

# Recent clinical studies on oxidized fragrance terpenes

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GOTHENBURG

- Show some of the work we have done
- Studies on:
  - Irritation from oxidized terpenes
  - Contact allergy to oxidized linalool
  - Contact allergy to oxidized limonene
  - Contact allergy to oxidized geraniol
  - ROAT

# Earlier clinical studies: contact allergy to oxidized limonene and oxidized linalool

- Ox *R*-limonene 3% pet
  - 1.6- 2.8%      5500 patients<sup>1,2,3</sup>
- Ox. linalool 2% pet
  - 1.3%      1511 patients<sup>4</sup>

1. Karlberg A-T et al. *Contact Dermatitis* 1997;36:201-206

2. Matura M et al. *Contact Dermatitis* 2003: 49:15-21

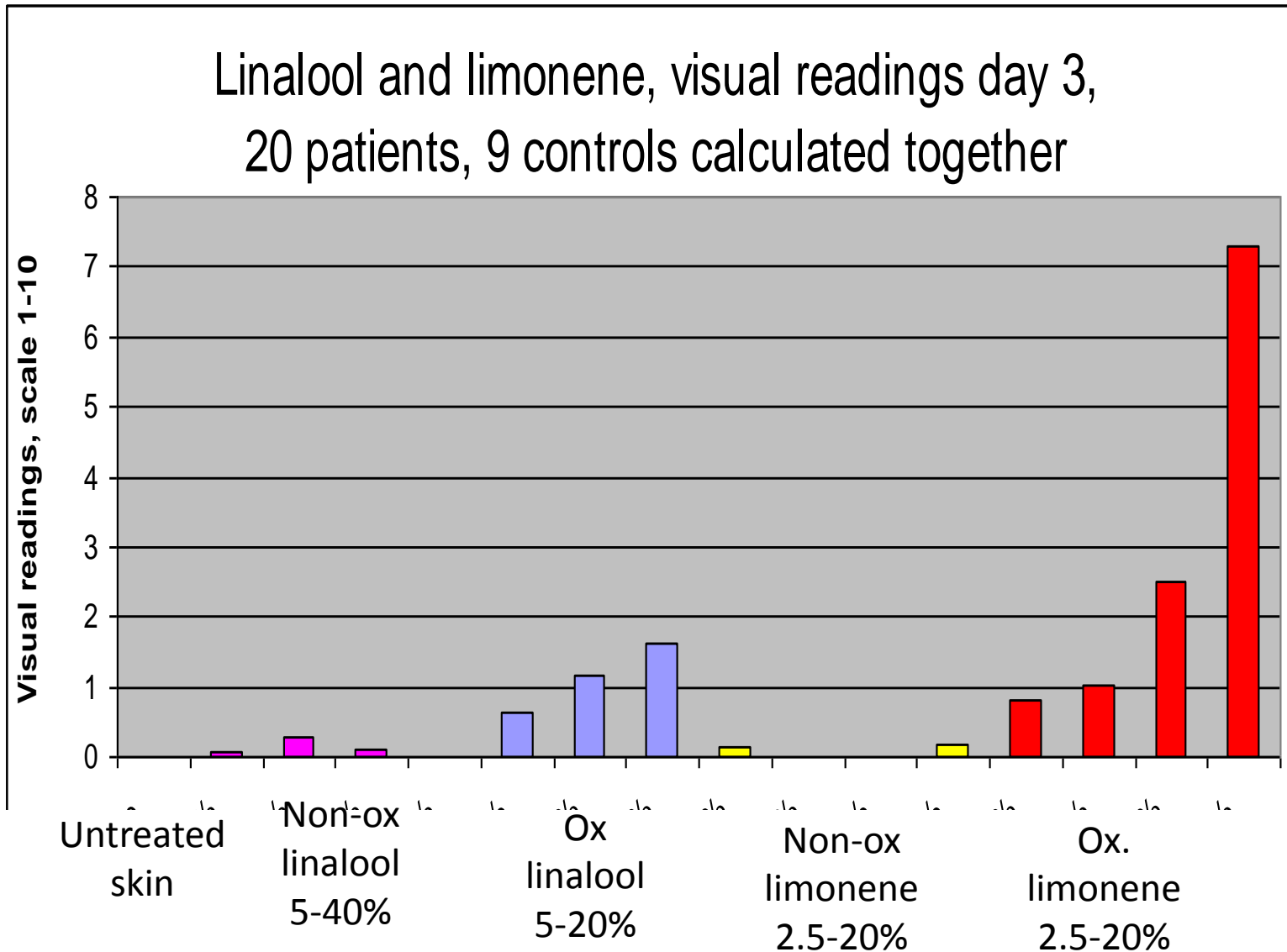
3. Matura M et al. *Contact Dermatitis* 2006: 55:274-279

4. Matura M et al. *Contact Dermatitis* 2005: 52:320-8

# Irritation study: non-ox vs ox linalool and limonene

- Linalool
  - non-ox 5- 40% pet
  - ox 5-20% pet
- Limonene
  - non-ox 2.5- 20% pet
  - ox 2.5-20% pet
- Visual reading (Basketter et al.)  
and Laser Doppler Imaging

# Results, irritation study



# Dose-response study ox linalool

- Based on irritation study-could the test concentration of ox linalool be raised?
- Linalool ox 45 weeks
- Consecutive patients
  
- Screening in 2 centra in Sweden:
  - 2 % pet.
  - 2 % and 4 % pet.
  - 4 % and 6 % pet.
  - 4 %, 6 %, 11 % pet.

Bråred Christensson J, Matura M, Gruvberger B, Bruze M; Karlberg A-T. Linalool-a significant contact sensitizer after air exposure. *Contact Dermatitis*: 2010: 62: 32-41.

## Results, dose response study:

<b>Ox linalool (pet.)</b>	No. tested	No.pos	<b>% Pos</b>
<b>2%</b>	1693	14	<b>0.83%</b>
<b>4%</b>	2075	67	<b>3.2%</b>
<b>6%</b>	1725	91	<b>5.3%</b>
<b>11%</b>	1004	71	<b>7.2%</b>

# Conclusions: dose response study ox linalool

- ✓ 5-7% of patients pos reactions
- ✓ Recommended patch test conc: 6.0% in petrolatum
- ✓ Should be included in the baseline patch test series?
- ✓ Many concomitant reactions to fragrance markers: support relevance

Bråred Christensson J, Matura M, Gruvberger B, Bruze M; Karlberg A-T. Linalool-a significant contact sensitizer after air exposure. *Contact Dermatitis*: 2012: 62: 32-41.



# International multicentre study oxidized linalool

- *Contact Dermatitis* 2012; 67: 247-259.
- Klaus E Andersen, Magnus Bruze, Jeanne Duus Johansen, Begoña Garcia-Bravo, Ana Gimenez Arnau, CL Goh, Rosemary Nixon, Ian R White, Johanna Bråred Christensson

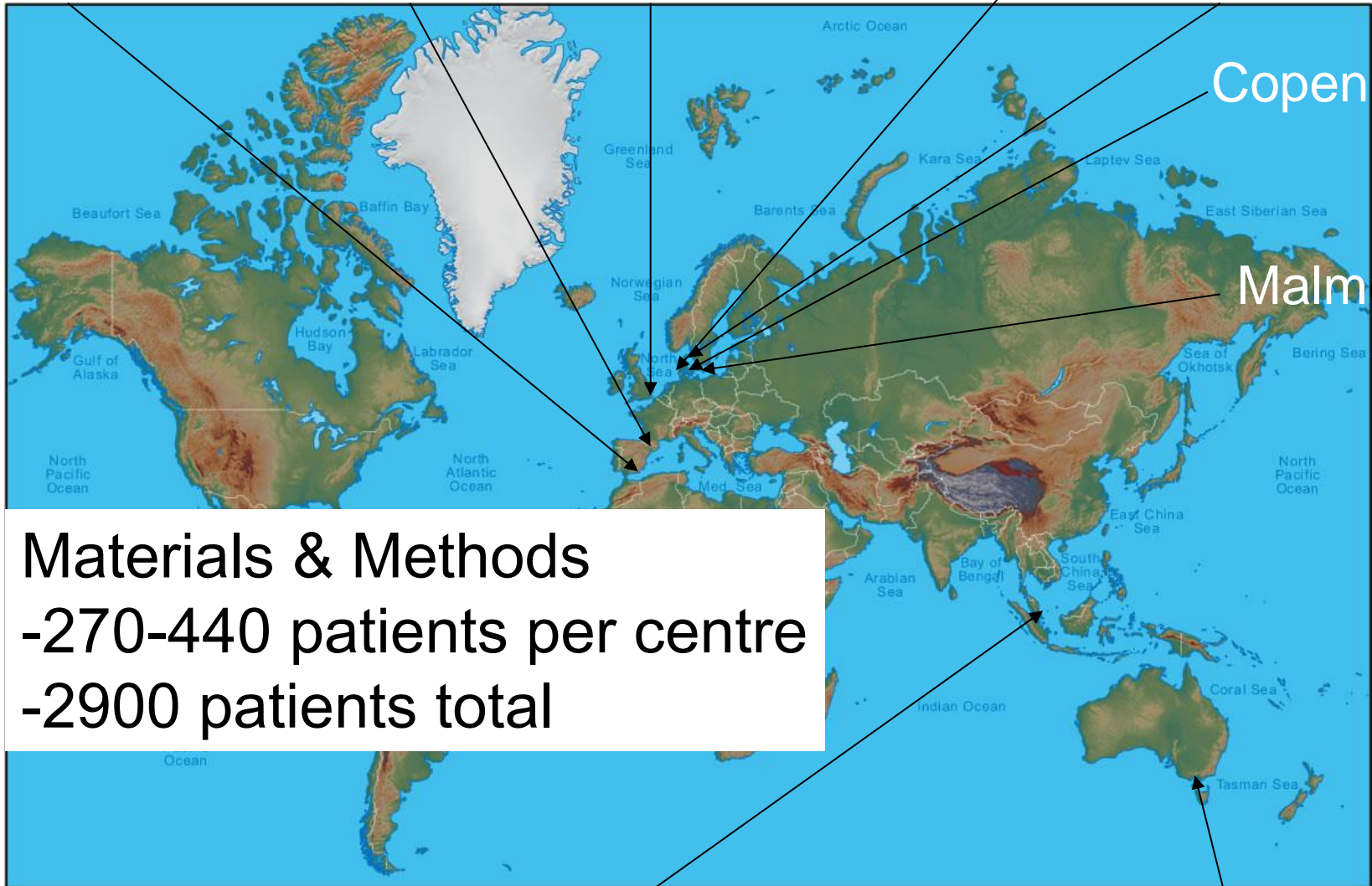
Sevilla

Barcelona

London

Odense

Göteborg



Copenhagen

Malmö

Materials & Methods  
-270-440 patients per centre  
-2900 patients total

Singapore

Melbourne

# Ox linalool 6% containing Lin-OOHs 1% pet.

- Test preparation: defined from main allergen content
- Carefully controlled test preparation
- Good stability of test material:
  - Several different handling situations: analyzed before study
  - Analyzed after 4 months normal use → stable

Results ox linalool 6% containing Lin-OOHs 1% pet.

Tested	Positive
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2900	200
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%	6.9%
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range	(3-14%)
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# Results ox linalool 6% containing Lin-OOHs 1% pet.

	n tested	Pos	Judged relevant to patients' dermatitis (present or past)?
Seville	300	14%	In 35%
Singapore	306	12%	In 21%
Melbourne	298	8%	In 33%
Odense	306	8%	In 12%
London	271	5%	In 50%
Copenhagen	440	5%	In 66%
Göteborg	398	4%	In 47%
Barcelona	300	4%	In 73%
Malmö	300	3%	In 10%

Linalool declared in products used in dermatitis area

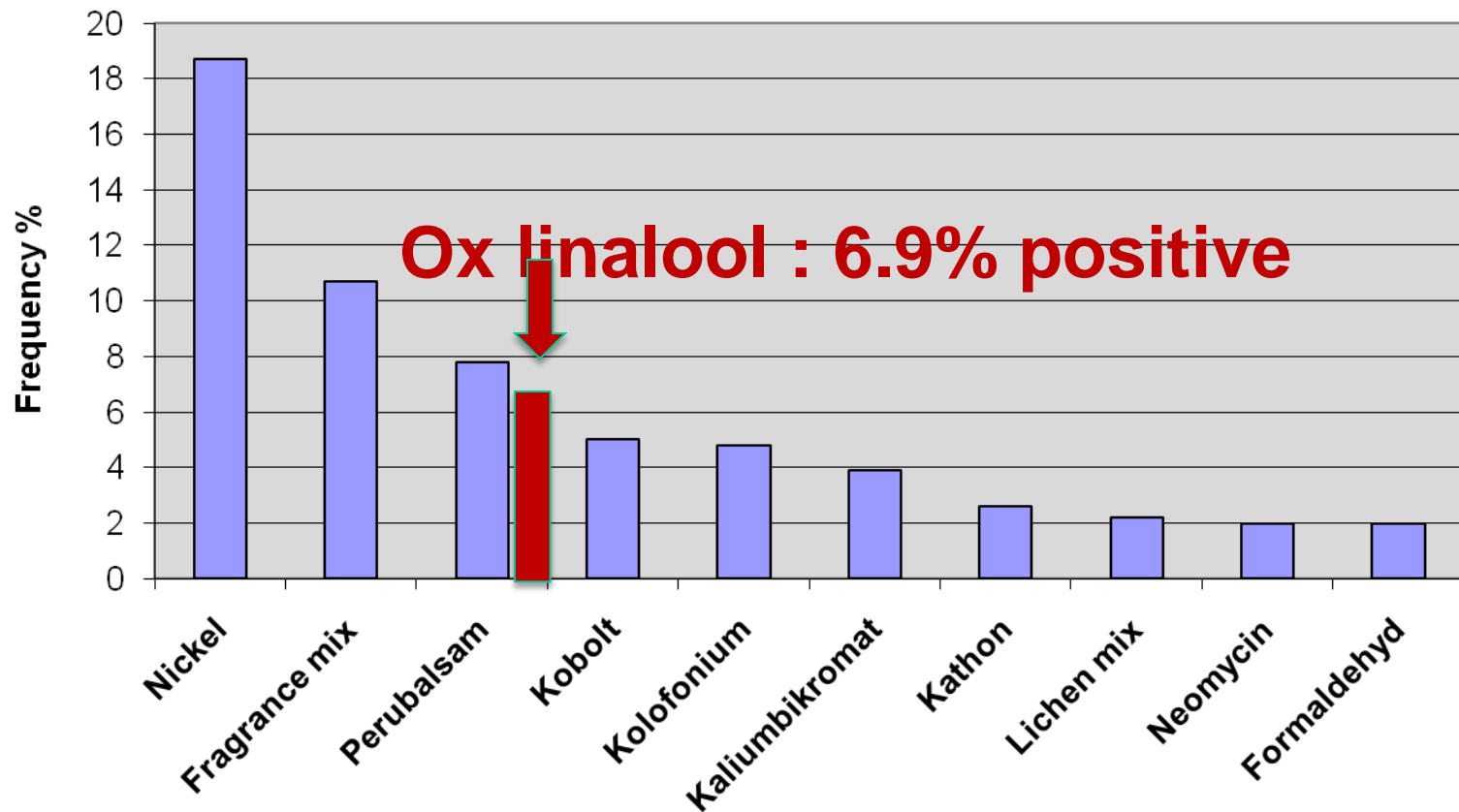
Results ox linalool 6% containing Lin-OOHs 1% pet.

Tested	Positive
2900	200
%	6.9%
range	(3-14%)

40% of pos had reaction to other fragrance marker and/or colophonium

# Discussion

## Top 10 allergens



# International multicentre study oxidized limonene

- *Contact Dermatitis* 2013; 68:214-223
- Klaus E Andersen, Magnus Bruze, Jeanne Duus Johansen, Begoña Garcia-Bravo, Ana Gimenez Arnau, CL Goh, Rosemary Nixon, Ian R White, Johanna Bråred Christensson



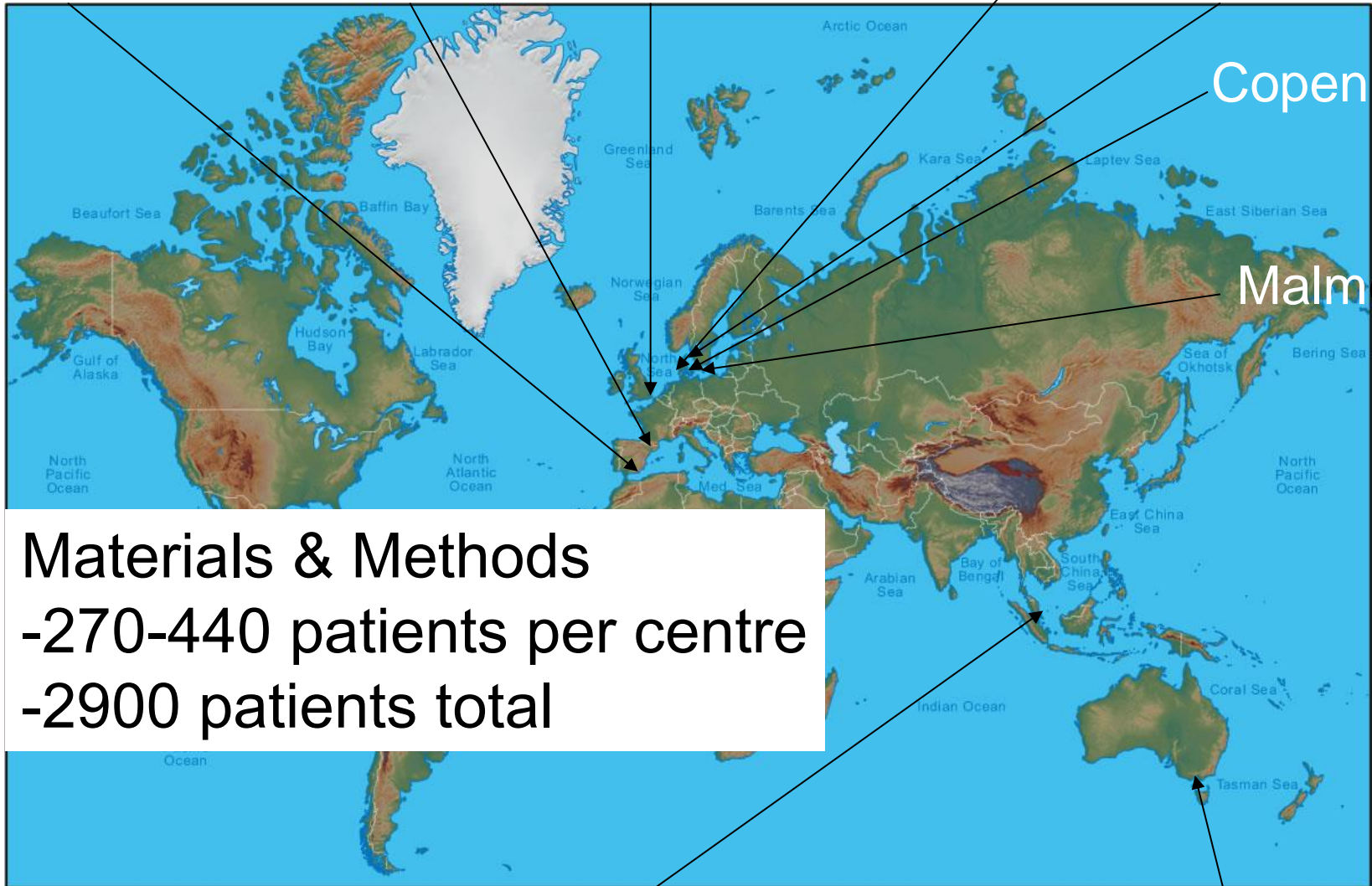
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Materials & Methods  
-270-440 patients per centre  
-2900 patients total

Singapore

Melbourne

# Ox limonene 3% containing Lim-OOHs 0.33% per

- Test preparation: defined from main allergen content
- Carefully controlled test preparation
- Good stability of test material:
  - Several different handling situations: analyzed before study
  - Analyzed after 4 months normal use → stable

Results ox limonene 3% containing  
Lim-OOHs 0.33% pet.

Tested	Positive
2900	152
%	5.2%
range	(2-12%)

# Results ox limonene 3% containing Lim-OOHs 0.33% pet.

	n tested	Pos	Judged relevant to patients' dermatitis (present or past)?
Seville	300	7%	In 40%
Singapore	306	12%	In 8%
Melbourne	298	6%	In 46%
Odense	306	8%	In 20%
London	271	3%	In 16%
Copenhagen	440	4%	In 71%
Göteborg	398	2%	In 43%
Barcelona	300	4%	In 70%
Malmö	300	3%	In 0%*

Limonene declared in products used in dermatitis area

\*No declared contact with oxidized limonen. In judging relevance, it was not considered enough to have contact with products containing limonene

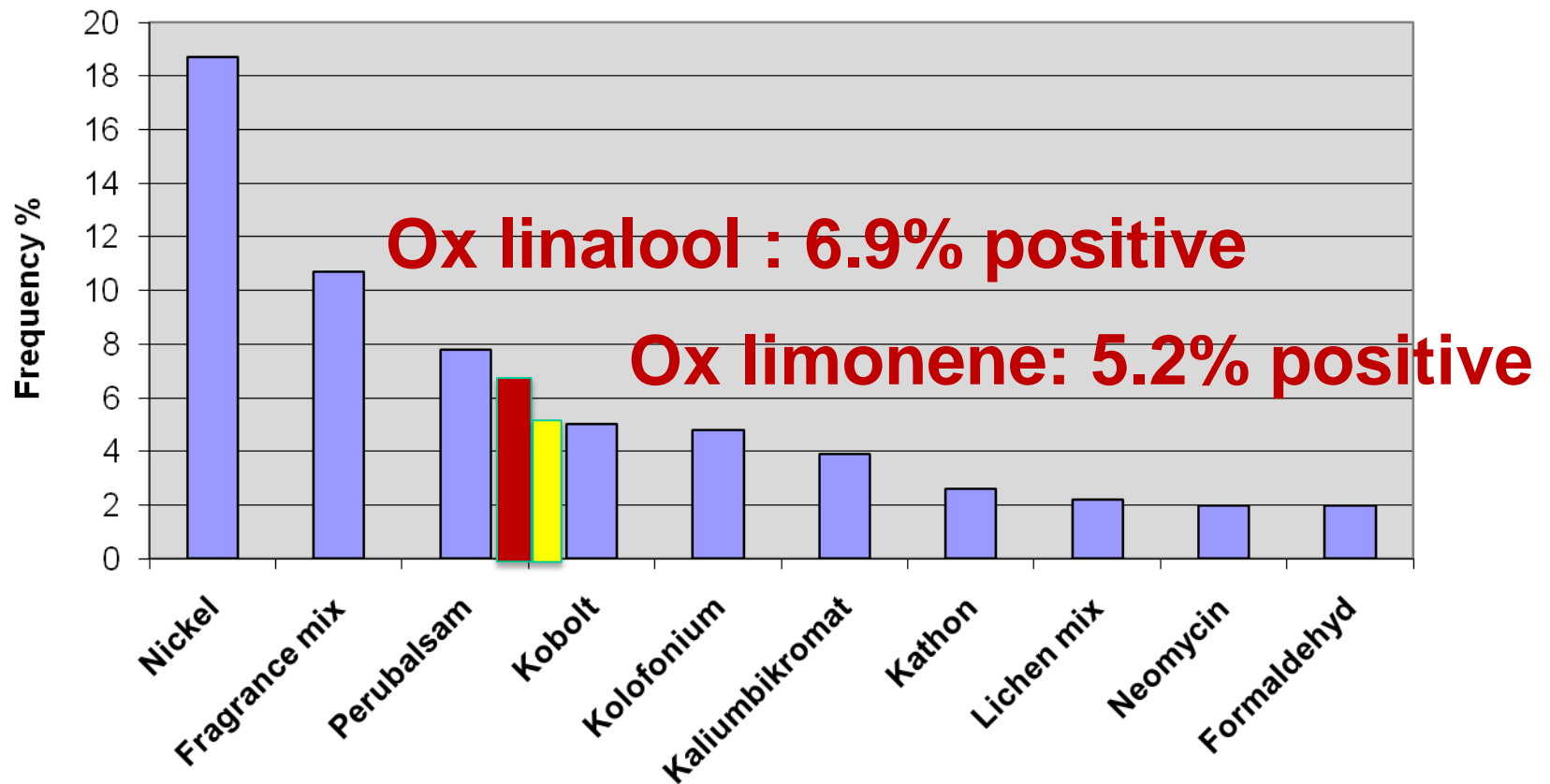
Results ox limonene 3% containing Lim-OOHs 0.33% pet

Tested	Positive
2900	152
%	5.2%
range	(2-12%)

42% of pos had reaction to other fragrance marker and/or colophonium

# Discussion

## Top 10 allergens



## Discussion/conclusion

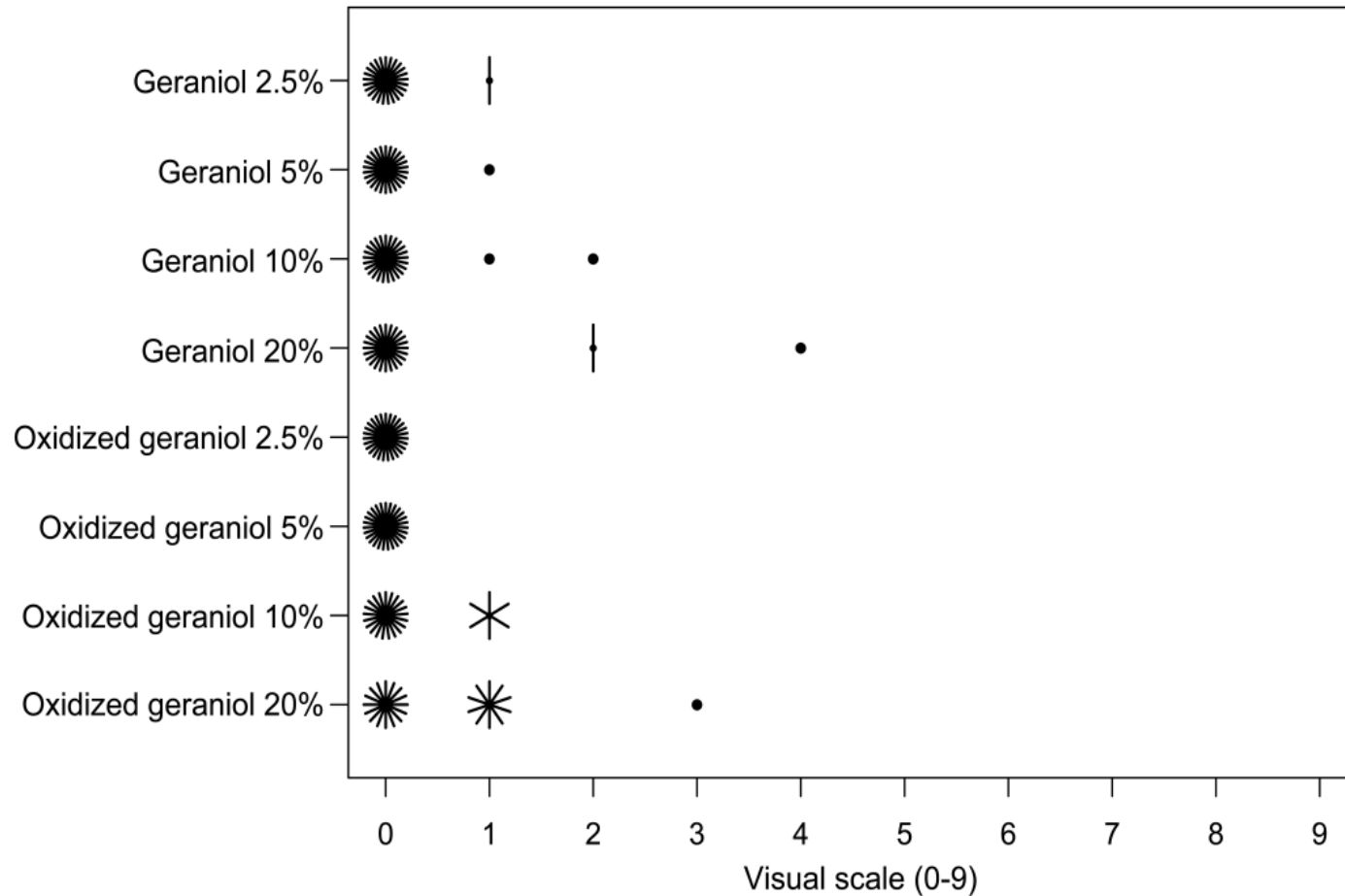
- Ox linalool and ox limonene are frequent causes of fragrance contact allergy
- Standardized patch test material is available
- Important to consider air oxidation
- Important to standardize ox patch test material
- Further work → ox linalool and ox limonene in baseline series? → improve diagnostic tools & information to patients

## Finding the optimal test material and patch test concentration to detect contact allergy to geraniol

- Hagvall et al. *Contact Dermatitis* 2013: 68: 224-231
- Geraniol in FM I, citral in FM II
- Irritation studies pure and oxidized geraniol 2.5%-20%
- Patch testing pure and oxidized geraniol at 4.0%, 6.0%, 11.0% in 650 consecutive patients



# Pure and ox geraniol gave very little irritation



Visual scale: Basketter et al. Contact Dermatitis 1997; 37: 218-220  
Hagvall et. al. Contact Dermatitis 2013; 68, 224-231

# Tested concentrations of pure and oxidized geraniol

<b>Testberedning</b>	<b>No tested</b>	<b>Positive %</b>	<b>Doubtful %</b>
<b>Geraniol 4.0%</b>	655	<b>0.1</b>	0.5
<b>Geraniol 6.0%</b>	649	<b>0.5</b>	0.5
<b>Geraniol 11.0%</b>	655	<b>1.1</b>	0.8
<b>Oxidized geraniol 4.0%</b>	655	<b>0.9</b>	0.8
<b>Oxidized geraniol 6.0%</b>	655	<b>2.3</b>	2.4
<b>Oxidized geraniol 11.0%</b>	653	<b>4.6</b>	4.9

# Clinical observations and report of 14 cases (positive reactions to ox geraniol or its oxidation products)

Exposure and relevance assessments:

- 6/14 present relevance. 4 of 6 work as masseurs. 2 of these 4 also allergic to ox linalool and ox limonene
- 5/14 probable relevance
- 3/14 unclear relevance

**Definition of present relevance:** Use of products with declared content of actual haptens on the site of exposure. Positive test reactions to the products and/ or improvement in eczema when not using the products.

# Repeated Open Application Test: conclusions

- Oxidized linalool can give reactions at low concentrations in allergic individuals if applied repeatedly

To be published

# Overall conclusions

- Oxidized fragrance terpenes give high rates of positive patch test reactions in dermatitis patients
- Oxidized linalool can give reactions at low concentrations in allergic individuals if applied repeatedly
- Hydroperoxides identified in essential oils and products
- High extent of clinical relevance reported

Thank you to:

Klaus E Andersen, Magnus Bruze, Jeanne Duus Johansen, Begoña Garcia-Bravo, Ana Gimenez Arnau, CL Goh, Rosemary Nixon, Ian R White and co-workers

Ann-Therese Karlberg

Lina Hagvall, Ylva Andersch Bkörkman, Mihaly Matura, Anna Börje, Maria Sköld, Katarina Emilsson, Pia Forsström, Marie Norbäck

Charlotte Siwmark, Bo Niklasson

**Thank you for your attention!!**