Opinion on QRA
SCCP 24 June 2008

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NATIONAL ALLERGY RESEARCH CENTRE

EUROPEAN COMMISSION

Health & Consumer Protection
Directorate-General

Scientific Committee on Consumer Products

SCCP

OPINION ON

Dermal Sensitisation Quantitative Risk Assessment (Citral, Farnesol and Phenylacetaldehyde)

Scientific Committees
on consumer products
on emerging and newly identified health risks
on health and environmental risks

The SCCP adopted this opinion at its 16th plenary of 24 June 2008

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Background

Many commonly used fragrance substances have a well-known sensitization potential.

Necessary to establish concentration limits below which they do not pose a danger for consumers

IFRA submission of documents to The Commission on the QRA approach

Submission

Dermal Sensitization Quantitative Risk Assessment (QRA) For Fragrance Ingredients

Technical Dossier
March 15, 2006

Revised May 26, 2006

Revised June 22,2006

QRA Expert Group
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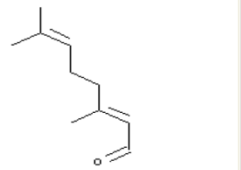
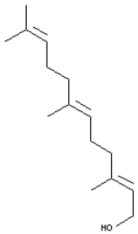
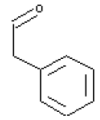
CITRAL

Citral	
CAS No.	5392-40-5

Farnesol

Farnesol	
CAS No.	4602-84-0

Phenylacetaldehyde

Phenylacetaldehyde	
CAS No.	122-78-1

Terms of reference

2. TERMS OF REFERENCE

The SCCP is requested to critically review the QRA methodology to answer the following questions:

1. *Taking into account the description of the methodology as well as the application to three example fragrances (Citral, Farnesol, Phenylacetaldehyde), does the SCCP consider the QRA approach appropriate to assess the sensitisation potential of fragrance substances in cosmetic products and set use restrictions on the basis of these calculations?*

2. *Could this approach also be used for assessing the risk posed by sensitising cosmetic ingredients other than fragrances?*

3. *If the answers to questions 1 and/or 2 are negative, can the SCCP identify additional scientific work (data generation, method development) that would support the use of the Dermal Sensitisation QRA approach for fragrances and/or other sensitising cosmetic ingredients?*

Introduction

IFRA standards

Most concerns sensitization

Historically:

1/10 of no-effect concentrations determined in experimental sensitization assays, such as Human Repeated Insult Patch Test

(Grundschober 1998; Api 2002).

New models

Based on:

Predicted no effect levels of sensitization from experimental models

Safety factors

Exposure assessment

(Robinson 2000, Gerberick 2001, Felter 2003)

Assessment

I. Target population
II. Dose-response assessment or hazard quantification
III. Sensitization assessment factors (SAFs)
IV. Exposure assessment
V. Risk characterization
VI. Confirmation of predicted use levels for fragrance ingredients
VII. General discussion/summary
VIII. Conclusion

I.a Target population

QRA-expert group:

The proposed dermal sensitisation risk assessment model (QRA) deals with the sensitisation phase only and is not targeting allergic contact dermatitis and its prevention (I/p.10).

Comments by SCCP
The model does not consider protection of consumers, who have already been sensitized to fragrance ingredients. Epidemiological data show that allergic contact dermatitis is frequent in the general population and that fragrances are one of the leading causes *(Schäfer 2001; Mörtz 2001)*, e.g. it is estimated that 1.4 -3.4 million Germans are sensitized to fragrance ingredients *(Schnuch 2002)*.

I.b Target population

QRA-expert group:

'Dermal sensitization risk assessment for fragranced consumer products is conducted for healthy skin and not on diseased skin. While individuals with diseased skin (e.g. psoriasis and eczema) may use regular consumer products, it can be assumed that at least some of these individuals may be under the care of a dermatologist' (I/p.23).'

SCCP:

It is not entirely clear whether the model covers individuals with diseased skin such as hand eczema and psoriasis. Hand eczema affects about 10% of the general population and is a chronic relapsing disease *(Meding 2005; Hald 2008)*, in Scandinavia 2/3 have seen a general practitioner and about 40% have seen a dermatologist at some time *(Meding 2005;Hald 2008)*. This may be different in other countries. About 2% of the population suffers from psoriasis *(Schäfer T, 2006)* and 15-20% of the younger part of the population from atopic dermatitis, some of these with hand eczema *(Mörtz 2001)*.

The proposed model seems not to take account of that significant proportion of the population who suffers from skin disease (e.g. dermatitis). For this important sub-population, an additional, scientifically justified, safety factor might be required.

II. Dose-response assessment or hazard quantification

QRA-expert group:

'No Expected Sensitizing Induction Level (NESIL) may be derived from animal and human data'.

'The dose response for induction of skin sensitization is typically determined in the first instance using animal assays such as the Local Lymph Node Assay (LLNA)' (I/p.12.) A human sensitization test is not used to determine hazard, rather it is a test to confirm the lack of sensitization at an exposure level which was identified as a NOEL in an animal model or derived as a likely NOEL from quantitative structure activity relationships' (I/p. 14).

Historically predictive human skin sensitization tests have been used for testing substances with unknown toxicological profile to detect sensitizers *(Draize 1944; Marzulli 1973/80; Kligman 1975).*

HRIPT are not identical to real life scenarios. To increase the sensitivity of the test whilst using a panel of 100 volunteers, if appropriate one generally tests a higher concentration of test material and usually more exaggerated exposure conditions than would actually be encountered in intended and foreseeable use situations among the general population *(Politano 2007)*.

Predictive sensitization testing in man, e.g. HRIPT, is considered unethical to conduct as stated by SCCP and in the outcome of a recent WHO-workshop *(SCCNFP 2000; van Loveren 2008)*.

SCCP:

No clear guidance is given in the performance of a HRIPT for the safe choice of test concentrations. It seems that levels that *a priori* may be suspected to sensitize the panel may still be used. The essential methodology of the so called confirmatory HRIPT and the original HRIPT is identical.

Epidemiological information obtained from patients undergoing diagnostic patch testing and from consumers who have developed allergic contact dermatitis to fragrance ingredients is not considered in the model.

III. Sensitization assessment factor

'The SAFs for dermal sensitization risk assessments for fragrance ingredients are specific for this toxicity endpoint and cannot be compared to the values defined for uncertainty factors in general toxicology' (I/p. 28).

Three groups of uncertainty factors are used:

I. A factor of 10 for inter-individual variability is assigned covering (I/p. 23/24):

- Genetic effects such as differences in metabolic activity in the skin
- Sensitive subpopulations e.g. those with multiple allergies
- Inherent barrier function. Healthy skin may have a compromised inherent barrier (e.g. dry skin) and lead to greater susceptibility
- Age. Decreases in the skin barrier function can occur at either end of the age spectrum – pre-term infants and geriatric. Pre-term infants are not normally part of the risk assessment since they are under medical care.
- Gender. No gender differences are assumed
- Ethnicity. No differences are assumed.

Diseased skin?

SAFs

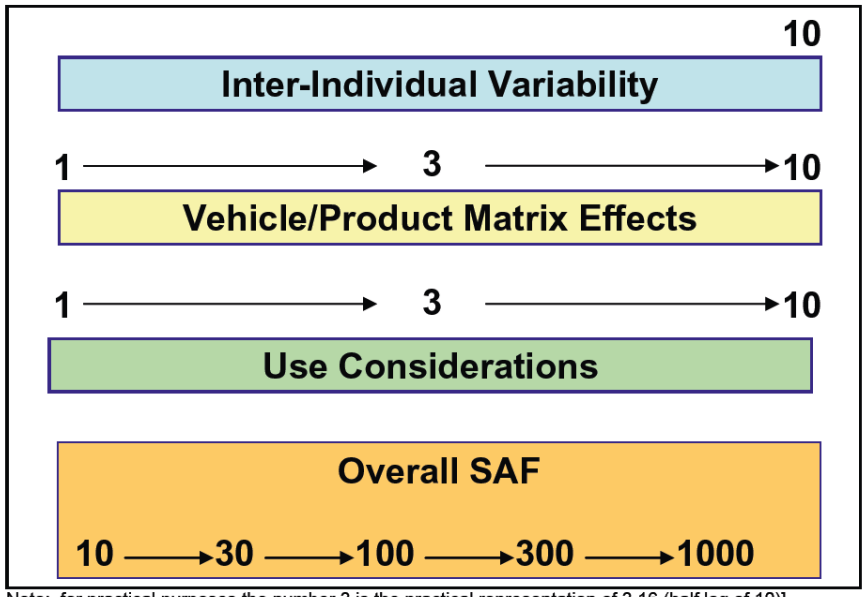
II. Matrix effects. Factors of 1-3 or 10 are assigned and covers (I/p.24/25)

- Differences between the matrix used under experimental conditions and real life exposure. The larger the difference between the experimental situation and real life exposure scenario, the greater the SAF.
- Irritants. Presence of irritants may cause inflammation and may affect thresholds of reaction
- Penetration enhancers. Little is known on the factors that affects the bioavailability of the single fragrance ingredients

III. Use considerations. Factors of 1-3 or 10 are assigned and covers (I/p.26/27):

- Site of contact. Regional differences in absorption are substantial.
- Barrier integrity. Can be influenced by consumer practices e.g. by shaving or dermatitis.
- Occlusion. Increases the hydration of the stratum corneum and may alter the penetration.

SAFs



Note: for practical purposes the number 3 is the practical representation of 3.16 (half log of 10)]

A table is given establishing SAFs for each of 33 product types (Table 2 p. 30-34), ranging from 10 for candle in a jar and closed air fresheners to 300 for e.g. aerosol deodorant. The typical overall SAF is 100. None of the 33 product types are assigned 1000.

Matrix

Examples from table 2 in the Technical dossier (I)		
Product type	Matrix SAF	Rationale
Aerosol antiperspirant	3	Matrix not the same as experimental conditions and may contain active irritating ingredients
Lip products	3	Matrix very different from the experimental test conditions, however not expected to be more irritating
Shaving creams	3	Matrix not the same as experimental conditions and may be designed to enhance penetration. May contain irritating ingredients
Nail care	3	Matrix not the same as experimental conditions, is highly solvent based and expected to be more irritating than the experimental test conditions
Baby cream	3	Matrix for the product is designed to enhance penetration
Hand wash laundry detergent	3	Matrix for the product is very different from experimental conditions and may contain irritating ingredients

A matrix SAF of 3 is assigned to very different product types such as aerosol antiperspirants, hand wash detergents and baby creams covering matrixes different or very different from the experimental conditions and the presence of irritating and penetrating enhancing substances in the products. Only one product type is assigned a matrix SAF 10, which is depilatory.

Table 2: SAFs, rationale and literature references for fragrance ingredients in different product types based on RIFM data.

Product Type	Inter-individual[1-27] SAF	Matrix SAF	Matrix SAF Rationale[6,26,28-32] (experimental** vs. real life exposure)	Use SAF	Use SAF Rationale (experimental** vs. real life exposure)	SAF
Aerosol Deodorant	10	3*	Matrix for the product not the same as the experimental** conditions.	10	The area is the underarm[33]; the skin is easily irritated[34], highly follicular[33] and an area that is shaved[35]. Type of occlusion is similar to that of the experimental** test conditions[36].	300
Hand Cream	10	3*	Matrix for the product not the same as the experimental** conditions and may be designed to enhance penetration.	3	The area is mainly the hands, which may include dry skin[39], there may be compromised skin due to dermatitis[34], but occlusion does not occur.	100
Depilatory	10	10	Matrix is very different from the experimental** test conditions and contains highly irritating ingredients.	3	The area is the underarm, upper part of leg and lower part of the leg[33].	300

SAFs

Under the experimental conditions in HRIPTs, ethanol is usually used together with 75 % diethyl phthalate *(Ford 1998)*. In patch test studies the use of diethyl phthalate has been reported to decrease the response to fragrance allergens *(Frosch 1995)*. It is unknown if this is considered in assigning the SAF for matrix. In the Technical Dossier by QRA expert group (I/p. 29) only emphasis on the presence of ethanol under experimental conditions versus the consumer product matrix is made.

Even though some criteria are given for the SAF assignment, it is a pragmatic approach (I) and the specific scientific justification for each of the 33 product types is weak.

A review of the scientific basis for uncertainty factors for use in quantitative risk assessment has been published by industry toxicologists *(Felter 2002)*. However, scientific consensus in determining safety factors for skin sensitization is yet to be achieved.

IV. Exposures

Aggregated exposures, i.e. the use of several product types containing the substance in question, e.g. use of both liquid soap and hand cream, may be important both for induction and elicitation *(Jensen 2005; White 2007)*. Aggregated exposures are not considered in the dermal sensitization QRA, but should be given priority. Occupational exposures are neither considered and have also been identified as an important area of development of the dermal sensitization QRA.

Structurally similar fragrance ingredients are used together and some may by enzymatic activity be converted into the same resulting allergen *(Smith 2000)*. Derivatives of isoeugenol may be used to an unknown extent together with or instead of isoeugenol *(Rastogi 2008)*. The dermal sensitization QRA model does not take this into account.

V. Risk characterization/limits

Old IFRA standard:

Isoeugenol	Restricted
1998:	0.02%

The QRA model allows:

0.1% in hydroalcoholic products ↑

0.04% for shaved skin ↑

0.01% for deodorants ↓

Out of 33 product categories:

- 25 are cosmetics with skin contact
- in 22/25 (88%) isoeugenol will be permitted in higher concentrations

Isoeugenol is often used in hydroalcoholic products were the permitted concentration will be increased and rarely in deodorants were it will be lowered.

Pragmatic levels

Table 14: Acceptable levels of cinnamic aldehyde in various product types based on QRA.

Product Type	SAF	Exp.	Cinn. Ald.	Maximum Pragmatic Level[1]
Aerosol Air Freshener	100	RIFM	23.6%	5% The maximum concentration will not exceed 5% and may be lower if determined by the QRA.
Bar Soaps	100	SCCP	11.8%	
Body Wash/Shower Gel	100	CTFA	39.3%	
Bath Foams, Gels, Mousses	100	SCCP	59.0%	
Handwash Laundry	100	HERA	5.9%	2.5% The maximum concentration will not exceed 2.5% and may be lower if determined by the QRA.
Hand Dishwashing	100	HERA	59.0%	
Hard Surface Cleaner	100	HERA	4.9%	
Baby Diapers	100	RIFM	100%	
Candles	10	FMA	100%	Due to negligible skin contact, the concentration of fragrance ingredient should not exceed the usual concentration of the fragrance compound in the finished product

Pragmatic levels

The need for using pragmatic levels in addition to the dermal sensitization QRA makes it difficult to use the dermal sensitization QRA as a general toxicological tool. It also questions safety of the levels identified by the dermal sensitization QRA.

The maximum pragmatic level is identical with the usual concentration of a fragrance compound, which is the blend of fragrance ingredients, in the final product. This means that citral as an individual fragrance ingredient cannot exceed the usual concentration of the whole fragrance formula in that product type.

VI. Confirmation of use levels

'An essential element of product risk management is to be able to determine that risk assessment was appropriate or needs further refinement. This can be achieved through monitoring the market place after product launch. Typically this is accomplished for fragrance ingredients through the dermatology community monitoring incidence rates of relevant positive patch tests to fragrance ingredients (p.61).'

N=3223 patients from Leuven, 133 reacting to their own products

Table 27: Identification of the type of product type and positive patch test reactions to cinnamic aldehyde, isoeugenol and citral from the patch test database (Contact Allergy Unit, University Hospital Leuven, Belgium).

Fragrance Ingredient	Product Type	Positive Patch Test Reactions to Product Type
Cinnamic aldehyde	Deodorant products	2
Isoeugenol	Aftershave product	1
	Deodorant product	1
	Hair dye product	1
	Toilet water/perfume products	5
Citral	Toilet water/perfume products	6

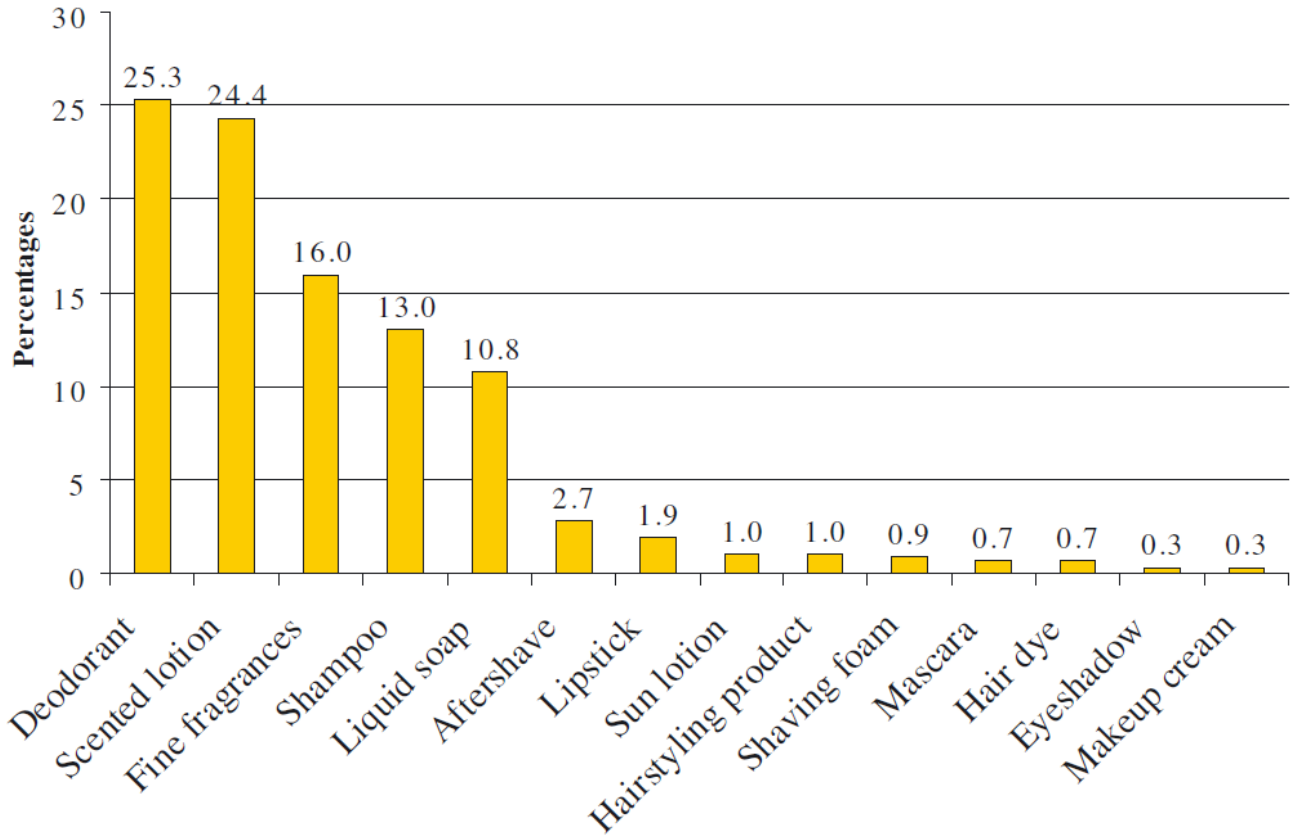
Comments by SCCP

No scientific data is given to support the levels identified by the model as safe for the consumer other than the calculations in the model itself. No validation has been done nor has a strategy been provided. Only one study on 16 reactions to cosmetics is mentioned. A substantial scientific literature on the epidemiology of contact allergy to fragrance ingredients is available *(Frosch 2006)*, but not applied. Most of the substances of concern are existing substances.

Example

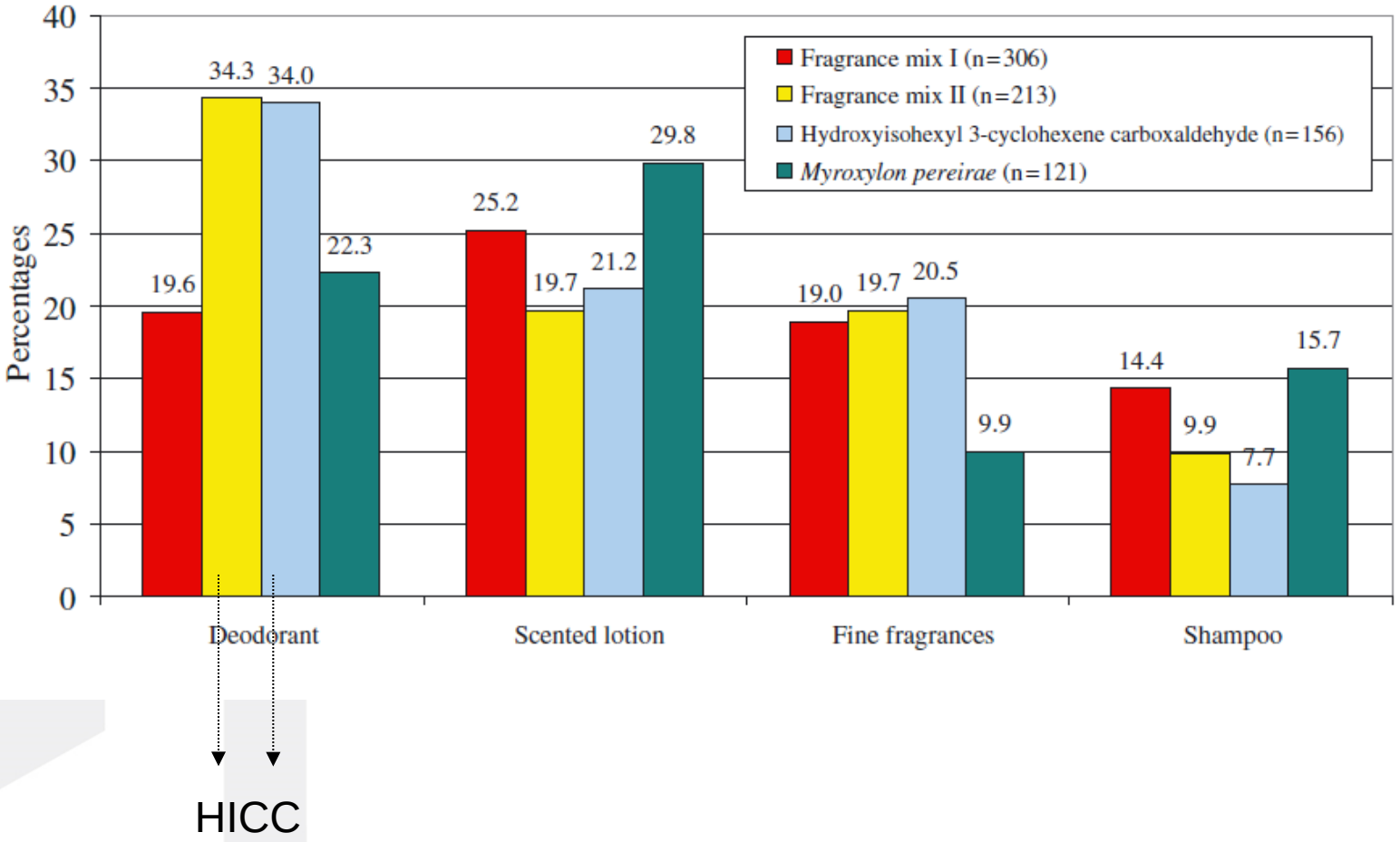
Products which have caused fragrance allergy

Analysis of 17.716 patients ; 10.1% had a fragrance allergy



Heisterberg M et al. 2011

Causative fragrance ingredients



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Heisterberg M et al. 2011

Trend of HICC allergy

Figure 1. Prevalence of positive patch test reactions to hydroxyisohexyl 3-cyclohexene carboxaldehyde over time

Subjects tested 37 860 by the Danish Contact Dermatitis Group

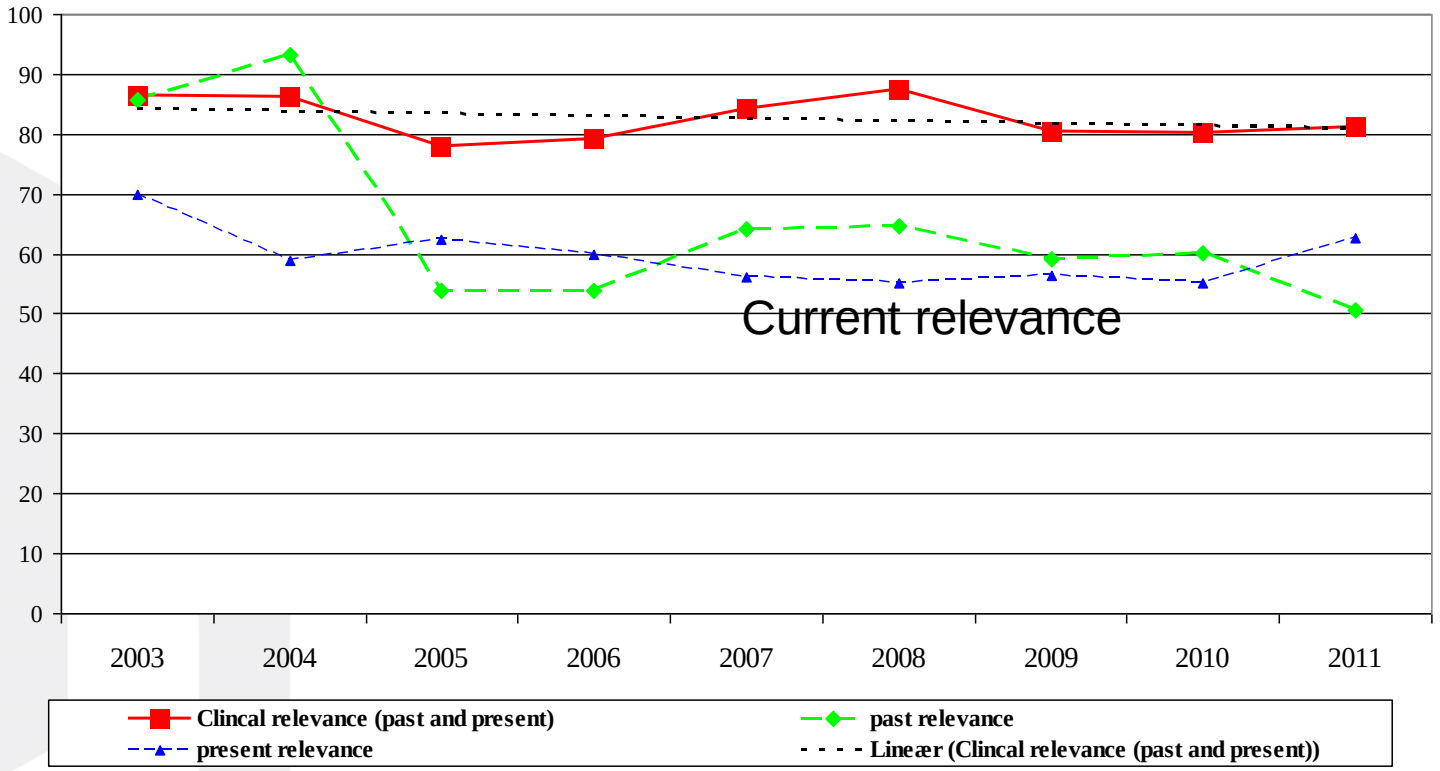
IFRA-limit: 1.5% 0.15% 0.02%

Heisterberg M 2012

Relevant exposures to HICC unchanged

Figure 2. Frequency of clinical relevance of a positive patch test reactions to hydroxyisohexyl 3-cyclohexene carboxaldehyde overtime

N= 928 with a positve patch test



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Summary

- HRIPT lack of in-depths method description
- No clear guidance for the choice of test concentration
- No experience outside industry: reliabilty, sensitivity.
- Ethical concerns

- Does not consider protection of consumers who have already become sensitized
- Unclear how the QRA model covers the substantial part of the population, who suffer from skin disease (SAFs?)

Summary

The QRA does not seem to consider:

The contents of:

- structurally similar ingredients
- cocktails of allergens

- Aggregated exposures (from several product types)
- Occupational exposures

Summary

- No scientific data exist to support the levels as safe for the consumer other that the calculations in the model itself.
- Implementation of the model will allow increased exposure to well-known allergens in most product types compared to the current situation
- Use of pragmatic levels makes it difficult to use out-side industry
- This makes it difficult to have confidence in the model.

Conclusion

Taking into account the description of the methodology as well as the application to three example fragrances (Citral, Farnesol, Phenylacetaldehyde), does the SCCP consider the QRA approach appropriate to assess the sensitisation potential of fragrance substances in cosmetic products and set use restrictions on the basis of these calculations?

The dermal sensitization QRA model is based primarily on data from experimental sensitization tests in humans e.g. Human Repeated Insult Patch Tests (HRIPT). There is a lack of in-depth method description and the experience with this test, its validity, sensitivity and reliability is sparse outside industry. Such experimental sensitization tests in humans are considered unethical to perform.

Epidemiological and experimental data, providing information on sensitization/elicitation reactions in consumers by fragrance ingredients in marketed products, are not integrated in the dermal sensitization QRA model. It is of concern that the model operates with multiple product categories without considering risk from aggregated exposures and that scientific consensus has not been achieved concerning the choice of safety factors. Occupational

Conclusion

Identification of safe levels of exposure to existing substances known to cause allergic contact dermatitis in the consumer should be based on clinical data and/or elicitation low-effect levels. Currently these are the only methods, which have proven efficient in reducing/preventing existing problems of sensitization/allergic contact dermatitis in the consumer.

From a scientific point of view, models like the dermal sensitization QRA approach may, after refinement and validation, in the future be applicable for risk assessment of new substances to suggest a safe level of exposure prior to incorporation into products. In such cases an independent post-marketing surveillance system would be essential.

Aggregated exposures must be incorporated in the dermal sensitization QRA model. Validation must be performed employing a broad range of different chemicals and data from substantial clinical investigations.

Scientific consensus must be obtained, especially concerning the choice of safety factors in the model.

Further development of dermal sensitization QRA models and establishment of scientific consensus are encouraged to improve the risk assessment of new substances for consumer protection.