Feasibility of a Study to Assess the Effectiveness of the QRA

Fragrance Considerations on Feasibility

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Objective

To determine the efficacy of the QRA.

QRA is aimed at the prevention of induction of skin sensitisation to fragrance materials present in consumer products.

- Unique challenge
- Diverse knowledge set needed
  - Clinicians, Risk assessors, Epidemologists (expertise in evaluation of public health interventions), Statisticians, Market knowledge
- Care and clarity in design and interpretation
- Have broad stakeholder agreement

Intervention

Evaluation

- Scope
- Which QRA
- Baseline data
- Controls
- Ingredients
- Population and Locations
- What is measured and how
- Time needed
- Study design
- Evaluation criteria Success and Failure Parameters

Scope
What QRA does and does not cover

- IFRA members supply 90% of the global market for fragrance compounds in **consumer goods** (source: IFRA).

IFRA Standards (QRA) Cover	IFRA Standards (QRA) Do not Cover
IFRA members	Non-IFRA members
Cosmetics	Occupational exposure (Hairdresser, Health worker)
Detergents	Pharmaceuticals
Air and Home care	Aromatherapy/Massage/SPA etc
Controlled consumer goods (90%?)	Natural exposures
	Uncontrolled consumer products (10%?)

Scope

Global market profile of some substances

Substance	«Fragrance»* use	Other use sectors
Cinnamaldehyde	less than 10%	Natural. Flavours, food, fungicide, industrial (e.g. corrosion inhibition)
Cinnamic alcohol	90%	Natural.
Citral	40 to 50%	Natural. Usage as intermediate for vitamin A , feed and food industry
Eugenol	50%	Natural. Pharma industry, Dentistry, Tobacco flavour, antioxidant for rubber and plastics
Isoeugenol	100%	
HICC	100%	
Coumarin	90%	Tobacco
Farnesol	Unknown	Natural. Flavour tobacco, pesticides
Geraniol	100%	Natural
Hydroxycitronellal	100%	
Limonene	20%	Natural. Painting industry, industrial cleaning and degreasing, insecticide
Linalool	100%	Natural

*Note fragrance use includes sectors not covered by IFRA and QRA and % given does not include natural exposures via indirect sources (e.g. essential oils)

Scope

«Traditional» therapies

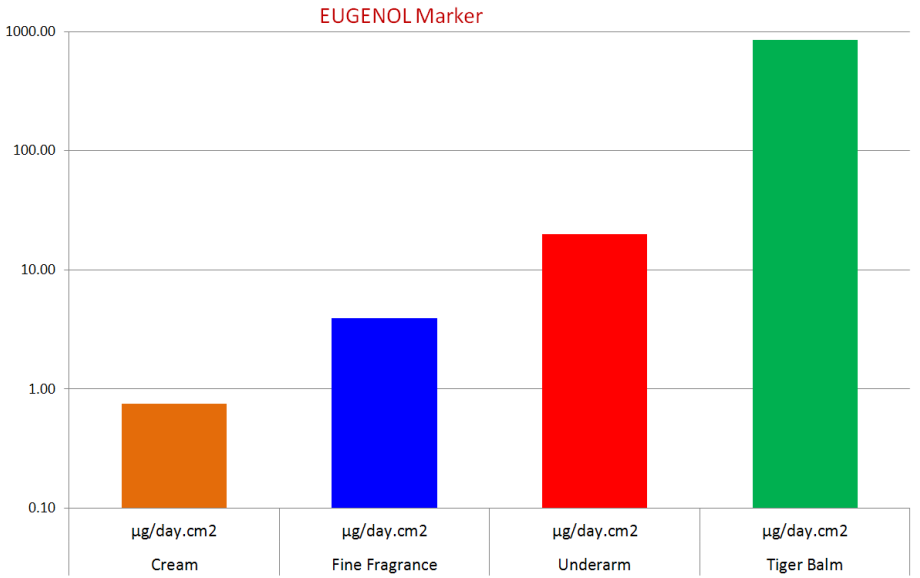
TIGER BALM: SAFE, FAST, AND EFFECTIVE TOPICAL PAIN RELIEF WITHOUT THE PILLS©

Don't let the strains and sprains of work, play, and everyday life hold you back.

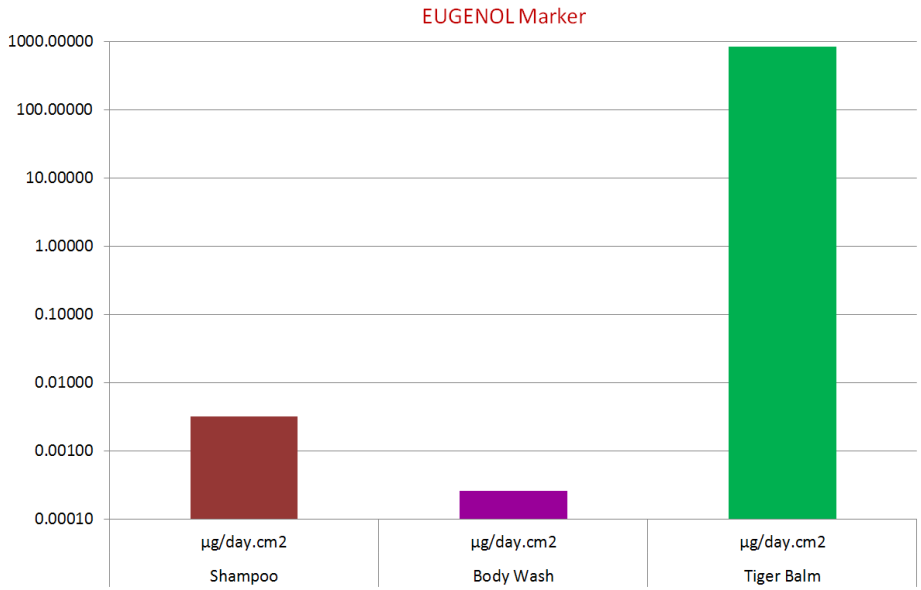
The time-proven blend of herbal ingredients in Tiger Balm provides safe and effective topical pain relief without the pills for sore muscles, arthritis, neck and shoulder stiffness, and just about any other minor muscle or joint aches or pains that may come your way.

Try it and see why millions of people around the globe say, "Get me my Tiger Balm!"

	Formula Baume du Tigre Liquide *
	%
Camphre	11
Menthol	10
Cajeput Oil	7
Clove Oil (75% Eugenol)	5
Mint Oil	6
Cinnamon Oil (76% Cinnamic Aldehyde)	5
Light Parrafin	q.s.



Log Scale



Scope

Pharmaceutical products

Contact Dermatitis 2009: 60: 303–313
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CONTACT DERMATITIS

Allergic contact dermatitis from fragrance components in specific topical pharmaceutical products in Belgium

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Table 2. The 48 fragrance-containing topical pharmaceutical products marketed in Belgium, found to be responsible for iatrogenic allergic contact dermatitis in 127 patients, along with their pharmacological activity and the fragrance ingredients present[a]

Topical pharmaceutical product (number of patients reacting)	Company	Application	Fragrance ingredients
Mycolog (cream)[b] ($n = 34$)	Sanofi-Aventis, Diegem	Antibiotic–corticosteroid	'Perfume'
Fastum (gel) ($n = 19$)	Menarini, Zaventem	Anti-inflammatory (NSAID)	Lavender oil, neroli oil
Flexium (cream) ($n = 9$)	Melisana, Brussels	Anti-inflammatory (NSAID)	Benzyl alcohol, eucalyptus oil, pine needle oil
Dermophil Indien (ointment) ($n = 5$)	Couvreur, Brussels	Wound healing	*Myroxylon pereirae*, rose oil
HAC (solution) ($n = 5$)	SSL Healthcare Belgium, Groot-Bijgaarden	Antiseptic–disinfectant	Benzyl benzoate, terpineol
Cicatrisan (ointment) ($n = 4$)	Unda, Brussels	Wound healing	*Myroxylon pereirae*
Calendula (ointment) ($n = 4$)	Unda, Brussels	Wound healing	Rose oil
Homeoplasmine (ointment) ($n = 3$)	Unda, Brussels	Wound healing	Benzoin, benzyl alcohol
Newderm (ointment) ($n = 3$)	Wolfs, Sint-Niklaas	Wound healing	Geranium oil
Polyseptol (ointment) ($n = 3$)	Qualiphar, Bornem	Antibiotic	Bergamot fruit oil, geranium oil
Borostyrol (solution) ($n = 2$)	A.C.P., Brussels	Wound healing	Benzoin, bergamot fruit oil, menthol, thymol
Phenergan (cream) ($n = 2$)	Sanofi-Aventis, Diegem	Antihistaminic	Lavender oil
Reparil (gel) ($n = 2$)	Madaus, Brussels	Anti-inflammatory, vascular disorders	Lavender oil, neroli oil
Madecassol (cream) ($n = 2$)	Bayer, Brussels	Wound healing	Geranium oil, lavender oil
Anusol (ointment) ($n = 2$)	Pfizer Consumer Health, Brussels	Antihaemorrhoids	*Myroxylon pereirae*
Hibitane (cream) ($n = 2$)	SSL Healthcare Belgium, Groot-Bijgaarden	Antiseptic–disinfectant	Pine needle oil
Oxyplastine (ointment) ($n = 1$)	Bournonville Pharma, Brussels	Wound healing	*Myroxylon pereirae*
Murazyme (ointment) ($n = 1$)	Grünenthal, Sint-Stevens-Woluwe	Wound healing	Lavender oil
Biogaze HN (bandage) ($n = 1$)	OJG Cons Care, Sint-Martens-	Wound healing	Niaouli oil

Scope

Occupational exposures

Table III. *Leading allergens in healthcare personnel. II: Relative risks of sensitization in different occupations. The "occupational pattern" of an allergen is given in the rows, the "sensitization pattern" in the columns.*

Allergens	Nurses (f)	Receptionists (f)	Med. lab. Workers (f)	Dental Nurses (f)	Dental Techn. (f+m)	Dentists (f+m)	Physicians (f+m)	Masseurs (f+m)
Nickel	1.1	**1.3***	0.9	1.0	0.9	0.9§	**0.7***	1.1
	0.98 1.23	1.04 1.62	0.7 1.16	0.74 1.36	0.64 1.27	0.47 1.7	0.5 0.97	0.8 1.5
Fragrance	**1.2***	1.1	1.0	0.9	0.6	0.8§	0.9	**1.5***
	1.05 1.43	0.76 1.57	0.67 1.48	0.55 1.47	0.3 1.2	0.3 1.9	0.6 1.3	1.04 2.16

- e.g. Buckley et al 2002
  - Health care workers and metalworkers – eugenol
  - Food handlers – cinnamic aldehyde and cinnamic alcohol

Scope

Natural Exposures – some examples

- ACD to Geraniol and Citral reported from cooks and bartenders handling Citrus fruits (Cardullo et al, 1989; Swerdlin et al 2010)

- Limonene a major ingredient found in citrus fruits. Peeling One Orange Per Day is Equivalent to:
  - 35 Sprays of a cologne type fragrance at 5 % in Alcohol
  - 140 Sprays of a modern women's fragrance at 12 % in alcohol
  - 170 Sprays of a masculine woody fougere at 8 % in alcohol

- Cinnamic aldehyde
  - CINNAMOMUM SPECIES 13000 - 750000 ppm
  - Cinnamon bark oil 740000 - 750000 ppm
  - Cinnamon leaf oil 13000 ppm
  - CINNAMON ROOT BARK (Cinnamomum zeylanicum Blume) 39000 ppm
  - CITRUS FRUITS ca 100 ppm
  - LEMON BALM (Melissa officinalis L.) 0 - 19000 ppm

Scope
Counterfeit and Piracy

OECD report «The economic impact of counterfeiting»

- "The (perfume) industry estimated their losses in 1996 at **more than 5 per cent of annual turnover** and spent on average 1 to 2 per cent of their annual turnover in combating the illicit trade (Comité Colbert, 1997). According to a 1995 survey by the French Institute of Industrial Statistics (Service des Statistiques Industrielles, SESSI), **more than 80 per cent of French perfume companies have experienced problems with counterfeiting**."

- **Health and safety.** Counterfeiters and pirates have limited interest in ensuring the quality, safety or performance of their products. This increases the potential of negative effects on consumers. Concerns about this appear frequently in the responses to the OECD surveys. The industries where health and safety effects tend to occur include: automotive, electrical components, food and drink, chemicals, **toiletry and household products**, pharmaceuticals and tobacco products.

Conclusions on Scope

We are operating in sector where exposure not controlled by IFRA members (i.e. non QRA) can be significant. In order to ensure the integrity of a study looking at effectiveness of QRA on prevention of induction it is recommended:

- Any study design needs to ensure the exposure (source of induction) is known and can be related to the use of a consumer product where QRA has been applied
  - Body site and current relevance to (A)CD (elicitation) would not provide unquestionable information on induction (QRA) unless induction exposure parameters are known

- Evaluation of synthetic substances used exclusively by IFRA members can help limit uncertainty around other sources of sensitisation induction

Which QRA?

- QRA 1 has been implemented stepwise by IFRA since 2006
- Underwent significant review during 2014 and 2015
  - SAFs, Aggregate exposure, pre/pro haptens
- QRA 2 now available with different (lower) use levels for some significant categories
  - Underarm (e.g. deos)
  - Hands exposure (e.g. creams)

- Timing issue
  - Once standard issued: Compliance time - Reformulation 14 months, New products immediate
  - Shelf life variable but minimum durability may be as long as 36 months
  - New fragranced products in development take 12-18 months to reach shelves

Which QRA?

Is the QRA really being tested?

- Majority of fragrance ingredients are not used up to maximum QRA limits in consumer products

- Reliance on general consumer products therefore does not allow test of whether maximum upper limit use levels from QRA are safe or not

Conclusions on which QRA

- QRA II is the most appropriate starting point as accounts for aggregate exposures, modified SAFs, will include pre/pro haptens etc
  - Market dynamics mean product reformulations to shelves and consumer use takes many years

- To truly test the QRA one would need to use products with an ingredient(s) incorporated at maximum upper limit use levels from QRA

Ingredients and Use of Controls

- Ingredient that are sensitisers and can be risk managed by QRA
  - Linalool Peroxide and Limonene Peroxide are not relevant to QRA evaluation
  - Oakmoss and Treemoss controlled by impourity limit not QRA
  - Balsam of Peru not controlled by QRA and quality in patch test not used in fragrances
  - HICC not controlled by QRA and now very limited in use
  - Eugenol, Isoeugenol, Cinnamic aldehyde use limits not fully QRA due to «IFRA capping» at previous restriction when below QRA limits
  - Sufficient information to establish a NESIL

- Ingredients where cross reactivity to other ingredients is not suspected
  - E.g. issue with cinnamic alcohol and ketoprophen

- Contribution to exposure from other sources is limited
  - See scope discussion

Which ingredients to study?

- Non sensitising control(s) should be included in a study
  - e.g. Phenyl ethyl alcohol, other?

- New Substance
  - If taking general consumer use then time to significant market penetration is long
  - Likely not used at maximum QRA levels
  - Much more appropriate for a targeted and controlled clinical study

- Existing Substance
  - Problem with knowing when/where induction occured
  - Some attempts made in past – e.g. Cyclal C – no significant reactions found
  - Likely currently not used at maximum QRA levels

Other considerations

Population and Location(s)

General vs. Patient?

EU only, USA as well?

Method(s) used

Patch test (standardised), Is clinical relevance important?

Does ROAT have a role?

Statistical considerations

Sample size

Definitition of outcome relevance parameters

Time frame

General population vs controlled clinical study

Schnuch analysis

Baseline

What, when and how is this set?

Market dynamics

Socio-economic factors

Are there alternative approaches to testing QRA?
Example – Controlled clinical (cohort) study

- **A bespoke set of panellists gets enrolled by a CRO**
- **They will be patch-tested for certain allergen(s)**
- **Only negative patch-tested panelists will continue with the main study**
- **They will get to use products that have a certain allergen included at QRA2 maximum allowable level**
- **They will use the prescribed product(s) according to their typical habits**
- **They will have to record the usage of the products, and products get weighed from time to time**
- **After a defined time, the panelists will get patch-tested for the bespoke allergen(s) again**

Conclusions

- The clinical prospective studies proposed would provide a measure of levels of contact dermatitis to substances found in fragrances in general and/or clinical population and may provide information on general effectiveness of risk management efforts (if confounding factors are fully considered) but cannot directly provide evidence of effectiveness of QRA

- A targeted controlled clinical study would allow control over confounding factors and would be a true test of QRA ability to prevent induction

- Both studies could provide complementary information but would not achieve the same goal – the goals, scope and limitations must be clearly stated

- A broad expertise must be consulted and included in next steps for development of protocol(s), criteria, definition of scope of outcome etc

Intenational Dialogue for the Evaluation of Allergens

Thank you

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