



EXPLANATORY NOTE

HOW THE COMMENTS RECEIVED DURING THE PUBLIC CONSULTATION WERE TAKEN INTO ACCOUNT FOR THE FINAL SCCS OPINION ON FRAGRANCE ALLERGENS IN COSMETIC PRODUCTS

1. INTRODUCTION

This note sets out the rationale for the modifications made to the opinion of the European Commission Scientific Committee on Consumer Safety (SCCS) on the opinion on Fragrance allergens in cosmetic products following a public consultation.

In June 2009, the European Commission requested the Scientific Committee on Consumer Safety (SCCS) to provide an updated scientific opinion on fragrance substances that are relevant contact allergens for consumers.

A SCCS Working Group was formed, comprising four members of the Scientific Committee on Consumer Safety (SCCS) and six experts from academia with relevant expertise on the subject matter. The WG produced a draft opinion which was discussed and approved by the SCCS plenary on 13-14 December 2011 as suitable for public consultation (pre-consultation opinion).

In line with its procedures for stakeholder dialogue, implemented in the Rules of Procedures of the new Scientific Committees¹, the European Commission's Directorate General for Health and Consumers (DG SANCO) then conducted a public consultation on this pre-consultation opinion between 20 December 2011 and 29 February 2012.

1.1. Results/participation

By the deadline, 112 contributions were received. They came from public authorities (2), standardisation bodies (1), research institutions (2), consumer/patient organisation (3), trade associations (7), companies (91) and individuals not claiming any affiliation (6).

Most company contributions endorsed submissions by one of the trade associations. Many of these contributions were identical in content without providing additional scientific elements for consideration in the opinion, while referring to possible economical impacts in case of legal implementation, which was not in the scope of this consultation on scientific matters.

1.2. Modifications to the opinion

All comments were reviewed and discussed by the Working Group during several meetings. Wherever considered appropriate, modifications were introduced into the opinion. The final opinion was adopted by the SCCS during its Plenary Meeting of 26-27 June 2012.

The Working Group modified the opinion to reflect submitted comments which were assessed to be pertinent and relevant for the subject matter and respected the clear

¹ set up by Commission Decision 2008/721/EC of 5 September 2008

separation between risk assessment and risk management that underpins the Scientific Advisory structure of the European Commission. Comments on policy, risk management, economic impact of possible risk management measures, legal clarification, the precautionary principle and related subjects were not considered. Although they may be pertinent to the subject matter, they are outside the competences of the Scientific Committees.

Detailed explanations of the way the eligible comments submitted during the public consultation were treated by the SCCS are provided below. They are structured according to the three questions in the Terms of Reference used to organize the public consultation and include comments/changes to opinion sections related to the respective question. The numbering of pages, chapters and references corresponds to the final opinion adopted by the SCCS.

2. QUESTION 1 AND SECTIONS OF THE OPINION RELATED TO IT

2.1. Determination of fragrance allergens relevant for consumers

Several comments questioned the general approach employed by SCCS to identify fragrance allergens which may pose a risk to consumers. In some comments it was stated that the SCCS pre-consultation Opinion presents a new classification methodology for (fragrance) allergens in using the number of positive patch test results from clinics as the qualifying element. This classification methodology was said not to have been validated through external scientific scrutiny, presented at scientific meetings and/or published in peer-reviewed scientific journals.

The SCCS is of the opinion that the use of human clinical data in the present opinion is consistent with the assessment in the SCCNFP 1999 opinion and with established risk assessment practices. Moreover, the use of clinical patch test data to identify relevant human allergens can hardly be considered to be a "new classification methodology". The SCCS is of the view that human clinical data delivers the most relevant information for the identification of allergens which do induce allergy in consumers during real-life exposure.

Along similar lines, several submitters questioned the approach by SCCS to identify fragrance allergens relevant for consumers by analysing the available clinical data (mainly patch test data), and, for those substances for which sufficient human data is available, not to take potency data obtained from animal studies into account. In particular it was criticised that animal data which have shown a substance to be a "non-sensitiser" or to be of low sensitisation potential has not been considered.

The SCCS maintains the view that, while animal data is valuable as a predictive tool, human data obtained by clinical patch tests, whenever available, provides the most relevant information on fragrance allergens which have caused sensitisation in consumers. The prediction of a low sensitisation potential in animal studies does not in all cases preclude a significant human sensitisation potential, as shown e.g. for the example of HICC. Chapter 6 and 7 have been revised in order to provide additional explanations on the rationale for the approach taken.

Commenters claimed that the majority of listed fragrance materials show very limited links to cases of allergic disease and very low incidences of induction. The large exposure to these materials, in relation to the very limited incidence of allergic disease, would not demonstrate a risk which justifies the characterization of allergens as being of concern. Further it was said that even for a material where the cumulative total of published cases of disease is above 100, given the enormous exposure and use history amounting to hundreds of millions of consumer uses per

day, a large degree of risk could not be established and that these low incidences would not be measurable from a statistical population basis. Further it was stated that mentioning raw data without comparison to sales figures or exposure data does not allow the drawing of any reliable conclusions. In the view of the commenter, there would be a need to determine the reporting rate for each ingredient to permit a comparison between ingredients on which a classification could be based.

The SCCS decided to base its categorisation on absolute numbers of cases of sensitisation and not on relative frequencies of positive patch tests to allow the combination of evidence obtained by different study types. Relative frequencies depend heavily on the selection of patients for patch testing. Thereby, an important allergen tested routinely, in the baseline series, may yield 1 to 2% positive reactions (usually in several thousand patients), while an allergen tested in a more selective fashion (in much fewer patients) may yield an even higher relative frequency. Moreover, case reports/series, which also give evidence for sensitisation, cannot be interpreted in terms of relative frequencies. Text further explaining the chosen approach has been added to chapter 7.1.

Concerning the comment that 100 published cases indicate a low incidence considering the extent of exposure, it needs to be understood that there is publication bias in the reporting of allergens. This is due to the fact that once a substance has been reported and accepted as a contact allergen in humans, further reports are less likely to be published unless they are part of a epidemiological survey or when there is a novel source of exposure. Moreover, only a certain fraction of consumers experiencing contact allergy to fragrances do seek medical diagnosis and treatment. Therefore the number of published cases always severely underestimates the total number of cases occurring in the population.

On the same topic, it was further commented that the method of grading the level of concern for substance (from + to +++) is based on absolute numbers of cases reported, and not on the reporting rate (example given: 101 reacting patients on 101 patients tested (100%) is much different from 101 reacting on 10 000 patients tested (1%). This classification scheme was considered invalid for identifying established human contact allergens. It was claimed that the 56 new allergens would include such with no documented human evidence of sensitisation. Further it was stated that as the use of consumer products exposing people to these materials is in the many millions of uses per day, it seemed unrealistic to present a model that does not attempt to quantify this risk.

The SCCS is well aware of the fact that the prevalence of sensitisation depends on the selection of tested patients, which differs in different study types (consecutive patients < aimed testing < case reports with testing of culprit agents). In the given hypothetical example (101 sensitised cases as 100% vs. 1% of tested) both studies will identify the same number of cases – if patient selection for patch testing was as 100% perfect as suggested in the “101 of 101” scenario, these 101 identified patients may actually be the same patients identified as when testing 10 000 patients consecutively, i.e. without employing selection criteria (other than for performing a patch test per se). Thus, basing a categorisation on absolute numbers may indeed be more consistent than basing it on relative numbers, which are highly variable. Relative numbers of patch tested patients are, at any rate, not equivalent to any useful measure for risk assessment, as the exposure denominator is rarely known and therefore usually cannot be taken into account. Hence, in the view of the SCCS, there is no justification for a preference of relative numbers. It is acknowledged, however, that some relation to the number of patients tested would

be necessary to put lacking, or very few positive cases in patch testing into some perspective pertaining to risk.

Commenters considered that the SCCS opinion constitutes a change from a risk based approach to a hazard based approach in identifying materials of potential concern in consumer products and in suggesting material usage restrictions. Reference was made to tables 13-2 and 13-3 which list substances that show contact allergy in animal studies or contain potential structural alerts. This was considered to have no relevance to the risk or incidence of contact allergy to these substances when used in fragrances and that there is no evidence that these substances are responsible for causing fragrance allergy in the general population.

It should be noted that the SCCS has suggested a limitation of exposure only for a subset of particularly important "established contact allergens in humans". The occurrence of hundreds of reported cases of contact allergy is clearly an indicator of risk, not only of hazard, even if the exposure cannot be exactly quantified. In contrast, only information requirements, allowing better diagnosis and allergen avoidance, have been suggested based on hazard information for the substances listed in tables 13.2 and 13.3. For this set of substances, no human data exist, but either valid animal models indicate a hazard for humans given sufficient exposure, or structural alerts combined with limited human evidence indicate that substances can act as haptens, prehaptenes and/or prohaptens. It should be noted that for 'possible' allergens as listed in Tab. 13.4, i.e. substances where only 'limited' human evidence or a positive SAR evaluation exists, no particular interventions were deemed necessary, although the SCCS is of the opinion that closer monitoring and more data would be important for a further assessment of these substances.

One submission commented on the fact that negative patch test results of several hundred patients was considered inadequate to rule out the existence of significant clinical contact sensitisation with sufficient confidence, whereas cohorts of 11 to 26 patients were used as a basis to establish an elicitation threshold as basis for regulation, which, in the view of the commenter, appeared to be inconsistent.

As described in the SCCS opinion chapter 7.1, a certain number of subjects have to be tested before being able to rule out a relevant prevalence of contact sensitisation based on a negative result of patch testing. To achieve an upper 95% confidence interval of 1%, 0.5% or 0.05% prevalence, $n=298$, $n=597$ or $n=7376$ patients, respectively, have to be tested, with no positive results. These sample sizes were not obtained in the presented studies. Furthermore, such presumptive 'negative testing' would need to be done on patients who actually have been exposed to the substance in question and did not become sensitised. If non-exposed groups are tested, the non-occurrence of cases of sensitisation obviously carries no information. Concerning the sample sizes in dose-elicitation studies, these are severely limited by feasibility factors. The precision achieved by them is expressed by confidence intervals which are obviously wider than those achieved by bigger sample sizes.

It was commented that the estimation that 1-3% of the general population in Europe are sensitised to fragrance was not supported by an explicit epidemiological study.

The SCCS does not agree with this view. The estimate of 1-3% sensitisation to fragrance ingredients in the general population is based on the first 5 studies in table 4-9 using FM I, yielding prevalences on the general population level between 1.1 and 2.7%. 3 other studies listed in that table show much higher prevalences but have not been considered as there are doubts whether their results can be

generalised. Moreover, FM I is known to detect less than 50% of patients sensitised to fragrances in patients, which, most likely, can be extrapolated to testing on the population level. Therefore, the SCCS considers that the given value of 1-3% sensitisation to fragrances in the general population is a realistic and even conservative estimate.

2.2. Data selection

Commenters questioned whether the review of the available scientific literature performed by the SCCS was systematic enough to retrieve all relevant data. It was stated that additional data could be identified by using other search engines and a number of publications were listed to illustrate this¹.

The SCCS maintains its view that the applied search strategy is adequate, as the vast majority of studies in the relevant field with significant scientific impact are normally published in Medline-listed journals. Moreover, supplemental searches have been performed, as outlined in chapter 6 of the opinion. The series of papers by Hostynek and Maibach were not cited in the opinion, as they are reviews and not original studies. A paragraph has been added in chapter 6.1.1. to clarify that only original studies were considered for the systematic overview of available clinical data, in line with scientific standards pertaining to systematic reviews. Reviews only served to identify additional literature on methodological aspects, and on LLNA results, as now mentioned in this chapter.

The study by Schnuch et al. 2007, which was stated to be missing by several submissions, was in fact included already in the pre-consultation opinion in the main text (as ref. 72) as well as Annex I (as ref. 4). The data from this publication were included in table 4-6, and in annex I in all sections related to substances included in this study.

¹ Hostynek J J, Maibach H I. Is there evidence that anisyl alcohol causes allergic contact dermatitis? *Exog Dermatol* 2003; 2: 230-233

Hostynek J J, Maibach H I. Is there evidence that linalool causes allergic contact dermatitis? *Exog Dermatol* 2003; 2: 223-229

Hostynek J J. (2004). Is there evidence that amylcinnamic aldehyde causes allergic contact dermatitis? *Exog Dermatol* 2004; 3:35-46

Hostynek J J, Maibach H I. Is there evidence that alpha-isomethylionone causes allergic contact dermatitis? *Exog Dermatol* 2004; 3: 121-125

Hostynek J J, Maibach H I. Sensitization Potential of Citronellol. *Exog Dermatol* 2004; 3: 307-312

Hostynek J J, Maibach H I. Is there evidence that geraniol causes allergic contact dermatitis? *Exog Dermatol* 2004; 3: 318-331

Hostynek J J, Maibach H I. Is there evidence that methyl heptine carbonate causes allergic contact dermatitis? *Cutan Ocul Toxicol* 2006; 25: 259-271

Gilpin S, Maibach H 2010 Allergic contact dermatitis from farnesol: clinical relevance. *Cutaneous & Ocular Toxicology* 29:278-287

Schnuch A, Uter W, Geier J, Lessmann H, Frosch P J. Sensitization to 26 fragrances to be labelled according to current European regulation. Results of the IVDK and review of the literature. *Contact Dermatitis* 2007; 57: 1-10

Heisterberg M V, Menne T, Johansen J D. Contact allergy to the 26 specific fragrance ingredients to be declared on cosmetic products in accordance with the EU cosmetics directive. *Contact Dermatitis* 2011; 65: 266-275

As the initial data search performed only covered data up to October 2010, the study by Heisterberg et al. was not included. However, the SCCS considers that a lack of positive reactions in smaller clinical samples does not contradict the existence of a relevant, high true prevalence in contact dermatitis patients for obvious statistical reasons already outlined above. Nevertheless, the results by Heisterberg et al. have now been added in chapter 7.

One comment criticised that data from already submitted and publicly available REACH Tier 1 dossiers have not been considered.

The SCCS acknowledges that the REACH registration process may make available additional data on the sensitisation potential of fragrance substances. However, the analysis in the present SCCS opinion is in the first place based on human clinical data. Therefore the fact that REACH data has not been included in the opinion does not invalidate the outcome of the analysis, as REACH dossiers are expected to contain mostly 'non-clinical', e.g., animal data.

One comment stated that the opinion omitted a large amount of validated data that was generated using accepted OECD guideline methods on the basis that the authors are not in agreement with the method; and that this has excluded evidence showing that many materials are weak to non-sensitisers. Furthermore, it was stated that HRIPT data, that support animal data in many cases, had not been considered.

Although not quite clear from the submission, the SCCS understood that the reference to large amounts of validated data seems to refer to additional animal data. As stated above, the SCCS does not consider that the omission of such data invalidates the outcome of the analysis in the opinion. Animal data is of great importance when predicting the sensitising potential of a substance for which no or little human data is available. However, the present SCCS opinion is mainly focused on human clinical data, which is considered to give the most relevant information in this context to identify allergens that have caused sensitisation in consumers. Text has been added to chapter 6 to illustrate this view.

Regarding HRIPT, no OECD test guideline exists. The SCCS considers studies involving induction in naïve subjects are not ethical. Hence, such studies are not encouraged, although historical studies had been taken into account, where appropriate (see annex I to the opinion). Moreover, the negative predictive value of human maximisation studies has not been proven, and the very limited number of tests (often $\ll 100$) renders results insufficient to rule out sensitisation hazard with acceptable certainty for statistical reasons already discussed in section 2.1 in the context of negative clinical patch test studies.

Some respondents commented that the data used for the assessment of fragrance materials largely predates the 1999 SCCNFP Opinion on allergens, not taking into account a possible effect of the actions that have been taken by industry since the SCCNFP opinion of 1999.

In its opinion, the SCCS has searched for literature pre-dating the 1999 SCCNFP opinion previous opinion only for substances not included in that opinion, as described in the methods. However, for the categorisation of allergens based on published clinical data all available evidence was indeed considered. This has been clarified in chapter 7. The SCCS is of the opinion that old evidence is not invalidated by new evidence (if methodologies are adequate), regarding the classification of a substance as contact allergen. Notwithstanding this, sufficient changes in exposure, along the lines of options of preventive action outlined in the opinion, can indeed be useful in limiting the problem for consumers. The identification of substances that

are the cause of contact allergy in consumers, as in the present review process, is understood to be a prerequisite and a crucial step towards adequate risk management.

2.3. Interpretation of clinical data for 26 allergens that are currently labeled/identification of "relevant" allergens

Submitters claimed that recent publications¹, in their view putting into question the relevance of a number of allergens identified in the original SCCP opinion of 1999, had not been included in the SCCS opinion. As the selection of the 26 allergens was based on a similar review of clinical data in 1999, in the view of the submitter, the evidence presented in these publications would invalidate the approach taken by SCCS.

As stated above, the SCCS has fully considered the clinical data contained in the quoted study Schnuch et al. (2007) in the opinion. The series of papers by Hostynek and Maibach were not cited in the opinion, as they are reviews and not original studies. Concerning classification of certain allergens as "less important" in the work by Schnuch et al., the classification is based on results from just one study in Germany/Austria, while the SCCS considered the full scope of published scientific studies, as explained below.

A comparison of methods employed by Hostynek and Maibach with the approach used by the SCCS shows considerable differences, which help explain why these reviews arrive at different conclusions even if based on largely the same original data. The SCCS considers their interpretation of clinical relevance very narrow and not in line with current clinical practice. One major difference is that Hostynek and Maibach set up very strict 'quality criteria', which are theoretically justifiable, but not applicable in practice. For instance, one item considered by these authors was "excited skin excluded". It is, and has been, part of pertinent guidelines to disregard results obtained in patients with suspected excited skin syndrome and to retest these patients. Such a self-evident prerequisite is almost never reported in studies, which is, however, still considered by Hostynek and Maibach to cast a shade of doubt on the results. This also holds true regarding items such as "ROAT or PUT used". This is, for several reasons, almost never the case in diagnostic patch testing. In conclusion, these authors arrive at a much lesser 'level of evidence' regarding the frequency, and thus the "importance" of an allergen than the SCCS, who has chosen its approach in order for it to be both consistent and applicable in practice and to obtain a good balance between quality and availability/eligibility of data. Moreover, newer data has become available since those reviews were written, which may partly contribute to arriving at different conclusions. It is, however, acknowledged that the cut-off used by the SCCS for identifying substances of special concern is evidently just one of several ways of defining 'importance',.

The approach by the SCCS is explained in chapter 6 of the opinion and outlines quality criteria as well as criteria for strength of evidence. As mentioned in this section, the SCCS considers that, while clinical relevance can provide important information, it is ideally based on comprehensive knowledge of prior exposures. Since the implementation of labelling of the 26 ingredients exposure to these can often be ascertained in the assessment of relevance to a positive patch test. However, exposure to substances not listed on a product ingredient label is obscure except in very rare cases, where elaborate diagnostics and chemical analyses are

¹ Same as footnote 2

feasible. Thus, a lack of information on relevance reported in studies does not invalidate the impact of diagnosed contact sensitization.

Notwithstanding this, it is very evident that the “importance” of fragrance allergens differs – and thus different levels of intervention may be necessary, ranging from simple information on the presence of substance of less concern, to use restrictions of substances with special concern, to withdrawal in case of outstanding allergens. Regarding the provision of information to the individual concerning the presence of a substance in a consumer product, this is as necessary for the fewer affected individuals as is information on “more important” allergens are necessary for a larger number of people sensitised.

Three substances of the 12 of special concern identified by the SCCS, namely, geraniol,¹ linalool² and farnesol³ are considered as ‘less important’ by Hostynek and Maibach. The background for the assessment made by the SCCS concerning geraniol is explained in detail in section 3.2. The evaluation of linalool is based on data for the non-oxidised compound; well in line with their interpretation (in this case) the SCCS considers non-oxidised linalool not a substance of concern, while, in contrast, there is considerable (new) evidence of the allergenicity of this substance in its oxidised form, as explained in chapter 5 of the SCCS opinion. The SCCS considers that there is no contradiction in this case. Farnesol was considered a less frequently reported allergen in the 1999 opinion. Since 2008, the European Society of Cutaneous Allergy has recommended inclusion of fragrance mix II (which contains farnesol) into the European baselines series, which contains substances which are considered important in the diagnosis of allergic contact dermatitis⁴. Following this inclusion, results from multicentre studies on fragrance allergy from Germany⁵, The Netherlands⁶ and Denmark⁷ document many cases of contact allergy to farnesol. It is also worth noting that farnesol was grouped as an important allergen by Schnuch et al. in their 2007 paper on the 26 fragrance ingredients, based on yet another algorithm for categorisation.

¹ Hostynek J J, Maibach H I. Is There Evidence that Geraniol Causes Allergic Contact Dermatitis? *Exog Dermatol* 2004;3:318–331

² Hostynek J J, Maibach H I. Is There Evidence that Linalool Causes Allergic Contact Dermatitis? *Exog Dermatol* 2003;2: 223–229

³ Gilpin S, Maibach H. Allergic contact dermatitis caused by farnesol: clinical relevance. *Cutan Ocul Toxicol.* 2010;29:278-87

⁴ Bruze M, Andersen K E, Goossens A. Recommendation to include fragrance mix 2 and hydroxyisohexyl 3-cyclohexene carboxaldehyde (Lyrall) in the European baseline patch test series. *Contact Dermatitis* 2008; 58: 129-133

⁵ Krautheim A, Uter W, Frosch P, Schnuch A, Geier J. Patch testing with fragrance mix II: results of the IVDK 2005-2008. *Contact Dermatitis.* 2010 Nov;63(5):262-9

⁶ van Oosten EJ, Schuttelaar ML, Coenraads PJ. Clinical relevance of positive patch test reactions to the 26 EU-labelled fragrances. *Contact Dermatitis.* 2009 Oct;61(4):217-23

⁷ Heisterberg MV, Menné T, Johansen JD. Contact allergy to the 26 specific fragrance ingredients to be declared on cosmetic products in accordance with the EU cosmetics directive. *Contact Dermatitis.* 2011 Nov;65(5):266-75

Several comments made reference to the publication by Schnuch et al. 2007¹, containing patch testing data obtained by "IVDK-Informationsverband Dermatologischer Kliniken" in the years 2003-2004 with the 26 allergens labelled under EU cosmetics regulation. In this study, Benzyl alcohol, Linalool, Limonene, Benzyl Salicylate, Benzyl Benzoate and Anisyl alcohol are described as rare sensitizers. Further it was stated that almost half of the current 26 allergens labelled under EU cosmetics regulation show zero or <0.1% incidence rates in patch tested patients.

The categorization of importance used by Schnuch et al. relies on the dataset presented in that publication and does not address the full scope of available information on the allergens. The SCCS opinion uses data from various centres across Europe, which indicate that the listed allergens do have a relevance for the consumer. Regional differences for sensitization to fragrance allergens do exist in Europe (see also discussion on geraniol, section 3.2). This was acknowledged by Schnuch et al. 2007, who stated that further studies in other European countries on large test populations should be performed as there might be regional differences in sensitization.

The statement in one comment that almost half of the currently labelled 26 allergens have zero or <0.1% "incidence rates" in patch tested patients is incorrect, as the publication lists only seven (of 26) substances with a proportion of positive reactions (standardised) of 0.0 or 0.1%, six of these yielding 0 or 0.1% crude positive reactions. Concerning limonene and linalool, it should be noted that these substances have only been tested in a non-oxidised form in the Schnuch et al. 2007 study, which are much weaker allergens than the oxidised compounds (see also section 4).

In some comments it was stated that several studies show a significant decline of allergies to the FM I since 1999 or that generalized sensitization rates for fragrance have been shown to decrease in recent years.

The SCCS acknowledges that some of the available studies have shown a decline in sensitization frequency to FMI during the early years of the last decade. However, recent data indicate that this decline does not further continue and that there is even a slight increase of FM I sensitization prevalence (as seen in recent, yet unpublished IVDK data).

In addition, the use of new screening tools for detection of fragrance allergy, e.g. oxidized limonene and linalool or inclusion of important essential oils in the baseline series in several contact allergy networks, shows the importance of continuous development of the patch test material and the adaptation of the composition of the baseline screening series, respectively, for being able to adequately diagnose fragrance allergy. Considering this extended scope of screening allergens, it is evident that the importance of fragrance contact allergy has certainly not declined in the recent years – notwithstanding changes in the relative contribution of single compounds to the overall load of morbidity.

In other comments it was criticised that the SCCS opinion did not consider that many of the 26 allergens which already have to be labelled, have not shown any increase in human allergic reactions.

¹ Schnuch A, Uter W, Geier J, Lessmann H, Frosch P J. Sensitization to 26 fragrances to be labelled according to current European regulation. Results of the IVDK and review of the literature. Contact Dermatitis 2007; 57: 1-10

The SCCS is of the opinion that there is no reason to expect an “increase in human incidence of sensitisation” after the introduction of labelling. If anything, a decrease might be expected due to avoidance of such ingredients by manufacturers and/or consumers. The SCCS moreover believes that an increase in human allergic reactions cannot be considered as the only criterion for relevant consumer allergens. Also substances which cause a persisting and/or particularly important clinical problem need to be identified and evaluated.

2.4. Clinical relevance of patch testing results

Several comments raised the issue of clinical relevance of the patch test data that have been considered in the opinion.

Doubts were stated whether the clinical relevance of patch test reactions according to the defined criteria (cited as references 92-95 in the SCCS Opinion) have been determined for the data used in the SCCS analysis. In addition, it was stated that other publications¹ giving more detailed criteria for clinical relevance, have not been cited in this opinion.

The SCCS acknowledges that clinical relevance is not addressed in most of the epidemiology studies forming the basis of its assessment. The assessment of relevance, while being theoretically well founded and described, often encounters practical difficulties and is thus not done in many of the large-scale clinico-epidemiological studies, such as the IVDK studies. While clinical relevance can provide useful information, it can often not be determined unequivocally, as it is based on comprehensive knowledge of prior exposures. Since the labelling of 26 fragrance allergens has been implemented, previous exposure to these substances can often be ascertained in the assessment of relevance of a positive patch test reaction, but for substances that do not need labelling, their presence in products is unknown, except in very rare cases where elaborate diagnostics and chemical analyses are feasible. Thus, positive patch test reactions as indicators for contact sensitisation have to be regarded as the primary outcome of such studies. The SCCS considers that the lack of established clinical relevance does, for reasons discussed in chapter 4.4.1 of the opinion, not exclude true sensitisation. Moreover, a true sensitisation diagnosed by patch testing, even if retrospectively without established clinical relevance, can become relevant prospectively, i.e. lead to allergic contact dermatitis upon future exposures. Additional text clarifying the SCCS view on clinical relevance has been added in chapter 6.2.1 of the opinion. A general chapter on patch testing has been added as chapter 4.2.

One comment doubted the figure presented in the opinion that 6% to 14% of patients are sensitised to fragrance mix, as only 50% to 65% of positive reactions are judged as relevant. Moreover, in the view of the submitter, this does not fit with the statement in the summary of 16% of eczema patients in EU being sensitised to fragrance ingredients, as the data would support only around half of this figure. Further, the most recent IVDK data (since 2005) were cited, which suggest that around 7% of patients are allergic to FM1 and that there is 50-65% clinical relevance.

¹ Lachapelle J.-M. (1997). A proposed relevance scoring system for positive allergic patch test reactions: Practical implications and limitations. *Contact Dermatitis*, 36, 39-43

Hostynek J.J., Maibach H.I. (2003). Operational Definition of a Causative Contact Allergen - A Study with Six Fragrance Allergens. *Exog. Dermatol.*, 2, 279-285

The SCCS does not see a discrepancy in these figures. As explained above in the general discussion on clinical relevance, a lack of established clinical relevance does not exclude true sensitisation. The prevalence of 7.3% reported in the latest IVDK study, which contrary to what is quoted in the comment makes no reference to clinical relevance, is just the prevalence of contact allergy to substances contained in FM I – the overall prevalence in IVDK studies (2005-2008) to the fragrance screening allergens included in the baseline series (i.e., also FM II, HICC, Myroxylon pereirae, and oil of turpentine) is 16.2%, as described in chapter 4.3.2 of the opinion.

One comment criticised that, in addition to lack of information on clinical relevance, the severity (+/-, +, ++, +++) of reactions has not been taken into account.

As explained above, information on relevance is available from a minority of patch test studies only. Thus, and for reasons of limited validity of the evaluation of clinical relevance in clinical routine, the target criterion the SCCS used was contact sensitisation per se, as diagnosed by patch testing. While the strength of patch test reactions (obviously depending on the patch test concentration and vehicle) carries information on the individual elicitation threshold, all reactions from + to +++ are considered allergic reactions in dermatological diagnostics.

It was commented that not everyone reacting positively to a patch test of a fragrance mix or individual constituents thereof, and therefore diagnosed as having contact allergy, also suffers an allergic contact dermatitis. It was claimed that many might never have issues with cosmetic products because of the low exposure levels. The relevance of patch testing was questioned as it involves greatly exaggerated exposure to a material compared to that arising from consumer use of cosmetics.

A positive reaction in a patch test indicates that a patient has contact allergy to a certain substance. This means that a permanent alteration in the immune status of the concerned individual has taken place. Contact dermatitis is the visible, clinical manifestation of this alteration, which may have occurred in the past or may occur in the future, given sufficient exposure. Patch test concentrations in clinical practice are well known not to mirror use concentrations in cosmetics. The patch test preparations used in clinical practice aim at achieving a suitable balance between sensitivity (avoiding false-negative reactions) and specificity (avoiding false-positive reactions). The comparison of levels of patch test exposure and consumer exposure is not appropriate (single vs. repeated exposures, anatomical sites, possibly impaired skin). In a ROAT test mimicking realistic exposures to cosmetic products, individuals do react to considerably lower levels of an allergen, applied repeatedly, than those used in diagnostic patch testing with its single application.

One comment questioned the usefulness of the SCCS's assessment by stating that a single fragrance may contain several hundreds of individual ingredients and it is commonly acknowledged that detection of allergy to one specific ingredient is difficult and false-positive and negative test results are possible. Interpretation of reactions was considered crucial for identifying allergens but it was said that it can be difficult to differentiate true allergic responses from irritant reactions.

In the view of the SCCS, the comment highlights the fact that those fragrance substances available for routine patch testing represent just a 'tip of the iceberg' of all fragrance substances used. It is not reasonable to assume that those substances not tested, which constitute the majority of those used, are not sensitising. Independently from this observation perceived difficulties in the reading of patch

tests are mentioned in the comment (see also recent editorial from D. Basketter¹). Although it is true that it can be difficult to differentiate allergic from irritant patch test reactions, especially in case of new, experimental patch test preparations, (i) there are international reading standards, which have been applied by the studies considered, and (ii) those allergens tested in many hundred or even several thousand patients, and especially the allergens included in the baseline series leave little room for doubt regarding the interpretation of patch test results as allergic or otherwise.

2.5. Study quality

It was stated in one comment that the criteria suggested in the opinion for categorisation of contact allergens have not been applied and study reports have been included that do not meet the basic quality criteria required. The validity of conclusion based on these data was questioned.

As outlined in the opinion, the SCCS has defined a set of basic quality criteria. These classification criteria have been applied to all studies used for qualification of a substance as an established contact allergen in humans. Notwithstanding this, if there are at least 2 studies with sufficient quality for categorisation as established contact allergen in humans, other studies that existed, but did not fully meet the quality criteria, may have been included, but they are irrelevant for categorisation. The methodology has been applied as a tool to make a best judgement of the available, heterogeneous data.

One comment pointed out that it is important that the material used for patch testing is of good quality and well characterised, including knowledge on impurities. This was stated in relation to natural essential oils, for which it was claimed that possible impurities from synthesis of substances, e.g. chlorinated intermediates, will not be present.

Raw materials for the test allergens are usually purchased from suppliers that also provide material for the manufacturing of fragrances used in consumer products. Thus, any putative (sensitizing) contaminant the patient has been exposed to would also be present in the patch test material. As long as the purity of the fragrance compounds (components) is not 100% it is important also to identify allergy caused by contaminants. Thus, even though from a theoretical point of view 100% purity is a goal, the current situation in dermatological diagnostics is considered, from a pragmatic point of view, quite adequate by SCCS. However, it cannot be excluded that additional contaminants are present in fragrance compounds from yet other suppliers. Once identified as sensitising, contaminants should be eliminated by good manufacturing practice. As long as no convincing evidence exists that an (avoidable) contaminant is the cause of allergenicity, the substance itself, in its standard purity, is considered as being the allergen.

Regarding natural extracts, contaminants from synthesis evidently do not occur, but could theoretically be introduced during extraction and storage, if inappropriate materials are used. One difficulty in case of natural extracts is the varying content of their single constituents, which limits standardisation of patch test material.

2.6. Data Reporting

One comment stated that the presentation of key measures, including percentage prevalence, in the opinion was often ambiguous and misleading and does not follow

¹ D. A. Basketter, I.R. White (2012). Diagnostic patch testing-does it have a wider relevance? Contact Dermatitis: 67:1-2

standard reporting guidelines such as those set out by the International Committee of Medical Journal Editors. It was further stated that basic study features that influence the significance of the result and might cause basic observations to be correlated need to be included so as to allow the reader to fully weigh the strength of the cited data. Despite the fact that the SCCS draft Opinion draws on the results of others, study units included in denominators (which then specifies the group examined) should have been clearly specified each time there may be any uncertainty.

The SCCS was unable to understand this comment based on the submitted evidence, as the ICMJE (<http://www.icmje.org>) guidelines, which are principally addressed to authors describing original research results, only contains a short section on statistics which does not recommend a particular way of reporting prevalences. Moreover, necessary information available in the clinical reports such as the number tested, the period of patch tests, the geographical area covered, and the proportion or number of positive results with a specific allergen are reported in the opinion. Beyond the screening allergens covered in chapter 4.3, such results can be found in the annex I, which is an integral part of the opinion. In addition, all data sources are clearly referenced giving the reader the possibility to access the original information.

2.7. Naturals

Several comments by producers of natural cosmetics and/or raw material suppliers stated that there is no evidence that fragrance substances have the same effect when they exist in a natural complex product such as an essential oil, as when applied as stand-alone component.

Along similar lines, commenters argued that it does not make sense to test single substances on animals and deduct from these tests that these substances are harmful to humans. These comments recommended that the only way to test substances in this context should be to test the whole essential oil. In their view, the isolation of compounds does not give the right perspective of the effects of the total product. It was claimed that plant compounds have an intrinsic way to balance each other out and create a bio-chemical and therapeutic harmony of sometimes hundreds of different compounds. This harmony is supposedly lost when single substances are separated from the totality of their synergistic environment.

The SCCS does not agree to the claim that allergenic substances in natural mixtures behave differently from the isolated substance. The SCCS predecessor SCCNFP issued an opinion on this topic in 2003¹, stating that:

"The above-mentioned opinions² of the Scientific Committee on Cosmetic Products and Non-Food Products intended for consumers (SCCNFP) concerning fragrance allergy in consumers are based on and supported by an extensive number of studies, published in leading scientific journals. None of these studies indicates a difference in allergenicity between a fragrance ingredient synthetically produced or extracted from a natural product. An important problem with fragrance substances

¹ SCCNFP (2003). Opinion concerning essential oils. Adopted 24-25 June 2003. SCCNFP/0673/03

² SCCNFP (1999). The Scientific Committee on Cosmetic Products and Non-Food Products intended for Consumers: Opinion concerning Fragrance Allergy in Consumers. A Review of the Problem. Adopted 8 December 1999. SCCNFP/0017/98

SCCNFP (2001). Memorandum on the SCCNFP opinion concerning fragrance allergy in consumers. Adopted 13 March 2001. SCCNFP/0450/01

of 'natural origin' is the difficulty of quality control. There may be considerable variation in the content of toxic/sensitising chemicals; oakmoss is an example. There is no demonstration in the peer reviewed scientific literature that fragrances compounds of natural origin are 'safer' than synthetics. On review of the information submitted, the SCCNFP is of the opinion that the data provided does not justify that the opinions adopted by the SCCNFP concerning fragrance allergy in consumers do not apply to essential oils."

The SCCS is of the opinion that since this opinion of the SCCNFP was issued, no additional scientific literature has become available to support a difference in allergenic behavior and endorses the opinion of the SCCNFP.

In relation to the above comments, the SCCS would like to further point out that the classification of natural extracts in tables 13-1 to 13-3 is based on data obtained using the essential oil, not individual constituents.

Concerning the safety of natural essential oils commenters made reference to a study on the tolerance of natural essential oils to humans allergic to the fragrance mix¹. The aim of this study was to quantitatively record the skin tolerance of true essential oils in patients with a documented existing contact allergy. The patients displayed a significant difference between their tolerance to the fragrance mix and the natural essential oils containing products. It was therefore concluded that persons with allergies to fragrance mix need not necessarily avoid products with essential oils.

The SCCS does not consider this publication convincing evidence that allergenic substances are generally better tolerated when being present as constituents of essential oils. The study contains methodological weaknesses (small samples size, specific allergens of patients and composition of essential oils not indicated) and has been published in a non-specialist journal for anthroposophist alternative medicine.

In addition, other published scientific literature on the subject exists, such as the recent publication on contact allergy to essential oils from the IVDK², which addresses concomitant reactivity between some essential oils and their (main) constituent(s). This study showed, for instance, that (i) concomitant reactivity between clove oil and synthetic eugenol, its main constituent, was exceptionally high and (ii) positive reactions to a number of essential oils were observed in a high proportion of patients, namely, > 1% in consecutively tested patients in case of 3 essential oils: sandalwood oil, ylang-ylang I+II oil and Jasmine abs.. As this threshold prevalence is considered to guide inclusion into the baseline series, these 3 essential oils were subsequently included in the German Baseline series. This is clear evidence of a yet underestimated role of these complex natural mixtures as contact sensitizers.

One comment said that botanicals or botanical fractions mentioned in table 13-1, table 13-2 and table 13-3 are all Natural Complex Substances possibly containing single allergenic substances but are not necessarily allergenic substances themselves. Furthermore it stated that the extraction processes can enable the elimination of undesirable allergenic substances. The commenter invited the SCCS

¹ Meyer U. Verträglichkeit natuerlicher aetherischer Oele bei ausgewiesenen Duftstoff-Mix-Allergikern. Der Merkurstab 2004: 57: 51-53

² Uter W, Schmidt E, Geier J, Lessmann H, Schnuch A, Frosch P J. Contact allergy to essential oils: current patch test results (2000-2008) from the IVDK network. Contact Dermatitis 2010; 63: 277-283.

to specify, for each of these botanicals or botanical fractions, the substance(s) which can be at the origin of an allergenic effect.

The SCCS acknowledges that the allergenic properties of botanicals or botanical fractions depend on their composition, i.e. the presence of allergenic components. The information on composition of natural extracts which was available from source documents has been included in Annex I. However, the classification of natural extracts in tables 13-1 to 13-3 has been based on data obtained with the natural extract itself, not individual constituents, which, until proven otherwise, need to be considered representative of natural extracts also used in marketed cosmetic products. Future research could aim at identifying main allergenic constituents of natural extracts, with a perspective of eliminating these, if possible. Sufficient elimination may, however, not always be possible, as illustrated by the case of oak moss abs. and its two main, but not only, allergenic compounds, atranol and chloroatranol.

Commenters stated that a threshold limit for allergenic constituents of essential oils would mean that the only product that will be allowed to be used as perfumes will be synthetic products. It was further said that, while more and more people are coming back to nature and natural products, perfumery industry will in this case be using only chemical and synthetic products.

To the SCCS it is not evident why concentration limits of single constituents of natural mixtures should jeopardize their use, especially in comparison to the respective single synthetic substances, which would be subject to the same restrictions. It is acknowledged that guidance regarding analysis and composition of natural mixtures may need to be developed in the risk management process.

Another contributor stated that the claim 'Hypoallergenicity tested' could not be valid when plant extracts are present in the product and requested SCCS to develop guidelines for test required to claim hypoallergenicity.

This comment is outside the scope of this opinion and the work of the SCCS as it deals with claims for cosmetic products which is an area related to policy, not risk assessment.

2.8. Cosmetovigilance data

Some comments from manufacturers of cosmetic products, in particular of natural cosmetics, made reference to in-house cosmetovigilance data, which were stated to not indicate a high rate of allergic reactions to products, in relation to the volume sold. It was claimed that the constant evaluation of this data together with pre-marketing tests would ensure that potential incompatibility risks are identified early. It was furthermore stated that these data indicate that even high concentrations of allergens listed in table 13-5 do not cause any elevated allergic reactions from consumers.

Apart from the fact that comprehensive and detailed cosmetovigilance data has not been made available to the SCCS, the Committee is of the opinion that cosmetovigilance information based on consumer complaints only is of limited value in the evaluation of sensitisation risk associated with cosmetic allergens, including fragrances. It does not identify specific causative substances, and is likely to severely under-estimate the frequency of contact dermatitis. An exception is the combination with qualified diagnostic work-up, as in the French REVIDAL/GERDA system, however, such data are generally published, thus publicly available, and are considered in the present opinion. Additional text on this issue has been added to chapter 13.1 of the opinion.

2.9. Industry self-mangement/QRA

Several comments made reference to the self-regulatory activities of the fragrance industry to assess and control substances with the potential for skin sensitization, in particular the Quantitative Risk Assessment (QRA) method.

It was stated that a number of new standards according to the QRA have been adopted and implemented, which will reduce consumer exposure to fragrance materials in product areas of concern (e.g. underarm products). Product category-specific standards were stated to apply to most substances listed in Table 13-5. Further it was said that, as some products (e.g. perfumes, aftershave products and deodorants) are the most frequent sources of sensitisation, possible restrictions should be product category specific. The need for such limitations, however, was in general, questioned. The criticism by SCCS that the dermal sensitisation QRA model has not been validated and provides no confidence that the levels of skin sensitisers identified by the dermal sensitisation QRA are safe for the consumers was rejected, and it was stated that such a risk management methodology could not be formally validated.

As already mentioned in the pre-consultation opinion, the QRA approach has been previously assessed in a separate SCCP opinion¹. There is no empirical evidence showing that any of the QRA-based interventions have had substantial impact on the frequency of sensitisation to fragrance substances. In the view of the SCCS, the 73 new standards introduced since 2008 have yet to prove their effectiveness. No evidence has been provided in the frame of this consultation that the measures have been successful in terms of reducing morbidity to a relevant extent.

The lack of validation of the QRA model is considered relevant, as it may result in inadequate risk management measures based on it. One important example is HICC, where an intermediate QRA-based IFRA standard did not arrive at adequate concentration limits. The use of the term "valid" or "validated" in the context of QRA indicates that this process, while having well-defined structural and process quality, cannot yet be assessed regarding its result quality, which is the ultimate criterion in terms of a validity of a broader sense. There is no demonstration that the QRA works prospectively to prevent sensitisation by fragrance ingredients. Moreover, a certain fraction of marketed products might not be covered by Industry self-regulation and result in higher exposures of the consumer.

Reference was made to a RIFM sponsored fragrance allergy prevalence study which is performed by the EDEN (European Dermato-Epidemiology Network) at six different geographical centres in Europe and includes over 12,000 subjects, with over 3,000 subjects patch-tested. First results have been obtained, and it is claimed that the data show a low prevalence of fragrance allergy in the general population in Europe. A final report is expected for July 2012.

Only preliminary information has yet been reported to the SCCS and the results have not been published in the scientific literature. Therefore the SCCS cannot comment on the outcome of the study. However, a number of studies have already addressed the prevalence of fragrance allergy on the general population level, as outlined in the opinion (chapter 4.3.3).

¹ SCCP opinion on dermal sensitisation quantitative risk assessment (citral, farnesol and phenylacetaldehyde), 24 June 2008.

http://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_135.pdf

2.10. Analytical issues

Several comments referred to possible analytical problems should the SCCS opinion be implemented.

One submitter considered that it is essential to have a standardized method for detecting and quantifying the presence of regulated materials. In this context, it was pointed out that the European Committee for Standardisation (CEN) has not yet finalized its development and publication of a method for quantifying the presence of the 24 chemically-defined substances originally proposed by the SCCNFP in its opinion of 1999. Addition of new substances to this list was considered to require additional standardization work. Another comment agreed that there are currently no validated analytical methods available to test the listed plant extracts in cosmetics. Mainly due to their complex formulations, matrix effects and variety of chemical classes, development of such analytical methods was considered to be time consuming, if feasible at all. It was considered of utmost importance that relevant validated analytical methods for quantification of the identified allergens are developed in parallel to the regulation, as such methods are presently not available.

It was further stated that the inclusion of a substance in Annex III to the Cosmetics Regulation for the purpose of labelling produces additional complications if this substance is also a constituent of natural extracts and essential oils. This was considered to be the case for most substances on Tables 13-1, 13-2 and 13-3 of the Opinion. Due to varying content of mixtures, manufacturers of cosmetics may have to determine the presence of the substance(s) and determine maximum acceptable levels, incurring additional costs and being a considerable burden for a manufacturer.

The CEN/TC 347 on Methods for Analysis of Allergens pointed out in its comment the necessity to base the regulation of natural extracts on the sensitizing and chemically defined constituents of natural extracts, or chemically defined and validated tracers, as it is not possible to base limits of natural extracts on thresholds of the mixes.

While the SCCS acknowledges the need for adequate analytical methods to verify the presence and concentration levels of fragrance allergens in extracts and formulations, comments concerning this aspect is related to risk management and out of the scope of the present opinion.

2.11. Labelling practicalities

Several comments were submitted concerning practical aspects related to the potential increase in number of substances to be labelled.

While consumer organisations called for labelling of all substances, in order to provide information also to consumers who are allergic to more uncommon allergens, other contributors doubted the value of increasing the number of labelled substances.

It was questioned whether information on an increased number of substances can still be provided on the product label. Some comments suggested making use of alternative means of providing this information. Another submission, in contrast, stated that the proportion of consumers who take note of these declarations was already small and that providing the information by the use of alternatives means would further reduce it.

Similar concerns were raised in relation to the inclusion of a large number of additional substances on the product label, which was considered to confuse the consumer more than provide relevant information.

It was further stated that for consumers who are aware that fragrance ingredients can be the cause of an skin reaction, the labelling of products with "fragrance" or 'parfum' is sufficient to allow the decision to avoid such products.

Concerns were raised about the use of labelling information by some non-governmental organizations to recommend against the use of products that contain more declared allergens than others.

Furthermore, it was suggested that there is no additional benefit of additional labelling for consumers or patients, as it will not be possible to include these substances in routine testing.

As detailed in the opinion (chapter 4.6.2), the SCCS is of the opinion that ingredient listing is important in clinical practice for the diagnosis of patients who are allergic to fragrance chemicals. It is also important for the patients in order to avoid future exposure to fragrance contact allergens which they may not tolerate. The comments in relation to possible practical implementation of labeling requirements and alternative ways to provide such information are aspects of risk management and therefore out of the scope of this opinion.

2.12. Socio-economic impact

A large number of contributions stated concerns about the economic impact of the possible implementation of the SCCS opinion, specifically on raw material suppliers, in particular small scale producers of naturals in developing countries, and, more general, on manufacturers of cosmetic products due to necessary changes in packaging, re-formulation etc. of a large number of products. Special reference was made to small scale producers in third world countries.

The comments regarding the socio-economic impacts of possible restrictive measures based on the SCCS opinion are related to risk management and therefore out of the scope of this scientific opinion. A public consultation on these aspects will be conducted in case the European Commission will in the future propose restrictions on fragrance ingredients.

2.13. Aromatherapy products

One comment stated that exposure to fragrance materials, resulting from other applications than cosmetics, e.g. aromatherapy, may present a source and contribution to contact allergy, which should be looked at before suggesting specific measures. In contrast, other comments claimed that there are many professional and reliable manufacturers of aromatherapy products and that aromatherapy products which are manufactured in compliance with the Industry self-regulation have a long history of safe use.

The SCCS acknowledges that use of fragrance substances used in aromatherapy applications can make a contribution to exposure to such substances. However, there is no harmonized definition of aromatherapy across the EU¹ and a detailed consideration of this aspect is beyond the scope of the opinion.

¹ European Commission. Manual on the scope of application of the cosmetics directive 76/768/EEC (art. 1(1) cosmetics directive), version 8.0 (June 2011)
http://ec.europa.eu/consumers/sectors/cosmetics/files/doc/manual_borderlines_ol_en.pdf

2.14. General toxicity

Concerns were raised by one submitter in relation to general systemic toxicity of fragrance chemicals, with the particular example of coumarin given.

While the SCCS agrees that risk assessment of a substance should in principle address all endpoints, this particular opinion is restricted to the issue of contact allergy to fragrance ingredients and the comment is out of the scope of this document.

2.15. Fragrance listings

Comments were received on alleged inconsistencies between some tables in chapters 7, 9, and 13. It was stated that the same material appears in two stereo isomeric forms in different tables with different CAS numbers: dimethyl tetrahydrobenzaldehyde (CAS 68737-61-1) in table 9.2 (possible sensitisers) and 13.3 (fragrance substances categorized as likely contact allergens by combination of evidence), while its isomers 2,4-dimethyl-3-cyclohexen-1-carboxaldehyde (CAS 68039-49-6) is also listed in table 9.2 but then appears in table 13.4 (fragrance substances categorized as possible contact allergens).

The SCCS does not share the view that the given example is an inconsistency. Both substances are listed, according to SAR considerations as 'possible sensitisers' (table 9.2); however, in the overall assessment in chapter 13 of the pre-consultation opinion, the former was categorised as 'likely CA' (table 13.3), the latter as 'possible CA' (table 13.4). The reason for this is that for the former, limited human evidence also exists, while for the latter this is not the case (and no animal data were available). The latter compound is, however, marked with R43 according to IFRA, and, in the updated opinion, is now also categorised as 'likely CA' (table 13.3 - See also comment below on *Citrus paradisi* and *Mentha arvensis*).

Further it was commented that Methyleugenol appears in table 13-3 but is not mentioned in chapter 7-2.

The erroneous entry has been deleted from Table 13.3

Another comment concerned the natural extracts *Citrus paradisi* (CAS no. 8016-20-4) and *Mentha arvensis* (CAS no. 68917-18-0) which are classified as R43 according to IFRA information. It was commented that the SCCS, while stating that they should be treated as likely contact allergens, has omitted these substances from list 13-3.

The SCCS initially did not include in table 13-3 the substances for which an R43 classification applies, but no other evidence was available. These substances were instead separately described in the text of chapter 13.1. To avoid confusion, the substances and natural mixtures for which this situation exists have now been included in table 13-3 and furnished with an explanatory footnote.

It was pointed out that artificial sandalwood is not a commercial product

The reference to the substance in chapter 4.1.3. has been deleted

In relation to chapter 4.3.2, a respondent commented that Balsam of Peru (crude) and Turpentine (especially without information on the quality and oxidation level) are not relevant markers for fragrances. It was stated that Balsam of Peru (crude) is not used anymore in fragrances and the qualities of both materials used for patch testing by dermatologists may present purity concerns, based on the source of supply.

The SCCS already stated in the pre-consultation opinion that crude balsam of Peru is not used in Europe, however extracts and distillates of *Myroxylon pereirae* are used in perfumery¹. Oil of turpentine is among the “top 200” used substances in perfumery (according to IFRA information), hence both mixtures can be seen as valuable screening tools for fragrance contact allergy due to their content of various single chemicals.

It was commented that the opinion states in chapter 4.6.1. “Deliberate avoidance of the use of fragrances where they are not essential to the function of a finished product, but used merely to add to its appeal.” In the view of the commenter, a definition for being essential versus adding to appeal does not exist and thus, such assessments cannot be made.

It is acknowledged that a continuum exists between products used/bought for their scent (e.g. perfumes, EDT, after shaves) and products not used primarily for their scent (e.g. moisturisers), and that in some cases, and possibly depending on a consumer’s preferences, categorisation of a given product would be equivocal. However, the existence of products which deliberately exclude fragrances, even if other, similar products on the market do contain fragrances (e.g., hand creams), show that such “deliberate avoidance” is a realistic option for certain consumer and household products.

2.16. Animal data

One comment questioning that an explicit request for guinea pig studies has been made to IFRA in the course of the development of this opinion

This statement has been removed from chapter 8.1.1 of the opinion.

One comment justified the use of Ethanol:DEP as a vehicle in the LLNA, as this was historically considered relevant to the vehicle and solvents used in fragrance compounds and fine fragrances. This justification was considered to be in line with OECD guidelines and it was stated that significant benchmarking work to compare and validate this vehicle against acetone:olive oil has been performed. It was concluded that Ethanol:DEP is a suitable vehicle for use in the LLNA².

Recommended vehicles according to the OECD test guideline were discussed in the opinion and are acetone: olive oil (4:1, v/v), N,N-dimethylformamide, methyl ethyl ketone, propylene glycol, and dimethyl sulphoxide. The guideline allows for the use of other vehicles if sufficient scientific rationale is provided. Although no rationale for the choice of other vehicles was given in the provided report³, the data obtained with Ethanol:DEP were not disregarded, but indeed used in the analysis.

One comment rejected the criticism by SCCS on using mean EC3 values when several studies on the same material existed. It was said that using the weighted mean value for EC3 means taking into account the intrinsic variability of biological responses and vehicles. Using only the lowest EC3 value would ignore biological and vehicle variability. Furthermore it was argued that the potency classifications do not

¹ Api A M. Only Peru Balsam extracts or distillates are used in perfumery. *Contact Dermatitis* 2006: 54: 179

² Betts C.J. et al (2007). The use of ethanol:DEP as a vehicle for the local lymph node assay. *Contact Dermatitis*. 56, 70-75. Api A.-M. (2004). Ethanol and Diethyl Phthalate: Vehicle Effects in the Local Lymph Node Assay. *International Journal of Toxicology*, 23, 171-177

³ RIFM. Local lymph node assay (LLNA) protocol summaries: Data presented at the 46th Congress of the European Societies of Toxicology. Research Institute for Fragrance Materials, Inc 2009

change for most fragrance ingredients in the potency classification schemes as only one out of 16 materials would change classification.

The SCCS is of the opinion that using a mean of EC3 values obtained in different experiments with identical setups, and the weighing of this mean by a suitable factor (eg. number of units in each experiment or variance of measurements in each replication of the experiment) is indeed a valid approach of aggregating results. However, as soon as experimental conditions differ, it is not valid any more, as information on variation introduced by a factor of experimental design, and not just chance variation, is concealed by the averaging process. Mean values in the submission by industry were based on experiments performed with different vehicles, and the experimental conditions thus did differ significantly. However, as mentioned, the categorisation into potency classes is hardly affected by choosing the mean vs. the minimum EC3 value. Mean values were not used by Gerberick et al 2005¹ or Kern et al 2012², and are not used in hazard identification for chemicals.

One comment criticised that the SCCS did not discuss or acknowledge the majority of fragrance allergens identified as weak to very weak, as defined by animal data. In Table 8-3, only 3 categories are presented with the moderate sensitising category having an EC3>2. In fact, many of the 127 materials in this group have EC3 values in excess of EC3>10-50, indicating weak to very weak induction potency. The fact that the SCCS did not attempt to discuss these low potency materials or establish proportional risk management measures was considered not to support a general approach to avoid disproportionate measures for allergens of differing potency.

The SCCS has chosen a potency categorisation according to an EC expert group on sensitisation, described in Basketter et al 2005, and in two memoranda by the SCCP. The same potency categorisation is proposed also in the ECHA guidance document on application of the CLP criteria³. In this context, it is considered inadequate to categorise substances as "weak" or "very weak" when they do generate an EC3 value and such substances are classifiable as skin sensitisers (R43 and H317).

Moreover, quantitative information on potency, especially in the range >10%, obtained in the LLNA has not been regarded as sufficiently valid to conclude a lesser hazard and subsequent lower risk for humans. For instance HICC with an EC3 value of 17.1% would then fall into a negligible category. Human experience, however, indicates that HICC is a potent allergen in humans. The SCCS in its opinion has therefore put the focus on human evidence, as explained above and in a new section added in chapter 6. Human data is considered to be more relevant than potency categorization derived from animal experiments.

¹ Gerberick G F, Kern P S, Schlatter H, Dearman R J, Kimber I, Patlewicz G Y, Basketter D A. Compilation of historical local lymph node data for evaluation of skin sensitization alternative methods *Dermatitis* 2005; 16: 157-202

² Kern P S, Gerberick G F, Ryan C A, Kimber I, Aptula A, Basketter D A. Local lymph node data for the evaluation of skin sensitization alternatives: a second compilation. *Dermatitis* 2010; 21: 8-32

³ ECHA Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures. Date: 04/2011. http://echa.europa.eu/documents/10162/17217/clp_en.pdf 2011

One comment concerned the statement "It can be concluded that skin sensitising potency, as assessed by the LLNA, is only one of several factors that are of importance for sensitisation to fragrance substances....Therefore, doses from repeated deposition onto skin must be considered a driving force of sensitisation risk." In the view of the commenter, this argument does not make sense scientifically. It was argued that sensitisation consists of 2 processes: induction and elicitation, and specific biochemical events are associated with each process. Sensitisation risk is based on the ability of a substance to trigger the biochemical events associated with both induction and elicitation. It was said that the LLNA is designed to measure events associated with induction and is validated for that purpose. The events for induction can be legitimately measured by the LLNA.

The SCCS would like to point out that repeated low-dose skin exposure is an effective sensitizing stimulus during induction, and a factor that needs to be taken into account in predicting sensitization risk. Recent findings identify an enhanced sensitisation efficacy when doses are split and applied repeatedly¹.

It was commented that a number of substances, for which the LLNA did not produce a tripling of the stimulation index, are indicated in Table 13-2 as "established allergens in animals". EC3 values are given as ">30", ">25", however, such values do not establish allergenicity in animals, but indicate that the material was not positive at the highest concentration tested.

The SCCS agrees to this comment and the substances in question have been removed from table 13-2.

2.17. SAR

One comment questioned the approach by the SCCS to use expert judgment for establishing similarity of materials to known allergens and to read across materials suspected of being allergens, as it was considered that no rationale or documentation had been provided. The approach was considered non-validated and not transparent in its criteria and it was criticised that no experimental evidence is presented to support the proposed classification.

The assessment by SCCS is based on long established principles in organic chemistry and in fact constitutes "text book knowledge" on chemical reactivity. The dependence of skin sensitization potency on reaction chemistry has been recognised since 1936² and has been confirmed in the peer reviewed literature many times ever since. The text in chapter 9 has been revised to better describe the above stated and to give additional references to support the approach. Moreover, it has been made clear that the approach is indeed based on expert knowledge, and is not quantitative (QSAR).

One contribution argues that the performed SAR could not be very exact, as the table of not predictable" substances contains Anisaldehyde, which can function as a Schiff's base and Trichlormethylphenylcarbinylacetate, which has a structural alert for high electron negativity of the trihalogenated substituent.

The SCCS would like to point out that in addition to structural alerts also considerations on reactivity were taken into account for the prediction. As an

¹ Paramasivan P, Lai C, Pickard C, Ardern-Jones M, Healy E, Friedmann PS. (2010). Br J Dermatol. Mar;162(3):594-7

² Landsteiner K, Jacobs J. Studies on the sensitization of animals with simple chemical compounds. J Exp Med 1936: 64: 625-629

illustration of the approach, the considerations for the two substances mentioned in the comment are detailed below.

Anise aldehyde can indeed form a Schiff base. For Schiff base electrophiles $R^1R^2C=O$ a quantitative relationship (QSAR) has been found. Sensitization potency in the mouse (LLNA) is correlated quantitatively with a combination of hydrophobicity (logP) and a reactivity parameter ($\Sigma\sigma^*$ for the two groups R^1 and R^2 in the Schiff base electrophile $R^1R^2C=O$)¹. However, this QSAR does not apply to compounds with the carbonyl group attached to a benzene ring. These tend to be non-sensitizers in the LLNA (examples that have been tested and found non-sensitizing are benzaldehyde and p-nitrobenzaldehyde). However there is clinical evidence for some aromatic aldehydes, such as benzaldehyde, being able to sensitize in human. Anise aldehyde is expected to be less reactive than benzaldehyde, so it should be a less potent sensitiser than benzaldehyde in humans, but whether it is sufficiently less reactive to make it non-sensitizing is not known. Because of this uncertainty, anise aldehyde was included in the "not predictable" table.

Trichlormethylphenylcarbinylacetate is an ester of the alcohol $PhCH(CCl_3)OH$. As pointed out in the comment, the CCl_3 group is electronegative, and it will make the alcohol more acidic than an aliphatic alcohol. If an alcohol is acidic enough (like a phenol), its esters will be electrophilic. Whether it is a sensitizer depends on whether or not this alcohol $PhCH(CCl_3)OH$ IS acidic enough for its anion to be a good enough leaving group to make the ester $PhCH(CCl_3)OCOCH_3$ a sufficiently reactive acyl transfer electrophile. This question can be addressed by calculating the pKa of $PhCH(CCl_3)OH$ from substituent constants: Taft constants (σ^*) of Ph and CCl_3 are 0.6 and 2.65 respectively. For alcohols, the $pK_a = 15.74 - 1.316 \Sigma\sigma^*$. The pKa of $PhCH(CCl_3)OH$ is 11.46, a weaker acid than phenol (pKa 9.9). So the acetate is less electrophilic than a phenyl ester would be and it cannot be predicted with confidence whether the acetate $PhCH(CCl_3)OCOCH_3$ will be reactive enough to sensitize. It might be possible to make a firmer prediction by looking for sensitization data other acyl transfer electrophiles, which could be used to predict $PhCH(CCl_3)OCOCH_3$ by read-across. However, such an exercise was beyond the scope of the present opinion.

2.18. Exposure

One comment opposed the statement in chapter 10.1 that "perfume oil of the same composition is used in different concentrations in the formulation of various cosmetics products within a brand of cosmetics". This was not considered generally true due to the technical needs to adjust fragrance formulations across product types, even within the same brand, in order to provide a consistent odour across different products.

This sentence in chapter 10.1 has been deleted.

One comment clarified that Isopropyl myristate is used in fragrance formulations as a solvent and not as a skin penetration enhancer. The influence on skin penetration depends very much on the overall product formulation and not just what is contained in the perfume component.

This sentence in chapter 10.1 has been deleted.

¹ Roberts D W, Aptula A O, Patlewicz G. Mechanistic applicability domains for non-animal based prediction of toxicological endpoints. QSAR analysis of the schiff base applicability domain for skin sensitization. Chem Res Toxicol 2006; 19: 1228-1233

3. QUESTION 2 AND SECTIONS OF THE OPINION RELATED TO IT

3.1. General issues

Several submissions commented on the approach for derivation of a general threshold for allergens of special concern for which no individual data is available.

One comment stated that the opinion does not explain the basis for the SCCS moving away from the previous approach of identifying allergens, where >2.0 % of clinical patients represents a concern level.

The SCCS would like to point out that it has never used or endorsed a concern level of 2% positive responses in clinical patients. The relative frequency of positive responses depends on the patient characteristics. Consecutive patients will yield around 1 to 2% for important allergens, whereas in aimed testing, prevalences will be much higher. Hence, the absolute number as a 'lower floor estimate' of the burden of morbidity due to the respective allergen was chosen. This introduces some bias in terms of an under-estimation of the importance, as many allergens are rarely tested, which limits their chance to reach any absolute threshold number. However, a consideration of relative frequency leads to an over-estimation of a substance if this is tested only in a few strongly suspected cases, yielding a high proportion of positive cases. In the extreme, case reports represent such a 'high relative, low absolute number' situation.

One submission commented that despite the fact that many more substances have been identified as being allergenic, the SCCS only proposes a ban for three of them. The commenter stated a need to prohibit the use of more substances and to address those sensitising substances in other relevant EU legislation such as toys and detergents. Moreover, a full declaration of fragrances was considered to be required also for other products than cosmetics as the use of fragrances in consumer products such as panty liners, tissues, toilet paper, candles, school items and toys.

This comments concerns possible regulatory measures in relation to fragrance allergens which are related to risk management and therefore are out of the scope of the opinion. While the SCCS can identify substances which may pose a risk to consumers, the decision on measures to be proposed is taken by the European Commission. However, as stated in the opinion, the SCCS is of the opinion that a restriction of the exposure to the allergens identified to be of concern, with the exceptions of HICC and *Evernia prunastri* and *Evernia furfuracea*, to the general threshold level of 100 ppm in cosmetic products would be protective for the majority of sensitised individuals as well as non-sensitised consumers.

The SCCS in principle agrees that exposure to fragrances from sources other than cosmetic products is also relevant and has extensively discussed such exposures in chapter 10 of the opinion. However, the scope of the present mandate, and thus the assessment in the opinion, is restricted to fragrance allergens in cosmetics.

3.2. Determination of "substances of concern"

It was commented that some of the allergens in the list of substances of special concern, namely cinnamyl alcohol, citral, coumarin, eugenol and geraniol have been classified as less important and less frequent allergens, with limited sensitisation potential, by Schnuch *et al.*¹. Moreover, the Heisterberg *et al.*¹ study of 2011 was

¹ Schnuch A, Uter W, Geier J, Lessmann H, Frosch P J. Sensitization to 26 fragrances to be labelled according to current European regulation. Results of the IVDK and review of the literature. Contact Dermatitis 2007; 57: 1-10

cited where the following frequencies were found: cinnamyl alcohol 0.7%, citral 0.3%, coumarin 0.2%, eugenol 0.3% and geraniol 0.0%.

The categorization of importance used by Schnuch *et al.*, based on the upper confidence interval accompanying the observed sensitization prevalence in this study, is, as all such classifications, arbitrary. More importantly, it obviously relies on the dataset presented in this publication and does not address the full scope of available information on the allergens. The SCCS opinion uses data from various centres across Europe, which show that the listed allergens do have a relevance for the consumer. Regional differences in Europe exist for sensitisation to fragrance allergens and are particularly pronounced in the case of geraniol (see also section 3.2). It should also be noted that the analysis made by SCCS is in general accordance with the ranking of allergens by Schnuch *et al.* 2007, i.e. the 10 chemicals in table 13.5 of the opinion are also among the most frequently detected allergens in the study by Schnuch *et al.* 2007, excluding linalool and limonene, which were tested in their non-oxidised form in the study (see also section 2.3).

A comment questioned the approach to set the same restrictions for all substances in Table 13-5, as there are differences in the frequency of sensitisation among the substances listed in this table. An example given was that, according to Krautheim *et al.*², (2010), HICC is by far the strongest single fragrance allergen in Fragrance Mix II, whereas Coumarin is much weaker.

The SCCS agrees that among the substances of special concern differences exist, which is evident from the available data presented in the opinion. As the substances in table 13-5 are defined by a threshold in absolute number of cases, evidently, numbers may be just above 100, or much higher than that. Any cut-off for inclusion of an allergen into the list of substances of particular concern has, by its nature, to be arbitrary. However, the choice of cut-off has been made based on informed judgment and additional rationale for the choice of cut off has been added in chapter 7.1 of the opinion. It should be noted that the general threshold of 100ppm is suggested for substances for which specific data to derive an individual threshold is not available.

Several comments specifically questioned the inclusion of geraniol in the list of allergens of special concern. Reference was made to a publication by Nardelli *et al.*³, which was stated to show a significant decrease of Geraniol allergies since 2007. Another comment claimed, based on Hostynek and Maibach 2006⁴, that a clear cause-effect relationship has infrequently or rarely been established in clinical tests. On the basis of the generally weak sensitizing potential of this substance, coupled with its generally low exposure conditions, the prevalence of clinical cases would not be expected to be particularly high. In another comment on the same topic it was said that geraniol had shown consistent low rates of sensitisation that

¹ Heisterberg M V, Menne T, Johansen J D. Contact allergy to the 26 specific fragrance ingredients to be declared on cosmetic products in accordance with the EU cosmetics directive. *Contact Dermatitis* 2011; 65: 266-275

² Krautheim A, Uter W, Frosch P, Schnuch A, Geier J. Patch testing with fragrance mix II: results of the IVDK 2005-2008. *Contact Dermatitis* 2010; 63: 262-269

³ Nardelli A, Drieghe J, Claes L, Boey L, Goossens A (2011). Fragrance allergens in 'specific' cosmetic products. *Contact Dermatitis*, 64, 212-219

⁴ Hostynek J, Maibach HI (2006). Is there evidence that Geraniol causes allergic contact dermatitis? *Exog Dermatol* 3: 318-331

have not escalated in recent years. It was considered that geraniol would be treated disproportionately compared to other materials that show very similar rates of sensitisation, but were not included in the list of allergens of concern. Reference was made to Schnuch et al.¹, where similar rates in eczematous patients of 0.4% incidence for geraniol versus 0.3% for Amyl cinnamic alcohol were shown, yet the SCCS Working Group has not included Amyl cinnamic alcohol for proposed restriction. In addition, the study of Heisterberg et al. was cited, where the frequency of sensitization to Amyl cinnamic alcohol was 0.1% and 0.0% to Geraniol.

The SCCS does not agree that geraniol should not be considered an allergen of concern. In the opinion of the SCCS, the study by Nardelli et al 2011 does neither mention nor show a "significant decline" specifically for geraniol. From the graph presented in the publication rather a marked fluctuation of sensitisation prevalence is evident. Moreover, the publication states that geraniol was among the most frequent ingredients for which presence could be confirmed in the causal specific cosmetic products.

Regarding the stated generally low exposure conditions for geraniol it should be noted that exposure assessments found geraniol to have one of the highest maximum daily exposures among the studied terpene alcohols due to the exposure from many different sources in everyday life, as described in a publication of the RIFM EXPERT Panel ².

Pronounced regional differences in Europe have been observed for sensitisation to geraniol. In Spain, geraniol is a top ranking fragrance allergen³. This may in part be due to the use of geraniol in topical treatments for leg ulcers, but shows the potential of geraniol to cause contact allergy. Moreover, in a study of contact allergy in hand eczema patients it ranked as number 6 of fragrance allergens with a prevalence of 0.9% positives⁴. Therefore, although the results of some studies have indicated low frequency of reactions to geraniol, considering the overall evidence the SCCS maintains the opinion that geraniol should be included in the list of allergens of concern. In relation to patch testing results with geraniol, the SCCS would furthermore like to point out that the diagnostic tool used for detection of contact allergy caused by geraniol might not be optimal. Geraniol acts as a prohaptens and a prehapten and forms allergenic compounds by metabolic or abiotic activation. It might not be sufficient to use the prohaptens in low concentrations to detect cases of contact allergy caused by the metabolites formed. A better way of detecting contact allergy caused by geraniol could therefore be to test with the metabolites directly. The major metabolites formed are the aldehydes geranial and neral which are the two isomers of citral. It was seen in the patch test study by Schnuch et al 2007⁸ that there was a clear correlation between the positive

¹ Schnuch A, Uter W, Geier J, Lessmann H, Frosch P J. Sensitization to 26 fragrances to be labelled according to current European regulation. Results of the IVDK and review of the literature. *Contact Dermatitis* 2007; 57: 1-10

² Belsito D, Bickers D, Bruze M, Calow P, Greim H, Hanifin JM, Rogers AE, Saurat JH, Sipes IG, Tagami H (2008). A toxicologic and dermatologic assessment of cyclic and non-cyclic terpene alcohols when used as fragrance ingredients. *Food Chem Toxicol* 46 Suppl 11: S1-S71.

³ Cuesta L, Silvestre J F, Toledo F, Lucas A, Perez-Crespo M, Ballester I. Fragrance contact allergy: a 4-year retrospective study. *Contact Dermatitis* 2010; 63: 77-84

⁴ Heydorn S, Menne T, Johansen J D. Fragrance allergy and hand eczema - a review. *Contact Dermatitis* 2003; 48: 59-66

reactions to geraniol and citral. Furthermore, geraniol and neral are the major allergens detected also after autoxidation of geraniol. A clear correlation between patch test reactions to oxidized geraniol and citral was seen in a recent study¹, which further underlines the importance of testing with the actual allergen and not with the parent compound.

Regarding amyl cinnamyl alcohol, the classification of + in the pre-consultation opinion has been corrected to ++ in tables 7-1 and 13-1. The same correction was made for amyl cinnamal, benzyl alcohol and benzyl salicylate

In another comment, it was claimed that geraniol-sensitised individuals can tolerate natural cosmetic products that contain several hundred ppm of geraniol. Reference was made to a recent clinical study on ACD patients (data to be submitted for publication). In the view of the commenter the 100 ppm threshold for elicitation would therefore have no practical relevance and would not provide any greater health reassurance than the current risk management measures which allow people to avoid exposures through ingredient labelling.

Concerning the tolerance of natural or other products containing geraniol, the SCCS at present cannot comment on the mentioned study, as the results mentioned have not been published or made otherwise available to the SCCS and thus cannot be evaluated.

It was stated that the classification of geraniol as +++ (> 100 PT results) in table 13-1 was not conceivable as the clinical studies with geraniol given in Annex I show a maximum of 80 cases.

In the annex of the updated opinion, the results of Cuesta et al.² have been added which were accidentally omitted from the pre-consultation opinion. Studies published since 1999, together with those studies already included in the previous opinion, comprise > 100 patients with positive patch test reactions to geraniol.

3.3. Derivation of limit

Commenters criticised that the Opinion used a non-validated statistical model based on a meta-analysis using a very small data set to try to establish a safe limit threshold for elicitation, in order to restrict materials that the SCCS considers of high risk. This approach to define a 'one limit fits all' was considered questionable, as it had not been scientifically or clinically validated, presented at scientific meetings or published in a peer-reviewed scientific journal. In the view of the commenter, this model would address a non-measurable subpopulation and does not serve any value to the majority population who are not sensitised. It was stated that it would require substantial research in order to ensure that regulatory authorities are not using unsubstantiated risk management measures.

The approach taken in this opinion by the SCCS is based on scientific evidence published in peer-reviewed journals the past 20 years. The meta-analysis deriving the general threshold limit at 0.8 µg/cm² limit has also been published in a peer-reviewed journal³. The use of threshold limits based on elicitation data is a well-

¹ Hagvall L, Karlberg AT, Bråred Christensson J. Contact allergy to air-exposed geraniol: clinical observations and report of 14 cases. *Contact Dermatitis* 2012; 67:20-27

² Cuesta L, Silvestre J F, Toledo F, Lucas A, Perez-Crespo M, Ballester I. Fragrance contact allergy: a 4-year retrospective study. *Contact Dermatitis* 2010; 63: 77-84

³ Fischer L A, Menne T, Voelund A, Johansen J D. Can exposure limitations for well-known contact allergens be simplified? An analysis of dose-response patch test data. *Contact Dermatitis* 2011; 64: 337-342

established methodology which has been successfully applied in the EU to prevent further cases of induction and elicitation (primary and secondary prevention) in the case of nickel allergy¹, chromium in cement², dimethyl fumarate in consumer items³, chromium in shoes in Germany⁴, and also in part –it seems– in IFRA guidelines e.g. concerning HICC.

It should be noted that the general threshold is only suggested to be used for substances of concern if no specific data of sufficient quality exist to set an individual safe threshold. In cases where specific data of sufficient quality are available, these data should be used to set an individual safe threshold.

One comment stated that elicitation thresholds are dependent upon individual factors including the dose exposed to in the acquisition of allergy⁵. Reference was made to experimental evidence showing that the threshold dose of elicitation varies in accordance with the conditions of induction⁶, i.e. when induction conditions are severe, the elicitation threshold dose is low, but when induction occurs under mild conditions, much higher exposures are required to elicit an allergic reaction. In the view of the commenter, this means that it may be possible for patients to have acquired allergies under low exposure conditions (e.g. from using cosmetics or other consumer products) that will never be elicited during their everyday lives as long as exposure remains low. However, these allergies may be artificially elicited under the higher exposure conditions experienced in patch testing. These positive reactions may not be clinically relevant and indeed may not represent a cause for concern for the patient as they reflect an allergic state which may never manifest itself under product use conditions.

The SCCS acknowledges that experimental evidence exist that if a naïve individual is sensitized by a single application to one high dose of an extreme allergen, this individual may react to lower levels at elicitation (one dose) than an individual sensitized by a single application of a low dose of allergen. However, it has recently been shown that repeated applications of a low dose of the same extreme allergen sensitizes individuals to the same extent (induces the same degree of reactivity) as

¹ Thyssen J P, Johansen J D, Menne T, Nielsen N H, Linneberg A. Nickel allergy in Danish women before and after nickel regulation. *The New England journal of medicine* 2009; 360: 2259-2260

Thyssen J P, Linneberg A, Menne T, Nielsen N H, Johansen J D. The association between hand eczema and nickel allergy has weakened among young women in the general population following the Danish nickel regulation: results from two cross-sectional studies. *Contact Dermatitis* 2009; 61: 342-348

² Zachariae C O, Agner T, Menné T. Chromium allergy in consecutive patients in a country where ferrous sulfate has been added since 1981. *Contact Dermatitis* 1996; 35: 83-85

³ 2009/251/EC: Commission Decision of 17 March 2009 requiring Member States to ensure that products containing the biocide dimethylfumarate are not placed or made available on the market. *OJ L 74*, 20.3.2009, p. 32–34

⁴ Bedarfsgegenständeverordnung in der Fassung der Bekanntmachung vom 23. Dezember 1997 (BGBl. 1998 I S.5), zuletzt geändert durch Artikel 5 der Verordnung vom 13. Dezember 2011 (BGBl. I S. 2720)

⁵ Friedmann P S (2007). The relationship between exposure dose and response in induction and elicitation of contact hypersensitivity in humans. *British Journal of Dermatology*; 157: 1093-1102

⁶ Hostynek J J, Maibach H I. Threshold of elicitation depend on induction conditions. Could low level exposure induce sub-clinical allergic state that are only elicited under severe conditions of clinical diagnosis? *Food and Chemical Toxicology* 2004;42:1859-1865

a single application of a higher dose¹. This finding is of relevance for the use of cosmetics as consumers usually are exposed to repeated lower doses of allergen through the use of cosmetics over a longer period, which may still be relevant for elicitation. This is in agreement with other studies, where a relationship between patch test results and elicitation by repeated application of lower (normal use) doses in sensitized eczema patients, have been shown ².

The comment on clinical relevance has been addressed in section 2.4.

One comment raised the point that the references used in the SCCS pre-consultation Opinion to support elicitation thresholds are largely based on studies for which the protocol would exaggerate the sensitivity of the patients due to prior patching with high levels of known sensitizers in order to confirm an allergy. It was said that this may serve to "prime" the immune system to a response, followed by subsequent patch applications at increasing concentrations, which exaggerate exposures (patch test followed by a ROAT), versus normal consumer products. This may therefore provide a subsequent lower value for the elicitation threshold than would be experienced versus day-to-day exposure.

While the theoretical basis of this hypothesis is understood by the SCCS, there is no objective evidence that in practice this occurs. In a study of individuals allergic to nickel repeated patch testing of 4 times over 7 months was performed. Variation in individual reactivity was recorded (increasing as well as decreasing) but no general increase in reactivity to nickel was identified over time³. The general threshold value is based on patch test dose-response curves, which have been shown to correlate with responses provoked under simulated use conditions (ROATs), but which has not been influenced by any prior diagnostic or experimental application of the allergen. ROATs are performed using repeated applications to confined skin sites (usually 9 or 25 cm²) to solutions of allergens in a matrix. Usually two applications are made per day for 2 to 6 weeks to the same skin site. The SCCS considers that this cannot be considered an exaggerated exposure compared to the normal use of cosmetic products e.g. moisturizers.

Along the same lines, it was stated that investigations aimed at determining the threshold of elicitation actually modify the threshold they are trying to identify. It was detailed that each successive application of the allergen, at exaggerated concentrations, to the skin of sensitised patients would lower the elicitation threshold and boost the allergic response. Such effects were considered evident from studies involving serial applications at the same dose, and would not occur under normal conditions of consumer product use. Reference was made to Repeat Open Application Tests (ROATs) on isoeugenol-sensitive patients⁴, where the

¹ Paramasivan P, Lai C, Pickard C, Ardern-Jones M, Healy E, Friedmann PS. Repeated low-dose skin exposure is an effective sensitizing stimulus, a factor to be taken into account in predicting sensitization risk. *Br J Dermatol*. 2010 Mar;162(3):594-7

² Fischer L A, Johansen J D, Menne T. Nickel allergy: relationship between patch test and repeated open application test thresholds. *Br J Dermatol* 2007; 157: 723-729

Fischer L A, Johansen J D, Menne T. Methylidibromoglutaronitrile allergy: relationship between patch test and repeated open application test thresholds. *Br J Dermatol* 2008; 159: 1138-1143

³ Hindsén M, Bruze M, Christensen O B (1999). Individual variation in nickel patch testing reactivity. *Am J Contact Dermatitis* 10, 62-67

⁴ Andersen K.E. et al (2001). The Time-Dose-Response Relationship for elicitation of contact dermatitis in Isoeugenol allergic individuals. *Toxicology and Applied Pharmacology*, 170, 166-171

subjects failed to react to the same dose of test material until they had experienced at least 14 applications. In an earlier study on the elicitation threshold of isoeugenol using a different type of use test¹, only two patients reacted after 11 and 14 days of repeated exposure to identical doses. In another study on cinnamic aldehyde sensitive patients², nearly half of these patients reacted to twice daily applications of the allergen only after day seven and some went up to day 14. The commenter stated that the observed boosting is believed to be a procedural artefact of use tests and, as such, it has been questioned whether tests like the ROAT provide 'real life' estimates of patient exposure to potential allergens. Typically, the ROAT employs twice daily applications of the allergen/product to a defined area of skin. In the opinion of the commenter, although the concentration employed is lower than standard clinical tests such as the patch test and is normally within the range of consumer product levels, the effect of continued application (above that usually experienced in day-to-day life) to a small region of skin needs to be explored.

The SCCS is of the opinion that the comment misinterprets the research results on effects of cumulative exposure of low doses of allergens, which in fact mimic closely the exposure found under real-life conditions. This holds true especially for fragrance substances that are present in products (cosmetics and household products) which are used several times a day every day during the whole lifetime by consumers. Moreover, it is not the area of application which is a driving force of induction or elicitation, but rather the dose per area, which, in ROAT studies, is often similar to that found in consumer products. In the view of the SCCS, the cited references do not support the notion of an enhancement of sensitivity of individuals by ROAT studies.

The comment further criticised that despite the above-mentioned technical difficulty of reliably quantifying elicitation thresholds, values obtained from studies on five substances used as or found in fragrance materials have been proposed to support the hypothesis that an elicitation threshold of 100 ppm applied to fragrance chemicals considered as contact allergens of special concern can be assumed to support prevention of disease in pre-sensitised people. It was further stated that, understanding the highly variable inter-individual threshold of response of elicitation, and the exceptionally few people with disease, it would be impossible to establish whether a general limit would provide any greater health reassurance than the current risk management measures that allow people to avoid exposures through ingredient labelling.

It was further commented that the elicitation threshold model does not contain data from materials of very low induction potency potential. The data used were said to come from mostly potent, non-fragrance allergens. It was considered inappropriate to propose a model for risk management before it has not been broadly discussed and validated by the scientific community and developed to proportionally handle materials that clearly have very wide differences in allergenic potency. A need for further research was seen to establish under real world use conditions whether there is a potential for elicitation from consumer products containing fragrance materials. The current approaches of identification of elicitation thresholds use vastly exaggerated exposures relative to real world product use to determine if a sensitized person can exhibit an elicitation response.

¹ Epstein W.L. (1982). The use test for contact hypersensitivity. Archives of Dermatological Research, 272, 279-281

² Johansen J D, Andersen K E, Rastogi S C, Menne T. Threshold responses in cinnamic-aldehyde-sensitive subjects: results and methodological aspects. Contact Dermatitis 1996; 34: 165-171

Concerning the criticism in relation to an elicitation-based threshold, the SCCS would like to stress that the model used is targeting the relevant end-point for the disease, namely allergic contact dermatitis. The potency of the allergen as determined by LLNA, is not sufficient to predict the extent of the problems of contact allergy/allergic contact dermatitis. Additional information is needed from clinical and epidemiological studies, exposure assessment and dose-elicitation studies. For instance, the elicitation thresholds of e.g. HICC and isoeugenol are very similar (0.85 µg/cm² and 0.89 ug/cm², respectively) despite very different potencies in the LLNA (EC3 values of 17.1 and 0.54, respectively). Both are frequent causes of contact allergy.

The elicitation threshold model is based on 16 studies of 8 allergens, two of which are fragrance ingredients. Based on EC3 values, the analysis included data from moderate (EC3=17) to extreme allergens (EC3=0.005), with a median EC3 value of 1.2. The fragrance allergens to which the limit is suggested to apply are ranging from extreme (cinnamal EC3=0.2) to moderate allergens (EC3=21). In one case (coumarin) an EC3 value has not been established. The median EC3 value was 4.8. Considering these ranges, the SCCS is of the opinion that the general potency profile of the fragrance substances of concern is not very different from those included in the model to provide the suggested general safe threshold, even though indeed some difference is existing and has been acknowledged by the SCCS, as mentioned in chapter 13.2 of the opinion.

The limited scope and nature of allergens underlying the generic threshold suggested has already been addressed by the SCCS in the opinion as a limitation of the approach. As unequivocal scientific evidence on a set of different, 'representative' fragrance allergens with regard to elicitation thresholds is not expected to become available in the near future, and, on the other hand, a substantial number of patients is affected by contact allergy to the allergens identified in the opinion, the derived general threshold is proposed as a 'pragmatic' approach to limit consumer exposure to the most frequent allergens.

Additional text has been added in chapter 11.2.2 in relation to the above points.

Commenters criticised that the suggested threshold limit of 100 ppm for all product categories does not differentiate between categories of cosmetic products leave-on and rinse-off products. It was stated that especially the application of deodorants occurs in a very sensitive area of the skin with occlusive effects on the skin, and is not directly comparable to the product application on e.g. legs or the face.

As stated in the opinion, The general threshold is indicative of a safe level for the majority of sensitised individuals, but does not preclude that the most sensitive subset of the population may react upon exposure to the allergen. These levels are based on patch tests and take no account of anatomical sites of exposure, frequency of exposure or vehicle effects. A general threshold would have to take into consideration the uncertainties in quantification of exposure and safe thresholds as well as the possibilities of aggregated exposures and exposure to chemically similar substances. Therefore, the SCCS, has chosen the product category carrying the highest risk of sensitisation and elicitation, which is deodorants, to drive the generation of a general threshold.

3.4. HICC

Concerning HICC it was stated in several comments that industry has taken multiple steps to severely restrict the use of HICC with a view to reduce the incidence of allergy to this substance, with the latest intervention in 2009. It was argued that the clinical data presented in the pre-consultation SCCS Opinion

predated this action and can therefore not be used to conclude that this action was ineffective.

The SCCS is of the opinion that no new evidence is presented in the comments. A recent analysis from the IVDK network¹ show that while the prevalence of HICC contact allergy in consecutively tested patients declined with statistical significance between 2002 and 2011, this trend is not consistent and the magnitude of change is very small, leaving the prevalence of contact allergy still on an extraordinarily high level of about 2% in consecutively tested patients. In a recent study from Denmark², some fluctuation around a mean prevalence of about 2.5% was noted, but no trend for a decline in reactions was observed. These most recent data on contact allergy to HICC have been added in the updated opinion.

3.5. Everia prunastri/Everia furfuracea

In one comment it was argued that the use of Everia prunastri and Everia furfuracea in fragrances is not the only source of exposure to atranol and chloroatranol. It was criticised that other important exposures may need to be considered and managed, but are not covered by the opinion. Reference was made to a publication describing four cases of occupational contact dermatitis from lichens in farmers and gardeners³.

The SCCS is of the opinion that other exposures than via perfumes, such as described in the cited reference are unlikely to play a significant role, as e.g. foresters, farmers or gardeners who might become sensitised by occupational exposure can be reasonable expected to constitute not more than a minute minority in the patch test patients. For instance, in a comprehensive analysis of IVDK data 1992 to 2000⁴, foresters and hunters comprised 0.06%, farmers 0.56% and gardeners/florists 0.78% of all patients tested; an increased prevalence of FM I contact sensitisation (including E. prunastri extract) has not been identified in this or similar analyses in these occupations.

It was pointed out that there have been on-going efforts by the fragrance industry since 2009 to demonstrate that commercial qualities with low atranol/chloroatranol content are effective in reducing allergy and also prevent those already sensitised to elicit. It was said that such work has been difficult to complete, partly due to the lack of available patients with relevant oakmoss/treemoss allergy. It was further reasoned that it would be inappropriate to implement a ban of atranol and chloroatranol, which would equal a ban of oakmoss and treemoss, before the above mentioned activities have been finalized.

¹ Schnuch A, Geier J, Uter W. Is hydroxyisohexyl 3-cyclohexene carboxaldehyde sensitisation declining in central Europe? *Contact Dermatitis* 2012; 67: 47-49.

² Heisterberg M V, Laurberg G, Veien N, Menné T, Avnstorp C, Kaaber K, Andersen K A, Sommerlund M, Danielsen A, Andersen B, Kristensen B, Kristensen O, Nielsen N H, Thormann J, Vissing S, Johansen J D. Prevalence of allergic contact dermatitis caused by hydroxyisohexyl 3-cyclohexene carboxaldehyde has not changed in Denmark. *Contact Dermatitis* 2012; 67: 49-51

³ Aalto-Korte K, Lauerma A, Alanko K. Occupational allergic contact dermatitis from lichens in present-day Finland. *Contact Dermatitis* 2005;52:36-38

⁴ Uter W, Gefeller O, Geier J, Lessmann H, Pfahlberg A, Schnuch A. Untersuchungen zur Abhängigkeit der Sensibilisierung gegen wichtige Allergene von arbeitsbedingten sowie individuellen Faktoren (Fb 949, Bundesanstalt für Arbeitsschutz und Arbeitsmedizin), Wirtschaftsverlag NW, Bremerhaven, 2002, ISBN 3-89701-819-5

The SCCP concluded in its 2008 opinion on Oak moss and Tree moss¹ that a clear correlation between the atranol/chloroatranol content in different preparations of oakmoss and treemoss and results of LLNA tests did not become apparent. Moreover, a human study using chloroatranol and atranol-reduced oakmoss² showed that the majority of patients sensitised to *E. prunastri* extract were still elicited by an alternative extract with reduced content of (chloro-) atranol. According to these results, a relevant decline in reactions to oakmoss/treemoss is not to be expected. The reference Nardelli et al., 2009 has been added to the opinion in chapter 11.4 and 13.2

3.6. Other issues

One comment made reference to the attempts by industry to determine a dermal sensitization threshold (DST) or threshold of sensitization concern (TSC), based on animal (Safford, 2008; Safford et al. 2011) or human data (Keller et al. 2009) and suggested to include this in the opinion.

The cited work aims to apply the concept of a general "threshold for toxicological concern" to the endpoint of sensitisation. The SCCS is aware of this work and has critically reviewed the approach in its opinion on TTC³. The approach is largely based on the dermal sensitisation QRA method published by Api et al.⁴ which was reviewed by the SCCP⁵ and considered to require further refinement and validation to be applicable for risk assessment of new substances (see also section 2.9).

One comment concerned the SCCS statement that most experimental studies are done on individual fragrance ingredients while exposure to allergens is usually a mixture of allergens and recommend taking into account the findings of the "State of the Art of the Assessment of Endocrine Disruptors" report⁶ (Kortenkamp et al., 2012) as it was considered to contain relevant information with regard to mixture toxicity. The comment concluded that because of the lack of knowledge how fragrances react together, it is important to use the precautionary principle, and have full declaration as well as banning the most allergenic substances.

The SCCS is of the opinion that the "State of the Art of the Assessment of Endocrine Disruptors" report has no relation to allergens. However, in a different

¹ SCCP (Scientific Committee on Consumer Products), Opinion on oakmoss / tree moss (sensitisation only), 15 April 2008

² Nardelli A, Gimenez-Arnau E, Bernard G, Lepoittevin J P, Goossens A. Is a low content in atranol/chloroatranol safe in oak moss-sensitized individuals? *Contact Dermatitis* 2009; 60: 91-95

³ SCCS, SCHER, SCENIHR (2012). Joint Opinion on the Use of the Threshold of Toxicological Concern (TTC) Approach for Human Safety Assessment of Chemical Substances with focus on Cosmetics and Consumer Products, 8 June 2012
http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_092.pdf

⁴ Api A M, Basketter D A, Cadby P A, Cano M-F, Ellis G, Gerberick F, Griem P, McNamee P M, Ryan C A, Safford R. Dermal Sensitization Quantitative Risk Assessment (QRA) for fragrance ingredients. *Regul Toxicol Pharmacol* 2008; 52: 3-23

⁵ SCCP. Opinion on Dermal Sensitisation Quantitative Risk Assessment (Citral, Farnesol and Phenylacetaldehyde). Scientific Committee for on Consumer Protection, adopted 24 June 2008. 2008

⁶ Kortenkamp A, Martin O, Faust M, Evans R, McKinlay R, Orton F, Rosivatz E (2011). State of the Art of the Assessment of Endocrine Disruptors. Project Contract Number 070307/2009/550687/SER/D3.
http://ec.europa.eu/environment/endocrine/documents/studies_en.htm

report by Kortenkamp et al. of 2009¹, reference is made to a study by Johansen et al. (1998), which showed an augmented reaction to the simultaneous challenge with two allergens as compared to reactions to each individual allergen.

The SCCS in its opinion has pointed out that the risk of sensitisation and elicitation may depend on the mixture of substances, but that very few studies addressing this issue currently exist. For this reason the request to improve the knowledge base on cocktail effects on sensitisation/elicitation has been included in the research recommendation.

In one comment, it was criticised that the SCCS opinion was not addressing in particular the exposure of children and does not differentiate between adult and children products when proposing a global threshold. This approach was considered questionable taking into consideration that children are in particular vulnerable and that allergies have to be prevented starting as early as possible in life through lowering exposure to allergenic fragrances.

The SCCS is of the opinion that in relation to allergy, there is no good scientific evidence showing that children have higher sensitivity than adults. As stated in the opinion, the proposed general threshold based on elicitation levels in sensitised individuals can be expected to also significantly reduce the risk of induction of non-sensitised consumers, independent of the age group.

4. QUESTION 3 AND SECTIONS OF THE OPINION RELATED TO IT (CHAPTER 5)

4.1. Presence of oxidised fragrance compounds in products

Several contributors stated that there is no evidence that oxidative activation does actually occur during the manufacturing and use of cosmetic products. In relation to limonene and other oxidisable products, it was stated that Industry purity standards exist to ensure low levels of peroxides in fragrance ingredients. The existence of purity standards was also reiterated for essential oils used in natural and organic cosmetic products. In relation to naturals it was additionally stated that the degree of oxidation depends on the purity and nature of the specific essential oils as well as abiotic conditions (temperature and light conditions)². Further it was detailed that cosmetic products are manufactured routinely with the presence of antioxidants to enable suitable stability for the shelf life of the product. Other measures reported to protect cosmetic products from oxygen were oxygen exclusion, use of inert gases during manufacturing and packaging, and special application systems. Finally, it was pointed out that testing of raw materials upon receipt and during storage as well as testing of cosmetic products is standard procedure.

The SCCS acknowledges that fragrance manufacturers are aware of the possibility of oxidative generation of allergens and actively apply measures to prevent these. However, a general absence of oxidised products in cosmetic products, or other fragranced consumer products, is contradicted by the high prevalence of contact

¹ Kortenkamp A, Backhaus T, Faust M (2009). State of the Art Report on Mixture Toxicity. Project contract No. 070307/2007/485103/ETU/D.1 http://ec.europa.eu/environment/chemicals/pdf/report_Mixture%20toxicity.pdf

² Turek C, Stintzing F. Evaluation of selected quality parameters to monitor essential oil alteration during storage. Journal of Food Science 2011;76:1365-1375

Turek C, Stintzing F . Impact of different storage conditions on the quality of selected essential oils. Food Research International: in press

allergy to oxidised (versus non-oxidised) fragrance substances that have been tested so far (mainly oxidised limonene and linalool). These results indicate that exposure to the oxidised compounds in fact must have occurred.

The discrepancy of these results could be due to exposure from products not complying to the mentioned standards or the use of inadequate methodology to identify the most relevant hydroperoxides (see also section below on analytical issues).

Reference was made to quality control data from manufacturers of natural cosmetic products which were said to show absence of oxidised species of limonene and linalool in finished products as proven by peroxide values of below 5 mmol/liter. Other comments cited a not yet published study which was claimed to show that significant levels of peroxides are not present in freshly manufactured fragrance oils, finished fragrance products purchased off the store shelf, or fragrance products that had been used over various periods of time and stored under various conditions of heat and light. Results for freshly manufactured fragrances and hydroalcoholics retrieved from retail were reported to show that none of the hydroalcoholic perfumes and only 2 (0.24%; 10-15 mmol/liter) of the recently manufactured fragrances had peroxide values > 10 mmol/liter. Peroxide values were < 5 mmol/liter for 848/872 (97%) of the recently manufactured fragrances and for all the products retrieved from retail.

The analytical results mentioned in the comments have not yet been made available to the SCCS, nor published in peer-reviewed scientific journals. From the preliminary information received it appears that at least for some analyses a colorimetric method has been used, based on iodine liberation titrated with thiosulfate solution, and a starch indicator for visualisation. This method is not specific for the allergenic hydroperoxides but indicates also the presence of the non-allergenic hydrogen peroxide as well as other peroxides. Moreover, and more importantly in this context, it is vulnerable for disturbances from other chemicals, so that there is the possibility of false negatives. The SCCS cannot assess the cited results without information on method validation, including detection limits. The issue of analytics was corroborated by another comment received, which stated that fully characterized and standardized methods for quantifying aerial oxidation products of limonene and linalool (including those that might arise from oxidation of these substances when they are constituents of botanical extracts and essential oils) have not yet been developed. The SCCS would like to point out that, in developing appropriate analytical methods for relevant oxidation products, it should be observed that not all allergenic oxidation products formed are hydroperoxides but also other oxidation products (e. g. epoxides and aldehydes) with allergenic properties have been identified. For geraniol the major oxidation products detected after air exposure were the aldehydes geranial and neral which are the isomers of citral¹.

4.2. Experimental conditions

In several comments it was stated that the cited studies which showed allergic reaction to oxidized products in animals and humans used extremely oxidized samples that would bear no relevance to levels of oxidation products found in consumer products. The regime used in the publications by Karlberg et al. was

¹ Hagvall L, Backtorp C, Svensson S, Nyman G, Borje A, Karlberg A T. Fragrance compound geraniol forms contact allergens on air exposure. Identification and quantification of oxidation products and effect on skin sensitization. Chem Res Toxicol 2007; 20: 807-814

considered unrealistic, as the test material was said to be produced under unrealistic artificial methods (namely “stirring and bubbling through oxygen for several weeks”) which would not relate to conditions during manufacture and use of cosmetics. It was claimed that in reality little to no oxidation of fragrances ingredients in new and aged consumer products such as fine fragrances occurs. For these reasons, it was considered that the concentration of oxidised linalool and limonene used in the experiments would likely be artificially high.

In relation to the autoxidized material used for patch testing in the used references by Karlberg et al., the SCCS would like to point out that in these studies conditions have been chosen which were intended to mimic real life exposure of fragrance ingredients to oxygen (e.g. maceration, product use). Fragrance samples were stored at room temperature, stirred 4 times a day during different time periods (weeks to months). Exposure was only to oxygen contained in the air and no deliberate addition of oxygen to the test material has been used. . Publicly available sources indicate that perfumes are macerated with contact to oxygen for extended time periods to obtain the maximum olfactory quality. In a study where the process maceration was investigated scientifically¹, bottles containing fragrances were daily opened and shaken in order to be oxygenated. Thus, the SCCS does not believe that the experimental conditions used in the cited references were exaggerated, but resemble those used at least by a part of the fragrance industry. For a discussion on the presence of oxidised fragrance derivatives in products, see also above.

The test concentrations of linalool and limonene used in the published data (up to 11.0 % of oxidised Linalool in Christensson et al., 2010) were considered too high by commenters, as it was said to be ca. 20 times higher than the real in-use concentrations of linalool in marketed products.

The SCCS does not agree that the patch test conditions used to obtain the results in table 5-1 are exaggerated. The cited concentration of 11% was exceptionally used in one study. Most studies on oxidised fragrances have been performed with concentrations of 2-3% test material. Moreover, patch test concentrations in clinical practice are well known not to mirror use concentrations in cosmetic products. The patch test preparations used in clinical practice are determined to ensure that false positive reactions should not occur, and also that false negative reactions should not occur. Further comparing exposure during patch test with consumer exposure, it should be observed that recent findings identify an enhanced sensitisation efficacy when doses are split and applied repeatedly². This is specifically true for fragrance substances that are present everywhere in consumer products and cosmetics repeatedly used in close contact with the skin. Therefore, low concentrations of oxidized fragrance compounds might cause sensitisation. General issues in relation to patch test concentrations versus use concentrations are further discussed in section 3.3.

4.3. Prohaptens and cross-reactivity

With regard to substances which could show cross reactivity due to metabolism in the skin, it was commented that the commonly employed methods (LLNA, HRIPT) already account for metabolic transformation.

¹ López-Nogueroles M, Chisvert A, Salvador A. A chromatometric approach for evaluation and selecting the perfume maceration time. *J Chromatography A* 2010;1217: 3150-3160

² Paramasivan P, Lai C, Pickard C, Ardern-Jones M, Healy E, Friedmann PS. Repeated low-dose skin exposure is an effective sensitizing stimulus, a factor to be taken into account in predicting sensitization risk. *Brit. J. Dermatol.* 2010; 162: 594-597

As regards the LLNA, which is most frequently used to estimate sensitization potential of a chemical, the SCCS is of the opinion that it has not yet been ascertained that animal studies (specifically mouse skin) adequately represent the metabolic capabilities of human skin. Furthermore, the LLNA does not allow for cross reactivity reading which is important for the elucidation of metabolic pathways.

One comment acknowledged that bioactivation via hydrolysis or via metabolism to a common allergen (e.g. geraniol, geranial) is a possibility, but stated that in the case of geraniol this concern is not supported by clinical data. In another comment on the same topic it was said that only a small number of scientific studies on the possible conversion of substances in the skin is available. It was criticised that the SCCS combines the aspect of cross reactions directly with a possible activation of prohaptens, as this connection was considered so far not scientifically confirmed. The publications quoted by SCCS were considered not to justify such conclusions. These studies show the conversions that geraniol and cinnamic alcohol/aldehyde can possibly undergo using various model systems (enzyme mixtures, cell fractions, dermal extracts), but it was judged that, based on these limited data, it cannot be generalised that newly created products can have an allergenic potential. Also the conclusion by SCCS that these processes can lead to an increase in cross reactions was considered wrong and not supported by the quoted literature.

The SCCS acknowledges that clinical data on the bioactivation of geraniol to geranial is scarce. However, in one key clinical study¹ concomitant reactions between citral (mixture of the isomers geranial and neral) and geraniol were frequently observed (83%). This was discussed to be maybe due to co-exposure, but probably also to cross-reactions, as both compounds are structurally closely related. This notion has since been supported by another study².

Moreover, this lack of clinical evidence does not contradict the relevance of the mechanism of allergen formation, the more so, as for the case of cinnamyl alcohol/cinnamal strong clinical evidence of cross-reactivity exists which is well compatible with experimental results in this field. Compounds like cinnamyl alcohol and geraniol, carrying allylic alcohols as structural alerts, are recognized as sensitizers, although usually weaker than their corresponding aldehydes. Also epoxides are formed which are strong sensitizers. For geraniol the formation of epoxygeranial has been identified in a case where both metabolic and abiotic activation ways are possible. Although metabolism to aldehydes is the most obvious potential prohaptent mechanism, it is not the only one. Furthermore, as commented above in the specific discussion about geraniol it might not be sufficient to use the prohaptent in low concentrations as a diagnostic tool to detect cases of contact allergy caused by the metabolites formed. A better way of detecting contact allergy caused by geraniol could therefore be to test with the metabolites directly.

For the case of esters such as isoeugenol it was commented that there is no evidence to support the suggestion that perfumers would be using isoeugenyl acetate (IEA) to replace isoeugenol (IE) to prevent labeling or that there would be uses of a combination of IE and IEA to intentionally deliver IE at levels above the

¹ Schnuch A, Uter W, Geier J, Lessmann H, Frosch P J. Sensitization to 26 fragrances to be labelled according to current European regulation. Results of the IVDK and review of the literature. *Contact Dermatitis* 2007; 57: 1-10

² Hagvall L, Karlberg AT, Bråred Christensson J. Contact allergy to air-exposed geraniol: clinical observations and report of 14 cases. *Contact Dermatitis* 2012; 67:20-27

IFRA Standard level or the labeling threshold under the EU regulation. Supporting data (volumes of use over time) for this was included. Further, it was stated that isoeugenyl acetate has an olfactory character different to that of isoeugenol and cannot be used to replace isoeugenol.

The SCCS notes that the provided data indicate that isoeugenol acetate has been used almost twice as often after the current regulation was set into force. However, the notion that isoeugenol is replaced by derivatives has been deleted from the opinion following the comment on different olfactory profiles. The SCCS maintains the view that additional exposure to fragrance allergens through use of hydrolysable derivatives needs to be taken into account and the text has been added in chapter 5.2 to emphasise this.

4.4. Other issues

One contributor raised a question about the description of alpha-terpinene in tea tree oil as "the antioxidant in Tea tree oil" in relation to the statement that antioxidants exert their function by being activated instead of the compound that they protect. It was argued that alpha-terpinene itself is a constituent (from 5% to 13%) of tea tree oil and that its oxidation actually would constitute an oxidation of Tea tree oil.

The opinion has been changed to better reflect that the example of alpha-terpinene from tea tree oil was given to describe the use of this compound as an antioxidant in other preparations.

4.5. Conclusions to Question 3

In one comment it was questioned that the presence of sensitising oxidized derivatives of limonene and linalool would justify the restriction of the substances to a safe threshold level of 100 ppm.

Non-oxidised limonene and linalool as such are not part of the list of substances of special concern, i.e. of the substances for which a limitation of exposure has been recommended. As stated in the opinion, chapter 13.3, the SCCS is of the opinion that the exposure to the *oxidised fraction* in limonene and linalool should be minimised. Specifically it is said in the opinion: "For these substances the presence of the oxidised fraction represented by the peroxide content should not be higher than 10 ppm. Alternatively, the suggested general threshold dose/area of 0.8 µg/cm² (100 ppm in cosmetic products) could be applicable to the total oxidised fraction, i.e. not only peroxides but also secondary oxidation products such as aldehydes and epoxides."

In another comment it was stated that the data presented do not justify excluding in general pro-haptens and their metabolic products, which possibly might cause allergenic reactions, from use in cosmetic products. More research was considered necessary and substances need to be evaluated on a case by case basis.

The SCCS would like to clarify that nowhere in its opinion, it expresses the view that pro- and/or pre-haptens should be generally *excluded* from cosmetic products on the sole basis that they can be transformed. Rather, it has suggested that the possibility that substances could cross-react or be transformed into other allergens or common metabolites needs to be taken into account in the risk assessment and regulation for a particular substance, i.e. regarding concentration restrictions and labelling requirement, respectively. Wherever substance-specific data is available, an individual assessment should be performed. This has been clarified in chapter

13.3. It should be observed that both clinical and experimental data are published for those pro-and or prehapens that are suggested to be regulated.

5. OTHERS PARTS OF OPINION

A typographical error was pointed out and corrected in the list of abbreviations (1000 ppm = 1% to 10000 ppm= 1%).