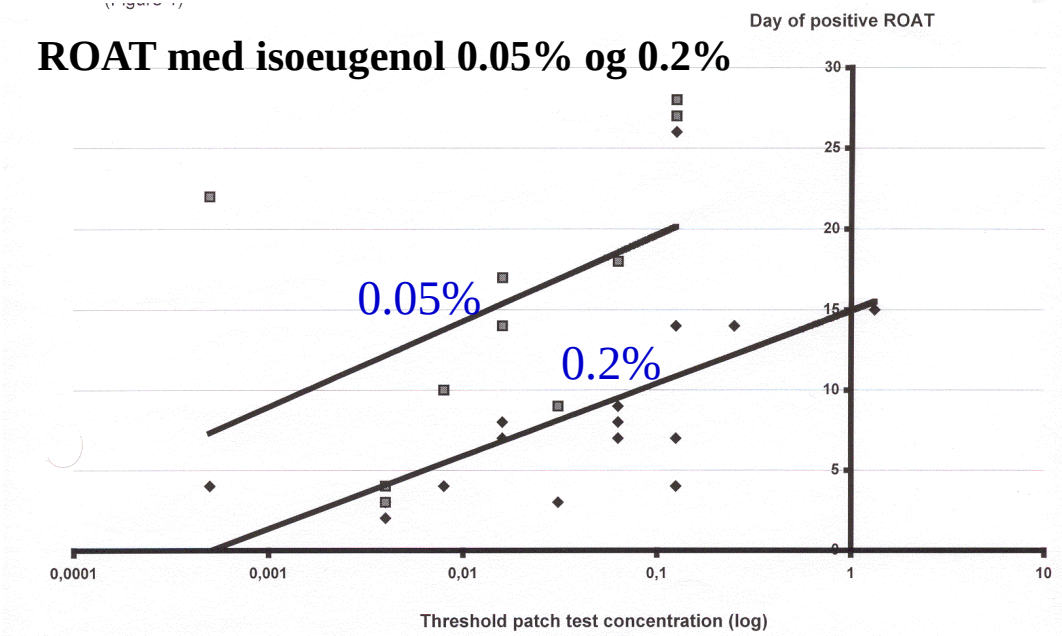
Concentration important



Number of days (exposures) until elicitation depends on exposure concentration:

0.2%: 7 days of exposure (median)
0.05%: 15 days of exposure (median)

-**And the individual level of sensitivity**



Andersen KE et al. Toxicol Appl Pharmacol 2001:170:166-171

Recommendation: 14 days of ROAT

Contact Dermatitis 2009: 61: 152–162
Printed in Singapore. All rights reserved

CONTACT DERMATITIS

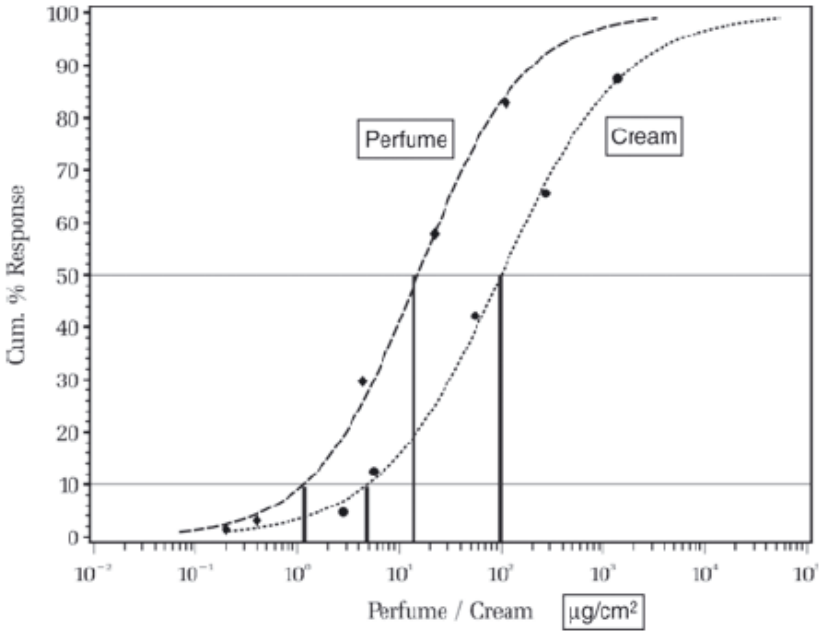
Quantitative patch and repeated open application testing in hydroxyisohexyl 3-cyclohexene carboxaldehyde sensitive-patients

Axel Schnuch[1], Wolfgang Uter[2], Heinrich Dickel[3], Christiane Szliska[4], Sibylle Schliemann[5], Ricarda Eben[6], Franziska Rueff[6], Ana Gimenez-Arnau[7], Harald Löffler[8], Werner Aberer[9], Yvonne Frambach[10], Margitta Worm[11], Margarete Niebuhr[12], Uwe Hillen[13], Vera Martin[14], Uta Jappe[15], Peter J. Frosch[16] and Vera Mahler[17]

64 subjects allergic to HICC

ROAT with 5 conc. of HICC in
a cream-base and in a perfume (ethanol)

Cumulative responders >80%



NATIONAL ALLERGY RESEARCH CENTRE

Exposure assessment

Tool: Cosmetics Directive

- Full labeling since 1998 except for fragrance ingredients
- In 2005 ingredient labeling of :
  - 24 chemicals
  - 2 natural extracts

Incl. All FMI/FMII ingredients

Limits:

Leave-on: 10 ppm or above

Wash-off: 100 ppm or above

Implemented:

- March 2005 for cosmetics

- October 2005 for detergents

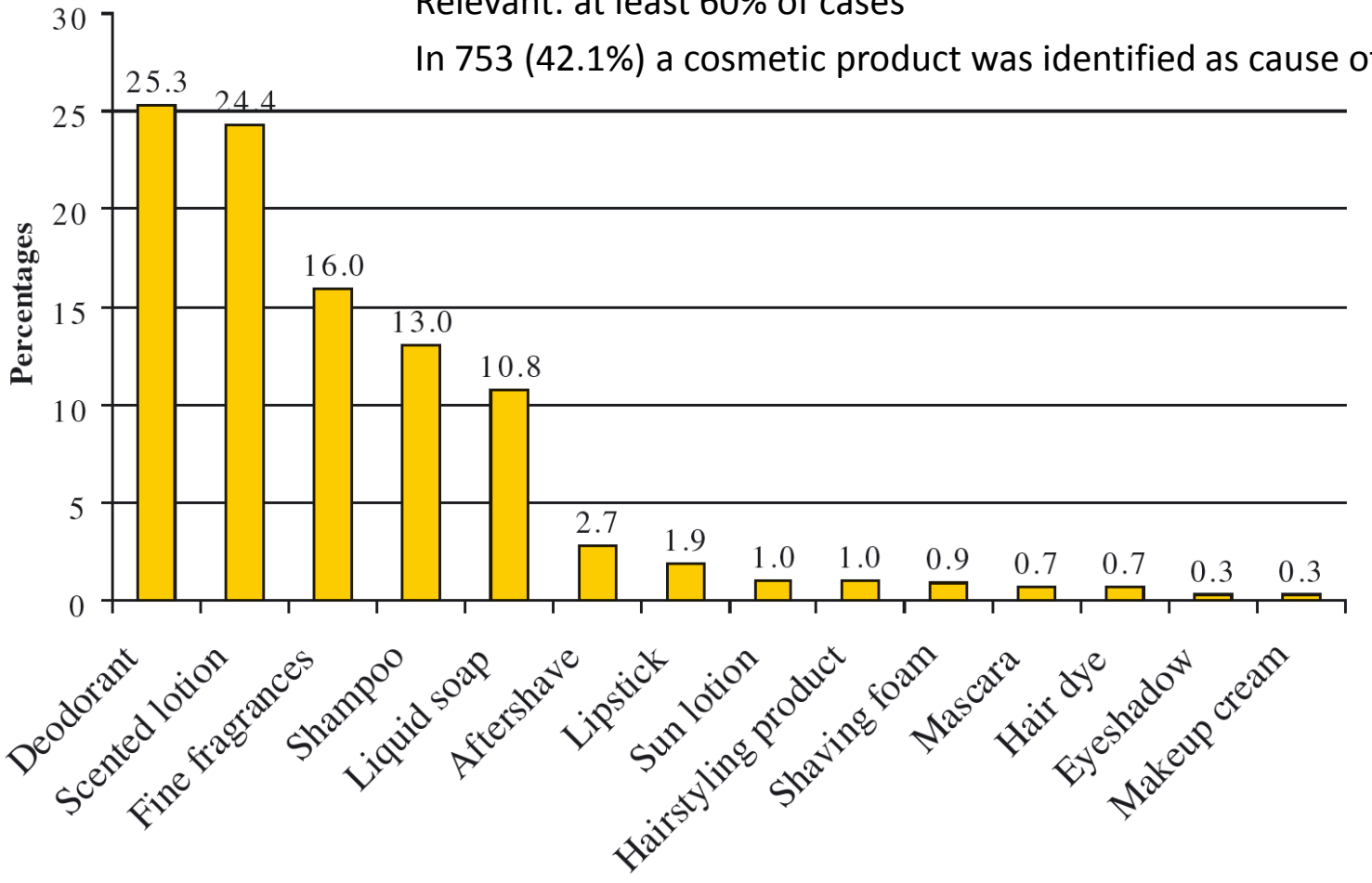
Name (INCI)	Cas no	FM I	FM II
Amyl cinnamal	122-40-7		
Benzyl alcohol	100-51-6		
Cinnamyl alcohol	104-54-1	X	
Citral	5392-40-5		X
Eugenol	97-53-0	X	
Hydroxycitronellal	107-75-5	X	
Isoeugenol	97-54-1	X	
Amylcinnamyl alcohol	101-85-9	X	
Benzyl salicylate	118-58-1		
Cinnamal	104-55-2	X	
Coumarin	91-64-5		X
Geraniol	106-24-1	X	
Hydroxyisohexyl-3-cyclohexene carboxaldehyde (Lyral)	31906-04-4		X
Anisyl alcohol	105-13-5		
Benzyl cinnamate	103-41-3		
Farnesol	4602-84-0		X
Butylphenyl methylpropional	80-54-6		
Linalool	78-70-6		
Benzyl benzoate	120-51-4		
Citronellol	106-22-9		X
Hexyl cinnamal	101-86-0		X
d-limonene	5989-27-5		
Methylheptinecarbonate	111-12-6		
Alpha Isomethyl Ionone	127-51-5		
Evernia prunastri (oak moss)	90028-68-5	X	
Evernia furfuracea (tree moss)	90028-67-4		

Products involved in fragrance allergy

1790 patients with fragrance allergy

Relevant: at least 60% of cases

In 753 (42.1%) a cosmetic product was identified as cause of dermatitis.



Heisterberg M on behalf of DCDG: 2011 May;64(5):258-64

Contact Dermatitis 2009: 61: 320–324
Printed in Singapore. All rights reserved

CONTACT DERMATITIS

Fragrance contact allergic patients: strategies for use of cosmetic products and perceived impact on life situation

Susan Hovmand Lysdal and Jeanne Duus Johansen

Gentofte N=147 patients with fragrance allergy

Questionnaire: Response rate 79.6%

86.3% read the label of cosmetics

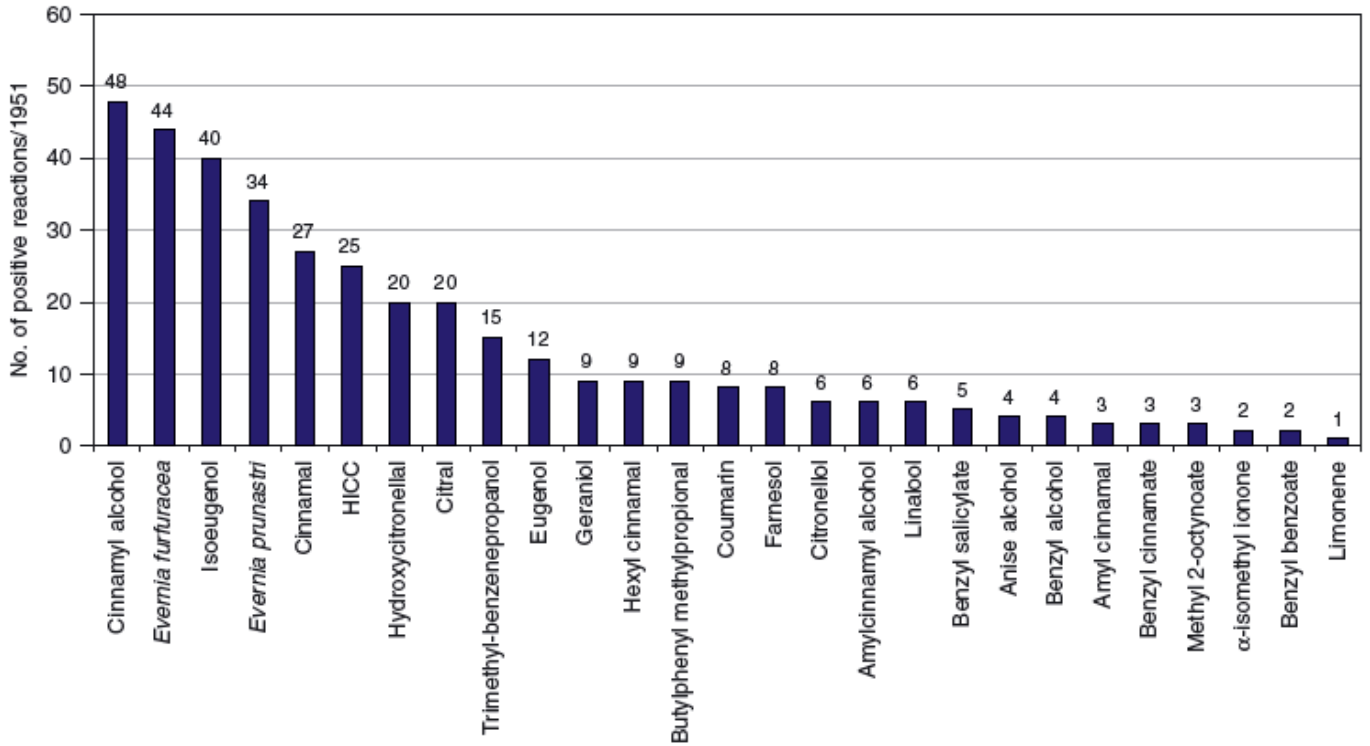
- 45.3% had found scented products which they could tolerate.
- 22 % had tried but could not find any.
- 31.6% had not tried to find any scented products

.

Baseline series fragrance markers fail to predict contact allergy

Jack Mann[1], John P. McFadden[2], Jonathan M. L. White[2], Ian R. White[2] and Piu Banerjee[2]

[1] *Friends Dermatology Centre, Kent and Canterbury Hospital, CT13NG Canterbury, UK and* [2] *St John's Institute of Dermatology, St Thomas' Hospital, SE1 7EH London, UK*



The selection of the 26

Based on human data:

Weight of evidence approach

Mir

of c

fror

Larg

req

Devided into: more or less proven allergens

Assessment 10 years later

Contact Dermatitis 2009: 60: 65–69
Printed in Singapore. All rights reserved

CONTACT DERMATITIS

Review Article

Nothing is perfect, not even the local lymph node assay: a commentary and the implications for REACH

David A. Basketter[1], John F. McFadden[1], Frank Gerberick[2], Amanda Cockshott[3] and Ian Kimber[4]

Conclusion

Patch tests

Simple test

Gold standard

Clinical relevance

Fluctuating

Complicated

Resource demanding

Absolutely necessary:

Exposure information

From a medical point of view

Full ingredient labeling