



EUROPEAN COMMISSION



Health & Consumer Protection  
Directorate-General

## Scientific Committee on Consumer Products

SCCP

### **OPINION ON**

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



The SCCP adopted this opinion at its 16<sup>th</sup> plenary of 24 June 2008

**Opinion on dermal sensitisation quantitative risk assessment  
(citrал, farnesol and phenylacetaldehyde)****About the Scientific Committees**

Three independent non-food Scientific Committees provide the Commission with the scientific advice it needs when preparing policy and proposals relating to consumer safety, public health and the environment. The Committees also draw the Commission's attention to the new or emerging problems which may pose an actual or potential threat.

They are: the Scientific Committee on Consumer Products (SCCP), the Scientific Committee on Health and Environmental Risks (SCHER) and the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) and are made up of external experts.

In addition, the Commission relies upon the work of the European Food Safety Authority (EFSA), the European Medicines Evaluation Agency (EMEA), the European Centre for Disease prevention and Control (ECDC) and the European Chemicals Agency (ECHA).

**SCCP**

Questions concerning the safety of consumer products (non-food products intended for the consumer).

In particular, the Committee addresses questions related to the safety and allergenic properties of cosmetic products and ingredients with respect to their impact on consumer health, toys, textiles, clothing, personal care products, domestic products such as detergents and consumer services such as tattooing.

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[http://ec.europa.eu/health/ph\\_risk/risk\\_en.htm](http://ec.europa.eu/health/ph_risk/risk_en.htm)

## **ACKNOWLEDGMENTS**

Dr. C. Chambers  
Prof. G. Degen  
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**Keywords:** SCCP, scientific opinion, sensitisation, quantitative risk assessment, fragrance, citral, farnesol, phenylacetaldehyde, directive 76/768/ECC

Opinion to be cited as: SCCP (Scientific Committee on Consumer Products), Opinion on dermal sensitisation quantitative risk assessment (citral, farnesol and phenylacetaldehyde), 24 June 2008

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## 1. BACKGROUND

Many of the commonly used fragrance substances in cosmetic products have a well known skin sensitisation potential. In order for these ingredients to be used in commercial preparations, it is necessary to establish concentration limits below which they do not pose a danger for consumers.

The Scientific Committee on Consumer Products (SCCP) and its predecessors SCC and SCCNFP have on several occasions advised the Commission on appropriate restriction levels and other measures like labelling of allergenic fragrances. These restrictions were set taking into account the available scientific evidence and re-evaluating industry use recommendations, especially industry standards set by IFRA<sup>1</sup>.

IFRA has recently developed a new exposure-based methodological approach to assess the sensitisation risks and identify concentration limits for fragrance substances, designated Dermal Sensitisation Quantitative Risk Assessment (QRA).

IFRA has expressed its intention to employ this methodology "*as the core strategy for primary prevention of dermal sensitisation to these materials in consumer products. This methodology will be used to determine global fragrance industry product management practices (IFRA standards) for potentially sensitising fragrance ingredients, the first of which will be implemented in April 2006.*"

As a first step, IFRA submitted to the SCCP three specific cases of perfume ingredients (Citral, Farnesol and Phenylacetaldehyde) assessed by the Dermal Sensitisation QRA approach.

## 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?*

### **3. OPINION**

#### **3.1. Introduction**

Allergic contact dermatitis is a result of a series of immunological events following skin contact with a chemical of low molecular weight. The first step is the sensitization phase or induction, where the immune system is specifically triggered. These changes are permanent. Continued exposure or re-exposure to the chemical in question in sufficient concentrations will give rise to disease: *allergic contact dermatitis*. This part of the immunological process is termed elicitation (*Frosch et al., 2006*).

Fragrance ingredients are among the most frequent causes of allergic contact dermatitis. The majority of cases are caused by cosmetic products (*Frosch et al., 2006*).

In 1973, The International Fragrance Association (IFRA) was created by a group of fragrance manufacturers. IFRA has since then issued recommendations concerning the use of fragrance ingredients in consumer products in the form of IFRA guidelines, later called IFRA standards. These standards contain recommendations either not to use an ingredient or to limit its use by quantitative restrictions based on toxicological effects. Most restrictions in the IFRA standards are the result of skin sensitization potential of individual ingredients (*Grundschober 1998*). The IFRA standards are based on opinions from an expert group under the Research Institute of Fragrance Materials (RIFM), financed by fragrance industry. The main methodology has been to test the fragrance ingredient at ten times the use concentration in a group of healthy human volunteers by a Human Repeated Insult Patch Test (HRIPT). If evidence of sensitization was obtained, the maximum permitted level was determined as one-tenths of the no-effect level (*Grundschober 1998; Api 2002*).

Other more recent attempts have been made by industry toxicologists to develop skin sensitization risk assessment models (*Robinson 2000, Gerberick 2001, Felter 2003*), several using fragrance ingredients as examples. These models are built on three elements: predicted no-effect levels of sensitization under experimental conditions, safety factors and exposure assessment.

The no-effect levels of sensitization are derived from predictive sensitization tests primarily in mice, The Local Lymph Node Assay (LLNA), and/or in healthy human volunteers, e.g. HRIPT.

Experiments have indicated that the crucial determinant of induction is the dose per unit skin and not the total dose (*Friedman 1990*), therefore the no-effect or low-effect level of sensitization under the experimental conditions are determined and expressed in dose/unit skin area e.g. in  $\mu\text{g}/\text{cm}^2$  (*Felter 2003*). In case animal data (LLNA) is used, default values of expected no-effect levels has been suggested based on the potency of the substance (*Felter 2003*). The no-effect or expected no-effect sensitization level (NESIL) is then divided by a set of safety factors ranging from 10-1000 depending on the differences between the experimental situation and the specific use situation of a cosmetic product (*Felter 2002*). This dose has been termed the skin sensitization reference dose (*Gerberick 2001*) or acceptable exposure level (*Api 2007*).

Exposure in dose/unit skin area per day of a specific type of cosmetic product e.g. facial skin cream is calculated and the dose of allergen/unit skin area per day should be below or equal to the skin sensitization reference dose to be considered safe (*Robinson 2000, Gerberick 2001, Felter 2003*). In one model attempts are made also to include data from elicitation (*Griem 2003*). So far none of these models has gained general acceptance.

In cases where control of allergic contact dermatitis has been warranted, regulatory decisions have been based on risk assessment using clinical data and/or elicitation low-

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effect levels e.g. for nickel (*Directive 2004/96/EC*), chromium (*Directive 2003/53/EC*) and for the preservative methyldibromo glutaronitrile (*SCCNFP/0581/02*). This methodology has proven effective in reducing incidence (sensitization) as well as elicitation, that is symptoms in those already sensitized (*Schnuch 2003; Thyssen 2007; Johansen 2008*).

The methodology for dermal sensitization quantitative risk assessment based on expected no-effect levels derived from experiments in healthy human volunteers have been implemented by fragrance industry as a basis of the future IFRA standards. The following assessment concerns this methodology as presented in the technical dossier from the QRA expert group (I), an informational booklet on quantitative risk assessment (QRA) for fragrance ingredients issued by RIFM/IFRA (II) and dossiers of the application of the QRA methodology applied to three fragrance ingredients: citral (III), farnesol (IV) and phenylacetaldehyde (V).

### **3.2. Target population**

*Technical Dossier by QRA expert group (I):*

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).

Further it is stated that:

'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).'

*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*).

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.

### **Dose-response assessment or hazard quantification**

*Technical Dossier by QRA expert group (I):*

'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

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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).

**Human data**

Human sensitization tests, e.g. the Human Repeated Insult Patch Test (HRIPT), are conducted on a sample of healthy volunteers. A series of skin exposures with the test substance is made over a time period, typically followed by a rest period and a challenge. It is stated that the preferred test method to feed the proposed dermal sensitization QRA is the Human Repeated Insult Patch Test (HRIPT) (I/p.17/18).

It is used as a confirmatory test 'to confirm the lack of sensitization at an exposure level which was identified as a NOEL e.g. in an animal model' (I/p.14). However to increase the sensitivity of the confirmatory test, generally a higher concentration of test material is tested than would actually be encountered in intended and foreseeable use situations among the general population (I/p. 14).

**Comments by the SCCP**

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*). Since the 1980s, the methodology of RIFM has reportedly been to use animal assays for hazard assessment followed by a human repeated insult patch test as a confirmatory test of a predicted safe concentration, possibly, if negative, followed by exposure to higher concentrations (*Api 2002*). On the other hand the test conditions in the 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*).

The HRIPT is a modified version of the Draize test described in 1944. This methodology has primarily been used by industry and data kept in-house on file or published as summaries. It is not included in any test guidelines, neither as confirmatory test. Assessments by independent research groups of the methodology or data has not been made for decades. Only recently a description of the current method used by fragrance industry has been published (*Politano 2007*).

**Methodology (Politano 2007):**

*The HRIPT is performed in panels of a least 100 healthy volunteers. A patch of 25 mm containing the test solution is applied to healthy skin on the upper back. The patch is held in place by semi-occlusive tape. Re-application to the same skin site is made for at least 9 times over a 3 week period. After a rest phase of ten to fourteen days a reapplication is made on naïve skin for 24 hours. Readings are made 24, 48 and 72 hours after the application according to a scoring scale, which has recently been modified. The scientific background for this modification is unknown.*

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.

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*Technical Dossier by QRA expert group (I):*

Weight of evidence approach (p.15)

'Historical data that are used to determine the sensitization potential of a material may be of variable quality and robustness. Therefore it is recommended to use a weight of evidence (WoE) approach using all available data for the identification of a no-expected sensitization induction level (NESIL).'

Guidelines are given for applying weight of evidence approach to induction sensitization data on fragrance ingredients. These guidelines have been developed specifically for fragrance ingredients and must only be applied to fragrance ingredients.

*The guidelines in brief:*

A NOEL from a well run HRIPT will give precedence over NOELs from other clinical tests that were conducted in human subjects (e.g. HMT (Human Maximization Test; earlier precursors to the HRIPT such as the Modified Draize Test), regardless of the NOELs indicated from other tests. A well run HRIPT is defined as one which employed a published methodology, was well documented and involved approximately 100 subjects or more.

In the absence of a NOEL from a HRIPT, a NOEL from a different predictive human test (e.g. HMT) can be used to set the NESIL, provided that it is supported by an EC3 value from a well conducted LLNA.

When only LLNA data are available (i.e. no historical human data exist), then a confirmatory HRIPT should be considered.

A NOEL from a well run HRIPT will (even if higher) have precedence over all other NOELs (including LLNA EC3 values).

Data from diagnostic patch test studies can not be used directly in a weight of evidence approach for the determination of NESILs for the induction of contact allergy to fragrance ingredients. These studies can be helpful to determine the need for additional data.

The absence of relevant positive reactions following testing in dermatology clinics may provide support to current exposures to the fragrance ingredient.

*Comments by the SCCP*

It is a well established principle of toxicological assessments to use the weight of evidence approach. In this specific instance the developed guidelines are specifically favouring data from HRIPTs, which takes precedence over all other data including other predictive human tests. It is suggested to perform HRIPT if such data is not available, also in a situation where a substance is already known to cause sensitization in consumers. Experience with HRIPT, its validity, sensitivity and reliability are sparse outside industry. HRIPTs are not part of any official test guidelines and very little method description exists. The weight of evidence guidelines are specifically designed to address the issue of fragrance sensitization, the use of data already collected by fragrance industry and included in their research programmes. The weight of evidence guidelines have no general validity and scientific support is missing.

## **Sensitization assessment factors (SAF)**

*Technical Dossier by QRA expert group (I):*

'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.

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.

### Defining SAF

A factor of 10 is always assigned for inter-individual variability. This is based on well established principles of general toxicology (I/p.27). Matrix-effects and use conditions are considered pragmatic to limit the values used to 1, 3 and 10. A value of 1 defines an experimental condition that is essentially identical to real life exposure. A value of 10 defines an experimental condition that is nearly unrelated to the real-life scenario. A factor of 3 is used to define differences, which is greater than 1 but not 10. 'These values chosen are consistent with the approach used by EPA for general risk assessment (I/p. 27)'. The overall SAF is a combination of the three key parameters. In theory SAFs could range from 10 to 1000. In reality, for fragrance ingredients it is unlikely that the SAF would exceed 300. However exceptions could include where there is mucosal contact where higher SAFs are assigned (I/p.28).

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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.

*Comments by SCCP*

In the proposed dermal sensitization QRA model, a factor of 10 is always assigned for inter-individual variability (I), which is in accordance with general principles of toxicology (*Dourson 1996*). Predictive sensitization tests in healthy volunteers have shown a difference of a factor 8 in susceptibility, when the potent and experimental allergen DNCB was tested (*Friedman 1990*). Kligman found a factor of 100 in difference in susceptibility to the hair dye ingredient p-phenylenediamine (*Kligman 1966*), that is 5/24 volunteers were sensitized by exposure to 0.1 % p-phenylenediamine and 24/24 at exposure to 10 % p-phenylenediamine. Other allergens gave similar results, while the sensitivity range for the weak sensitizer neomycin was a factor 2.5. In elicitation studies e.g. of nickel, a difference in susceptibility of 400 between individuals is seen (*Fischer 2007*).

In the dermal sensitization QRA model the presence of irritants are considered in assigning SAF for matrix, but no consideration is given to the possible presence of other structurally similar substances in the finished product compared to the experimental circumstances of exposure to only one substance. Matrix SAFs are established for 33 product categories. Examples of product types all assigned SAF matrix 3 is taken from table 2 in the technical dossier (I) and reproduced below.

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.

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.

Dermatitis is frequent in the population and cosmetics are used by all groups daily. It is not entirely clear to which extent the SAFs covers individuals with diseased skin.

Dermatitis is mentioned under SAF use conditions (barrier integrity). In table 2 (I/p. 30-34) dermatitis is specifically mentioned as part of the rationale for a use SAF of 3 for hand cream/liquid soap, while for other products such as facial creams/masks dermatitis is not considered in assigning a use SAF.

A defect barrier as in atopic dermatitis may increase the penetration of hydrocortisone with a factor 2-10 (*Turpeinen 1988*). In experimental models, a 46-fold increase in penetration of salicylic acid in mild experimentally induced dermatitis and 146-fold in severe dermatitis in humans have been found (*Benfeldt 1999*). Further individual differences in barrier function in humans have a large impact on the variability in topical drug penetration, accounting for 60% of the variance (*Benfeldt 2007*).

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 reference is given in the Technical document (I) to EPA's approach (*Dourson 1996*). This paper concerns in general the need for data driven safety factors and not specifically matrix-effects.

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.

## **Exposure assessment**

*Technical Dossier by QRA expert group (I) and RIFM booklet (II):*

'Consumer exposure level (CEL) is an essential element of QRA.' 'Exposure levels occurring under intended and foreseeable conditions of use, but not abuse need to be addressed.' 'The CEL is expressed as dose/unit area/day. This takes into account that frequency of product use may be more than once a day'. 'Although it is desirable to aggregate exposure, there are insufficient data to allow this to occur at this present time. This is an area of refinement for a QRA approach'. (I/p40)

'The applied dose is taken to be the delivered.' A definition of consumer exposure to 33 different product types is listed (I/table 9 p. 44). These are condensed into 11 categories by RIFM, based on exposure and SAFs, which, when combined, lead to similar acceptable use levels of fragrance ingredients (II). 'It may appear that for many product categories there is a wide diversity of product types. However, this is because the categories are based on scientific rationale (SAF and exposure), and not on the functional similarity of each product type'. 'Several product types have been placed in specific IFRA categories even in the absence of exposure data by taking into account how the product is used, what it contains and the extent of likely skin exposure' (II/p3-4).

'Baby shampoos and washes include the assumption that the dose/unit area is similar to this value for adults (i.e. for babies, less product used over smaller surface areas). Should specific exposure and surface area data for babies become available, these product types may be re-categorized' (II/p.4).

Maximum pragmatic level: Practical considerations require setting a default maximum level of fragrance ingredients identified as dermal sensitizers for some product types. The pragmatic level will be defined as that 'not exceeding the usual concentration of the fragrance compound in the finished product.' 'If the Acceptable Exposure Level (AEL) derived from QRA for fragrance ingredients in a specific product type is less than the concentration identified as 'Maximum Pragmatic Level', the AEL will take precedence and be applied. IFRA and RIFM will determine whether the AEL or the 'Maximum Pragmatic Level' should be applied (II/p.4).

*Comments by SCCP*

A useful and detailed overview is given on data and data sources concerning consumer exposure to different product types. The exposures used in the dermal sensitization QRA model are highlighted in the table. It is noted that when exposure data were available from more than one source, then the highest value was generally used in the dermal sensitization QRA model, except that the data from Cano, Tozer and Rich (Cano & Rich, 2001; Tozer et al., 2004 and Cano, 2006) on hydroalcoholic products were given precedence. These data are not published in full. Also COLIPA data from 2005 (unpublished) were given precedence over CTFA data. In two instances, this gives a significant difference in the estimates: for hydro-alcoholic products for unshaved skin, where the estimates chosen from Cano, Tozer and Rich is 2.21 mg/cm<sup>2</sup>/day while the same estimate from CTFA is 17.70 (I/p45) and for women's facial creams where the chosen estimate is 2.70 mg/cm<sup>2</sup>/day, while the CTFA estimate is the highest (6.31 mg/cm<sup>2</sup>/day). In this last instance the SCCP estimate is 2.88 (2003 value).

It is important to have reliable data on habits and practices for risk assessment in general. It seems that the work on QRA for sensitization have stimulated investigations on exposure (Loretz 2006). Publication of all recent investigations on exposure to consumer products is encouraged.

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.

In some cases, the result from the dermal sensitization QRA is disregarded and instead a pragmatic limit is chosen based on usual use levels (II), e.g. pragmatic levels are given for citral in liquid soaps, shampoo and face wash and a range of other products (I/p.54) as the dermal sensitization QRA allows higher concentrations (e.g. 8.2%;7%;9.3%) than the usual concentration of the fragrance compound of 5% in the finished product. Citral is a known allergen in consumers (Frosch 2005), as well as an irritant. 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.

### Risk characterization

*Technical Dossier by QRA expert group (I):*

The level not expected to cause sensitization (NESIL) is divided by the safety factors (SAFs) to derive the acceptable exposure level (AEL), expressed in terms of dose/unit per diem (p. 48). This is compared to the consumer exposure level (CEL), and for an acceptable risk assessment, the AEL has to be greater than or equal to the CEL (i.e.  $AEL \geq CEL$ ) (p. 48/49).

Examples of risk characterisation for cinnamic aldehyde (INCI: cinnamal) is given p. 51, for citral p. 53, isoeugenol p. 55, eugenol p. 57 and phenylacetaldehyde p. 59 using the dermal sensitization QRA.

In addition dossiers of the application of the dermal sensitization QRA methodology to three fragrance ingredients: citral (III), farnesol (IV) and phenylacetaldehyde (V) have been submitted for evaluation by SCCP.

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The model allows levels as high as 100% of moderate sensitizers such as cinnamic aldehyde and isoeugenol in baby diapers (p. 52/56) and 59% and 25% respectively in hand dish washing products (p. 52/56). This is explained by a low estimated exposure (p. 52/56). Instead pragmatic permitted levels are given corresponding to the maximum used level (p. 52/56). See comments above.

The dermal sensitization QRA would permit 1000 ppm (0.1 %) isoeugenol in hydroalcoholic products (unshaved skin), and 400 ppm for shaved skin. Since 1998 isoeugenol has been limited to 200 ppm in both stay-on and wash-off products and 2000 ppm in products not intended for skin contact by IFRA-standards (*IFRA.org*). The level in deodorants (non-spray) would be lowered to 100 ppm. Isoeugenol is one of the most frequent causes of contact allergy and has been for years (*Schnuch 2004*); a recent study from London has shown a still significant increase in allergic contact dermatitis to isoeugenol from 2001 to 2005 (*White 2006*).

Table 20 p. 56 gives 33 product categories, 25 of these are cosmetics with skin contact. Compared to the current situation (200 ppm limit), the level of isoeugenol would be increased for 22 product categories and lowered for 3. Isoeugenol is often used in hydroalcoholic products (e.g. *Rastogi 2003; Johansen 1996*), where the allowed concentrations would be increased and less often in deodorants (*Rastogi 2007*), where it would be lowered.

Similarly, the level of cinnamic aldehyde (INCI: cinnamal) would be increased for most product types applying the dermal sensitization QRA and lowered for deodorants, lip products and intimate wipes compared to the current IFRA standard (I/p. 52). Cinnamic aldehyde is and has been one of the most common causes of contact allergy to fragrance ingredients (*Schnuch 2004; 2007*).

In the submitted separate dossiers on citral (III), farnesol (IV) and phenylacetaldehyde (V), the 33 product categories are condensed into 11 categories based on exposure and SAFs, which when combined, lead to similar acceptable use levels of fragrance ingredients. The dossiers list the predictive sensitization studies in humans and animals, which are used for determining NESIL. Clinical patch test data is listed, only.

No IFRA restrictions have been previously applied to these three substances, except that citral and phenylacetaldehyde should be used together with other specified substances to 'quench' their sensitization effect (III), however, the 'quenching phenomenon' could not be scientifically supported and has been abandoned (III).

Citral is a well known allergen in the consumer (*Frosch 2005*) and irritant. It is included in one of the diagnostic tests for fragrance allergy (*Bruze 2008*). The largest number of reactions mentioned in the validation study of the predicted use levels for fragrance ingredients was caused by citral (n=6) (see below section 3.7). The limits based on the dermal sensitization QRA will be e.g. 0.05 % citral in deodorants and 0.6 % in hydroalcoholic products for unshaved skin. In liquid soaps 7 % citral can be used according to the dermal sensitization QRA model, 8.2 % can be used in shampoos and 100 % citral in baby diapers and hand dishwashing (I/p.54). The limits calculated from the dermal sensitization QRA-methodology for these wash-off products are changed into maximum pragmatic concentrations of 5 % for liquid soaps and shampoos and 2.5 % for baby diapers and hand dish washing (I/p.54; III). 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.

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Farnesol is also a known allergen in the consumer (*Frosch 2005; Schnuch 2004*). The same maximum pragmatic limits for liquid soap, shampoos, baby diapers and hand dish washing as mentioned for citral i.e. 5 % and 2.5 % in the final product will apply. In deodorants the limit will be 0.11 % and 1.2 % in hydroalcoholic products for unshaved skin (IV). An investigation of 88 fragranced deodorants on the Danish marked showed that 13 (14.8 %) contained farnesol. A chemical analysis of 9 of the 13 deodorants showed a median concentration of 0.06 %; a maximum of 0.17 % was found (*Rastogi 2007*). Only two deodorants exceeded the new limit of 0.11 %, which indicates that no major reduction in exposure to farnesol in deodorants would be expected by applying the dermal sensitization QRA.

No data is given to support whether the dermal sensitization QRA limits would effectively mean a reduced exposure to citral and farnesol, status quo, or if increased exposures would be indicated as safe by the given limits. Both substances are well-known causes of contact allergy in consumers.

Phenylacetaldehyde (V) has previously been described as an allergen in consumers, but no current investigations exist. It is a moderately potent allergen (V). The dermal sensitization QRA permits the use of phenylacetaldehyde in concentrations from 0.02% (e.g. deodorants) to 3.0% (e.g. liquid soaps). It is presently not known, if phenylacetaldehyde causes allergy in the consumer.

Fragrance products are complex compositions containing ten to hundreds of fragrance ingredients. Fragrance allergens are often used together in these compositions. In a study of international brand deodorants a subset of 23 deodorants were chemically analysed and contained median 8 (range 5-17) of 26 investigated allergens (*Rastogi 2007*). 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.

### **Confirmation of predicted use levels for fragrance ingredients**

*Technical Dossier by QRA expert group (I):*

'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).'

One validation study is mentioned concerning 3223 subjects in Leuven, Belgium. 9.1 % of these patients were found to have a positive patch test reaction to fragrance mix; 6.7% to balsam of Peru; 4.8% to colophony. 133 patients exhibited positive patch tests to their own cosmetic products, of these 66 involved fragrance-related contact allergic reactions. A table is given (table 27, see below) of an undefined number of patients having reacted to cosmetic products and at the same time a fragrance ingredient. 16 products are mentioned, the largest number is 6 toilet waters/perfume products with a simultaneous allergic reaction to citral. No conclusions are drawn in the technical dossier (I).

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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

The dermal sensitization QRA-data for cinnamic aldehyde and isoeugenol is mentioned in relation to the IFRA-standards.

*Comments by SCCP*

Comments on cinnamic aldehyde and isoeugenol are given above cf. 3.6.

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.

### General discussion

The proposed model of quantitative risk assessment (QRA) for skin sensitization is based on general principles of toxicology. It is obvious that considerable efforts have been made over several years to develop the model and that advances have been made in this area. This development is welcomed.

The dermal sensitization QRA model is not generic but specific for fragrance ingredients. It is mainly a retrospective model, which is aimed at reusing data previously collected by industry. In addition to calculations of acceptable exposure levels, the model operates with maximum pragmatic levels for reasons of practical management. This means that the calculated accepted levels (AEL) can be changed to a smaller usual use concentration dependent on individual considerations for selected product types. This further makes it difficult to use the model outside industry.

The preferred test, The Human Repeated Insult Patch Test (HRIPT), which forms the basis of the proposed dermal sensitization QRA model, is not part of any test guidelines. There is a lack of in-depth method description and no clear guidance exists in the choice of test concentrations in the HRIPT. The experience with this test, its validity, sensitivity and reliability is sparse outside industry. Furthermore, the predictive sensitisation testing in humans (e.g. HRIPT) are considered unethical as stated by SCCP and in the outcome of a recent WHO-workshop.

The dermal sensitization QRA does not consider the protection of consumers who have already been sensitized to fragrance ingredients. Further, it is unclear if and how the proposed model covers the significant part of the population, who suffers from skin disease without prior sensitization to fragrance ingredients.

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Fragrance products are complex mixtures often containing both structurally similar substances and several known allergens. The allergen load of structurally similar substances is not considered in the model. Aggregated exposures from different products (including occupational exposures), which may be important both for induction and elicitation, are not considered.

Risk assessment is made for 33 product categories. The many products categories imply a precision of the model unsupported scientifically. Also the precision of the model suggested by values calculated to two decimal points, e.g. farnesol 0.11 %, could be misleading.

There is no data to support the proposed levels scientifically as safe for the consumer other than the calculations in the model itself. The dermal sensitization QRA is a theoretical model and no validation has been done nor is a strategy for validation proposed. It is unknown if the levels identified by the model are safe for the consumer. An non-validated predictive model such as the dermal sensitization QRA cannot be used to increase exposure levels to allergens.

Examples are given of risk characterisation of well-known fragrance allergens, which currently are causing allergic reactions in consumers e.g. isoeugenol and cinnamic aldehyde. Implementation of the dermal sensitization QRA model would mean increased exposure to these allergens in most product types compared to the current situation. This makes it difficult to have confidence in the model.

In April 2008, IFRA informed its members that, for the time being, existing IFRA standard would be maintained and not raised until more experience with the model is obtained, even if QRA calculations would result in a higher maximal allowed concentration for certain substances (IFRA 2008).

After validation and refinement, including consideration of aggregated exposures, the value of dermal sensitization QRA models in general lies in the prospective application to new substances identified as skin sensitizers, as safe levels may be identified before allergens are being incorporated into finished products to which the consumer may be exposed. In such cases effective and independent post-marketing surveillance is essential. As for established fragrance allergens causing allergy in the consumer, clinical and epidemiological data must be used as the critical decision point in risk assessment.

#### **4. 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

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exposures are not considered although they have been identified as an important area of development of the dermal sensitization QRA.

The data provided shows that the application of the dermal sensitization QRA approach would allow increased exposures to allergens, already known to cause allergic contact dermatitis in consumers. The model has not been validated and no strategy of validation has been suggested. There is no confidence that the levels of skin sensitizers identified by the dermal sensitization QRA are safe for the consumer.

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.

In view of the comments above, the SCCP cannot endorse the industry proposed QRA-approach for setting safe levels of exposure to citral, farnesol and phenylacetaldehyde.

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

The strategy has been developed for fragrance ingredients, but could in principle be applied to other cosmetic ingredients provided that the concerns stated above, are addressed.

*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?*

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.

## **5. MINORITY OPINION**

Not applicable

## **6. REFERENCES**

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