

Comment (Position Paper)

on

Scientific Committee on Consumer Safety

SCCS

**OPINION**

**on**

**Fragrance allergens in cosmetic products**

The SCCS adopted this opinion at its 15<sup>th</sup> plenary meeting  
of 26-27 June 2012

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## Introduction:

The SCCS opinion refers to an extraordinarily comprehensive and thorough compilation of data on fragrance contact allergens. Factors interfering with sensitization were extensively displayed (such as quantitative aspects of several factors), although it is not clear if all these factors (e.g. different exposures; different doses of induction) were adequately considered when discussing a chemical. Nevertheless, the 'academic part' of the opinion is excellent. The transparency and algorithms presented are highly appreciated.

By contrast, the "interpretation parts" are to be discussed more critically.

First of all: There is broad consent. All in all I agree largely with the group of substances of "special concern" (table 13.5; p. 114). According to our studies<sup>1</sup>, which were later corroborated by others, we had classified the "26 fragrances" of 1999 as "of great importance" (e.g. isoeugenol), "important" (e.g. hydroxycitronellal), and "less important" (e.g. benzyl alcohol). Most of the chemical "substances of concern" (SCCS) are included in our groups of "(great) importance" (IVDK).

However, the Opinion does not include a category of "less important". It even adds a list of "likely allergens" (n=26) to the list of "established allergens" (n=82), although of 54 substances classified as "established", 19 belonged to impact class "+" (only 1-10 cases published in the literature\*), and although already some of the "established allergens" (SCCS) could be considered not only "less important" (IVDK) but of "*no importance*" at all because of being very likely non-sensitizers (see below and Appendix I (p. 89)). Not to mention the rather weak "evidence" of the "likely" category. Finally the opinion comes up with 126 substances and mixtures of which the consumer "should be made aware of".

Thus there may be tendencies to exaggeration. Furthermore, I believe to have ascertained some inconsistencies or flaws. Some are debatable, whereas others may have had a *systematic* impact (meaning: because of a systematic fault) on the outcome of the opinion.

These are the main reasons to express my opinion.

While maintaining my earlier personal comment on the pre-draft (SCCS; 13/14 Dec. 2011), I would like to comment on the following

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\*It was put forward that that a small number of cases (or of none cases at all) was due to the fact that the substances were not tested (sufficiently often). However, a substance should be tested only *if there is a case suspected of contact allergy* (according to pertinent guidelines) which is the normal way a new contact allergen emerges. Obviously these cases were lacking and patch testing was not indicated. Testing without medical indication would be rather critical from an ethical point of view.

<sup>1</sup> Schnuch, A., Geier, J., Uter, W., Frosch, P.J. Another look at allergies to fragrances: frequencies of sensitisation to the fragrance mix and its constituents. Results from the IVDK. Exogenous Dermatology 1:231-237 (2002)  
Schnuch A, Uter W, Geier J, Lessmann H, Frosch PJ. Sensitization to 26 fragrances to be labelled according to current European regulation. Results of the IVDK and review of the literature. Contact Dermatitis, 57: 1-10 (2007)

- Patch testing (chapter 4.2. of the opinion)
- Evidence and Classification (chapter 6)
- The answer to question I (the case of benzyl benzoate and others)

I repeat my willingness to contribute to a fruitful discussion and sensible decision on the important question of “fragrance allergens in cosmetics”.

**Declaration of conflict of interest:** The IVDK is sponsored by IFRA, DVRH, Symrise, Givaudan and IFF. I have been an *ad hoc* consultant, partly remunerated.

## I. COMMENTS ON PATCH TESTING (the scientific basis of evaluation)

(Chapter 4.2.)

Although this seems to be a boring “technical” issue, the way of evaluating and using patch test results is of utmost importance, as the opinion is essentially relying on patch test results. Therefore, some critical remarks seem indicated.

The inclusion of some explanations on patch testing is welcomed. While agreeing with the first 4 statements (p.15), I cannot agree with the 5th statement,

“Most allergen test preparations, and certainly those that are included in international baseline series, have evolved from studies critically (re-) appraising their diagnostic validity, i.e., sensitivity and specificity”.

For assessment of sensitivity and specificity, an external criterion, such as a positive ROAT confirming sensitization diagnosed first by patch testing, is needed. Only very few substances (probably < 20) were evaluated in this way.

More often (regarding base line allergens), the suitable concentration emerges from patch testing with different patch test concentrations. Usually, by increasing the concentration, the number of positive reactions increases, but this is often accompanied by an increase of irritant reactions, which may be misinterpreted as positive (allergic), and thus may be “false positive”.

But for most of the hundreds of contact allergens/patch test preparations, even such dose-finding studies were not done.

More importantly in this context: For the majority of the 82 fragrance compounds considered in the SCCS opinion such extended studies (ROAT and / or dose-finding studies) have *not* been done. Therefore, results with such less (or not) evaluated and less (or not) quality-controlled preparations should be interpreted with caution.

Nevertheless, there are many substances yielding unequivocal positive patch reactions. They are justly identified as contact allergens. This is not in dispute.

A crucial prerequisite to maintaining such a position is that a “positive” patch test is really positive/allergic. However, a patch test result is a semi-quantitative measure (the reactions are described as weak (+) or strong (++/+++). Two aspects should be considered:

### 1. Reaction strength

In stronger reactions, the relevance of the patch reactions (e.g. to essential oils or the fragrance mix) can often be shown, whereas in weak reactions, this is much less often (~1/3) the case. And there is a good correlation between (i) a positive history, (ii) a positive ROAT

and (iii) the strength of patch test reactions (de Groot & Frosch)<sup>2</sup>, associations confirmed by others (e.g. Johansen 1996 (ref 100 of the opinion) or Schnuch 2009 (ref. 105).

*De Groot and Frosch*<sup>2)</sup> had put forward the view that:

“False-positive reactions (to the Fragrance mix) are not rare, and a single weak (?+ or +) reaction to the mix should not be taken as evidence for fragrance contact allergy but should be substantiated by other tests (e.g. ROAT.....)”

I share the view of these two eminent representatives of the European contact dermatitis community. This was not considered by the opinion (as it should have been), in particular, when a just “positive” or a weak (+) reaction (not further specified or accompanied by further data) were counted uncritically as a “case”. Many of the “established allergens” of category (1-10 cases) (table 13.1; p. 106) rely on such evaluations (see below and Appendix I of this paper).

## 2. Documentation and analysis of reaction strength.

Documentation of the reaction profile<sup>3</sup> of an allergen in patch testing is considered an important part of a patch test study. Uter et al.<sup>4</sup> pointed out:

“Usually, not only the number or percent positive reactions, but also of doubtful and irritant reactions should be given, to obtain a complete view on the reaction profile of the allergen in question. If there is uncertainty about the interpretation of reactions recorded as + (erythema, infiltrate, possibly papules), these should be presented and analysed separately from stronger positive reactions”<sup>4)</sup>

Remark: These requirements are not part of the quality requirements of the opinion (see chapter 6.2.1.)

Two statistical tools are used to describe quantitatively the reaction profile of an allergen (doubtful, irritant, [weak/strong] positive): The Reaction Index (RI) and the Positivity Ratio (PR)<sup>5</sup>

The RI and the PR (i) provide concise information on a certain allergen patch test preparation and (ii) may help to put solitary information on “percent positive” into a

<sup>2</sup> DeGroot AC; Frosch PH, Adverse reactions to fragrances. A clinical review. Contact Dermatitis 1997; 36: 57-86 (See also ref 35, 67, and 97 and chapter 4.4.2 of the opinion)

<sup>3</sup> The number of + / ++/ +++ allergic reactions as well as the number of irritant and doubtful reactions

<sup>4</sup> Uter W, Schnuch A, Gefeller O: Guidelines for the descriptive presentation and statistical analysis of contact allergy data. Contact Dermatitis **51**, 47-56 (2004)

<sup>5</sup> The RI ranges from “-1” (all reactions irritant/doubtful), over “0” (half of reactions “+ / ++ / +++”) to “+1” (all reactions + / ++ / +++). The PR gives the proportion of (only) “+” out of all positive reactions. A negative RI indicates the majority of reactions being not allergic. A PR of 100% indicates that “+” (=weak positive) occurred only.

more balanced perspective. As an example: Octyl gallate (0.3% pet.), tested in 16935 patients, caused 3.5% “positive” reactions. However, the RI was  $-0.4$ , and the PR 92%, casting severe doubts on the validity of the majority of “positive” test results, and also on the suitability of the patch test preparation (Uter et al (2004) <sup>4</sup>

The usefulness of quantifying the reaction profile (with RI and PR) to evaluate the results of patch testing critically was shown with the following:

- The irritant benzalkonium chloride (“The majority of + reactions to BAC can probably be interpreted as false positive, as these reactions are hardly reproducible”)<sup>6</sup>
- Cocamidopropylbetain (“The vast majority of positive reactions to CAPB are presumably false positive. Allergic reactions are very rare. This would support the notion of CAPB being “not a significant skin sensitizer”, in line with current classification systems”)<sup>7</sup>
- Propylene Glycol (“The profile of patch test reactions is indicative of a slightly irritant preparation and thus many of the “weak positive” reactions must probably be interpreted as false-positive”)<sup>8</sup>.
- Petrolatum (the vehicle of patch tests) “Many of the “positive” (+) reactions have to be considered as irritant.....True allergic patch test reactions to white petrolatum are extremely rare and probably due to an individually increased susceptibility to allergens and/or irritants. This is in agreement with considering petrolatum as a non-sensitizer”<sup>9</sup>

**Note:**

The 4 last fragrances of our group III of the “26 fragrances”<sup>10</sup> (benzyl salicylate, alpha methyl ionone, benzyl benzoate and anisyl alcohol) had very low RIs ( $-0.6$  to  $-0.9$ ) and a PR of 100% (indicating exclusively + and no stronger allergic reactions).

The results of a Danish study<sup>11</sup> support our results in an even more accentuated way.

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<sup>6</sup> Uter W, et al..Is the irritant benzalkonium chloride a contact allergen? A contribution to the ongoing debate from a clinical perspective. *Contact Dermatitis* 58:359-363 (2008)

<sup>7</sup> Schnuch A, et al . Is Cocamidopropyl Betaine a Contact Allergen ? Analysis of Network Data and Short Review of the Literature. *Contact Dermatitis* 64, 203-211 (2011 b)

<sup>8</sup> Lessmann H, et al. Skin sensitizing and irritant properties of propylene glycol.Data analysis of a multicentre surveillance network (IVDK) and review of the literature. *Contact Dermatitis*, 53:247-259 (2005)

<sup>9</sup> Schnuch A, et al. White petrolatum (Ph. Eur.) is virtually non-sensitizing. Analysis of IVDK data on 80000 patients tested between 1992 and 2004 and short discussion of identification and designation of allergens. *Contact Dermatitis*, 54:338-343 (2006)

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

<sup>11</sup> Heisterberg MV, Menne 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; 65: 266-75.

The rarity of reactions to the above compounds cannot be explained by low exposure, as benzyl salicylate, alpha methyl ionone, and benzyl benzoate are used in volumes greater than 175 tons (chapter 10.1).<sup>12</sup>

From the above considerations it can be concluded that

1. The evidence that a weak positive (+) patch reaction identifies a subject to be allergic, and that the substance is therefore a sensitizer *may* be weak, particularly, if further (patch test inherent) information (reaction profile) and further (external) information (ROAT, positive history) are lacking. In such cases, a “positive” reaction may be false positive. This said I want to stress that, of course, the + reaction should generally be interpreted as allergic, according to the international guidelines on patch testing.
2. The patch test results indicate, therefore, contact allergy to different degrees of probability (high with ++/+++ and lower with only (+). This is supported by higher or lower associations, respectively, with additional test results (e.g. ROAT), meaning that the reaction strength confers important additional information on the validity of the patch test result.
3. The evidence expressed by position 1 and 2 of the chapter “patch testing” (a positive patch reaction identifies a subject to be allergic, and identifies a substance as a sensitizer) is therefore graded.
4. The designation of a substance as an allergen is a probabilistic statement, with higher or lower probabilities<sup>13</sup>. The number of human cases (+ to +++) could well have been used for grading evidence within the group of established allergens. However, this categorisation (+ to +++) was only used to describe the “impact” of the allergen, not to grade evidence.

In this regard: A quantitative approach is also used in the LLNA<sup>14</sup>, by setting a threshold: The stimulation index must be 3 or above to qualify a chemical as an allergen. Potency as well is graded<sup>14)</sup>

Furthermore, the GPMT as well as the Bühler test require 30% and 15% sensitized animals, respectively, for qualifying a chemical as sensitizer.

5. The opinion is essentially relying on patch test results and only partly on the number of diseased cases. Not every patch test positive case suffers from manifest disease, a fact well known to the experts and discussed at length in the opinion. (Striking example: benzyl benzoate, where manifest clinical cases are virtually missing). Therefore it is misleading to state, that the established allergens (of table 13-1) “*clearly have caused disease in man*” (p.113).

The last phrases on patch testing in the opinion deal with the question of false positive and false negative as follows:

“Notwithstanding this, false-positive and false negative reactions do occur (as with any diagnostic tool). While in the individual case such diagnostic misclassification may have

<sup>12</sup> See also below: General comment on the approach for designating a substance as “established allergen”. The argument (see “Notes”; Footnote 15) that the patch test concentration of certain substances may be too low to identify every case may be right or wrong. A scientific position should be based on facts (identified cases), and not on mere assumptions (possible cases not identified, how many?, sufficient to derive a threat to the consumer?).

<sup>13</sup> **Of which “the consumer should be made aware of”, according to the ‘philosophy’ of the opinion**

<sup>14</sup> LLNA: Local lymph node assay, an animal test to detect sensitizing properties of a chemical

unfortunate consequences, it will hardly impair epidemiological estimates of contact allergy frequency – at least as long as a reasonable balance between false-positive and false-negative reactions is achieved.”

One could agree, if we knew something about “false negative” reactions. But the rate of “false negatives” is never reported in epidemiological studies. How could they be? Thus the assertion that “false positives” are counterbalanced by “false negatives” is not substantiated.

By contrast, we know that false positive reactions do occur, in particular in allergens with an unfavourable reaction pattern (negative RI, PR=100%). In a situation of only a low number of weak positive reactions the conclusion “indicative of a contact allergen” (or even stronger: “*established* allergen”) may be premature or wrong.

If there is a certain number of weak positive reactions *only*, the actual frequency of true allergic reactions, the importance of the allergen, and - according to the evaluation scheme of the SCCS - the “evidence” is bound to be overestimated (or wrong).

**In summary:**

**A positive patch test is indicative of an individual allergic to the substance and indicative of the substance being an allergen. There is agreement.**

**A positive patch test is, however, a graded measure, with higher, lower or very low evidence. The so called evidence itself is nothing but higher, lower or very low probability (as almost every “fact” in life sciences).**

**The fact should have been considered in the opinion. The failure to do so could be regarded as systematic flaw of the opinion, as the notion of an “established allergen” is essentially relying on patch test results (see also “Explanatory note” of the SCCS<sup>15</sup>).**

**This may have contributed to the somehow inflated list of “established” allergenic fragrances.**

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<sup>15</sup> HOW THE COMMENTS RECEIVED DURING THE PUBLIC CONSULTATION WERE TAKEN INTO ACCOUNT FOR THE FINAL SCCS OPINION ON FRAGRANCE ALLERGENS IN COSMETIC PRODUCTS



## II: COMMENTS ON “EVIDENCE” and “CLASSIFICATION” (chapter 6)

In the introduction to this chapter the opinion refers to existing systems of classification.

“Regarding the classification of substances as allergens, a number of approaches have been suggested (ref 158-160)<sup>16</sup>.... For this opinion, these discussions were extended to reconcile different perspectives and to arrive at a strategy that is both consistent and applicable in practice..”

In particular, “assembled evidence had to be graded in two steps (p.41):

- (i) the quality of each single study, and
- (ii) the strength of evidence underlying the eventual classification as an allergen”.

I appreciate the “grading of evidence” approach (i.e. the strength of evidence underlying classification), which was adopted from the existing schemes. Therefore no further comments on paragraph 6.3.1. (Established contact allergen in humans).

However, the paragraph (6.2.1) dealing with the “Quality of a clinical study” deserves some comments.

The introduction to this paragraph distinguishes between (i) case reports and (ii) clinical series. Data outcome “implies that the majority of patients *can* be used [*note*: not ‘must be used’] to illustrate the proportion of irritant, doubtful and negative reactions”.

In the “basic criteria”<sup>17</sup> these reaction types are, however, not included.

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<sup>16</sup> 158. Flyvholm M A, Andersen K E, Baranski B, Sarlo K. *Criteria for classification of skin- and airway-sensitizing substances in the work and general environments*. RegionalOffice for Europe: WHO, 1996.

159. Basketter D A, Flyvholm M A, Menne T. Classification criteria for skin-sensitizing chemicals: a commentary. *Contact Dermatitis* 1999; 40: 175-182.

160. Schnuch A, Lessmann H, Schulz K H, Becker D, Diepgen T L, Drexler H, Erdmann, S, Fartasch M, Greim H, Kricke-Helling P, Merget R, Merk H, Nowak D, Rothe A, Stropp G, Uter W, Wallenstein G. When should a substance be designated as sensitizing for the skin ('Sh') or for the airways ('Sa')? *Hum Exp Toxicol* 2002 a: 21: 439-444.

<sup>17</sup> “Some of the basic quality criteria in clinical patch testing which should be considered are:

- Adherence to international patch test guidelines
- Material(s) tested should be characterised.
- Total number of patients tested must be given.
- Patient selection should be described.
- Relevance may be demonstrated either on a case-by-case basis, following pertinent guidelines, or in terms of a significant epidemiological association between sensitisation and exposure or valid markers of exposure.”

It is somehow surprising that the parameters<sup>17)</sup> to assess the quality of a study (clinical series) remain much below the quality requirements laid down in a review by Uter et al (ref. 268)<sup>4</sup>

The above requirements give up basic information such as the reaction strengths and the number of doubtful/irritant reactions (see comments above on chapter 4.2). Without such data, with only the percentage of “positives” tested, a further critical evaluation of a study is impossible. (For example, with 2 “+” reactions, no stronger reaction and 40 irritant/doubtful reactions in 2000 patients tested, the positive reactions need to be put into perspective). A concrete example is a Korean study which was cited uncommented (see footnote 21).

However, the above quality assessment juxtaposes uncritically and uncommented studies with poor data presentation (footnote 21) and studies with “good” (more extensive) data presentations (such as ref 170)<sup>18</sup>

Obviously the evidence provided by different studies differs, and the evidence of “positive=allergic” is graded: low or high. This, however, is disregarded by the opinion.

#### **In summary:**

**The quality requirements for a study to be included for evaluation are low. If still included studies should at least be graded according to the variable extent of data presentation.**

#### **General comment on the approach for designating a substance as “established allergen”.**

I have already commented on that issue on occasion of the public consultation of the pre-draft. It was submitted to the Commission.

Briefly the main objections are:

1. The SCCS criteria have never been published and were not subject to an open critical discussion. A general agreement cannot be claimed.
2. The three existing approaches of designation (ref 158 – 160)<sup>16)</sup>, partly from official bodies, were just briefly mentioned. The SCCS, however, does not discuss these approaches explicitly (applicable? To what extent? or not applicable? and why so?) and does not justify derogations, in particular, by omitting the 4<sup>th</sup> category contained in all three approaches.

It is:

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<sup>18</sup> Heisterberg MV, Menne 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; 65: 266-75.

“Many people have been extensively exposed to the substance for a long time, but contact allergy is extremely rare”. This is considered as evidence that the chemical is not a significant contact allergen.

This would mean that e.g. 4 cases observed worldwide during a 40 years period with a substance widely used (and sufficiently often tested) do not only indicate *quantitatively* “extremely rare” but also *qualitatively* “probably not being a sensitizer”.

In contrast, these 4 cases observed within two series (2 from 2 different centres) would qualify a substance as an “*established*” allergen, according to 6.3.1. of the opinion. It should be emphasized that the qualifier “*sufficient human evidence*” is just referring to the number of cases<sup>19</sup>, not to the cases (and their quality) themselves. Thus, the (clinical) evidence of these four cases may be high or very low.

It is noteworthy that 19 out of 54 “established allergens” are based on not more than “up to 10 positive test reactions reported” (table 13.1). (Mind again: Not necessarily “diseased”, as claimed on p.113).

Of these, 12 were re-evaluated (see below Appendix I). In 8 /12 = 66.7% (or 8/19 = 42%) evidence for classification as “established” could be considered poor taking into account

- a) the number of cases relative to use volume,
- b) the possibility of false positives
- c) the quality of data presentation.

The next category (++/ 11 to 100 cases; observed in the course of several decades and worldwide) comprising further 22 substances could be subject to a similar re-evaluation, with a probably dubious outcome as well (see e.g. benzyl benzoate, next page).

A considerable number of unequivocal sensitizing fragrances does exist. However, the overall impact of “sensitizing fragrances” (derived from including additional rather dubious substances) as put forward by the SCCS seems exaggerated.

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<sup>19</sup> ...which can well be considered as a valid step in evidence assessment, when accompanied by further evidence. This shall not be questioned. (See also above, p.8 point 4)

### III COMMENT ON THE ANSWER TO QUESTION 1 (The case of benzyl benzoate and others )

#### 13.1. Question 1

*Does the SCCS still consider that the fragrance allergens currently listed in Annex III, entries 67-92, for labeling purposes represent those fragrance ingredients that the consumer needs to be made aware of when present in cosmetic products?*

#### Conclusions - Question 1

The studies since the SCCNFP Opinion on fragrance allergy in consumers (1) have confirmed that the fragrance allergens currently listed in Annex III, entries 67-92 are still relevant fragrance allergens for the consumers from their exposure to cosmetic products.

This answer is probably not correct, in particular taking benzyl benzoate (BB) as an example. I have extensively (in a point to point evaluation of studies presented) commented on BB in my "Personal Comment" given to the pre-draft of the SCCS opinion of Dec. 2011. My objections against designating BB as a contact allergen were, however, ignored. There were no comments in the explanatory "notes" <sup>15</sup>.

I just want to emphasize, that in the 12-years period after the first opinion (1999) there was **no unequivocal case published**, although the number of patients tested amounts to 4,888 (not 3385 – as 2 additional studies published later were not yet considered in the profile on BB in Appendix I of the opinion).

Even if the one case with a + reaction (from the IVDK data set; ref 74 of the opinion) is counted as an allergic reaction, and not, as it should be, as a probably false positive reaction based on the additional information on the reaction profile of BB (see above), then the frequency would be 0.02% (95% CI -0.02% to 0.06%).

The virtually complete absence of cases in a twelve years period is contrasted by high exposure. BB belongs to the high volume products (>175 tons per year) (chapter 10.1). It is also used as a topical drug (scabicide) using a concentration of 10% for children and 25% for adults. Despite such a high concentration applied to the skin, no cases of allergic contact dermatitis have been reported during the last twelve years.

It can be concluded that no study since the SCCNFP Opinion on fragrance allergy in consumers has confirmed that BB is an "established allergen", nor a "still relevant fragrance allergen" which should be maintained in Annex III.

## Other fragrances from the “26 list” (SCCNFP/0017/98 (1999); ANNEX III (2003))

### Anisyl alcohol

Cited from Annex I

“Since the last SCCNFP-opinion of 1999, the IVDK 2007 study yielded n=1, i.e., 0.1% (95% CI: 0.00 – 0.3%) positive reactions in 2004 consecutively P<sub>T</sub>ed patients, patch test concentration: 1% pet. (4). Similar results were obtained in the following period, with n=1 (and n=3 irritant and n=6 doubtful) reactions in 986 patients tested with 1% in pet. (30). In the Groningen 2009 study, no positive reactions to this allergen, tested at 5% pet., were observed in 320 patients (6).”

In total there were 2 cases, both from the IVDK network. The reaction pattern RI and PR were very unfavourable, casting doubts on the “positive case” (see above). The Groningen study did not observe a positive case<sup>20</sup>.

However, there was one case to be added (not considered by Appendix I of the opinion) with a ++ reaction and few (n=3) doubtful reactions in the Heisterberg study<sup>22</sup>.

So, with 1 probably unequivocal case out of 4 large studies, including several thousands of patients the notion of an “established allergen” was confirmed (?). One may have doubts.

### Methyl-Ionone

Cited from Annex I

The IVDK 2007 study yielded n=1, i.e. 0.1% (95% CI: 0.00 – 0.2%) positive reactions in 2004 consecutively P<sub>T</sub>ed patients (4). In the subsequent period (2005-2008), n=986 patients were tested in the IVDK 2010 study, with no positive reactions (7). In the Groningen 2009 study, n=2, i.e. 0.6% (95% CI: 0.1 – 2.2%) had positive reactions to this allergen, tested at only 1% pet. (6). In a Korean study with 422 consecutive patients, 2.1% reacted positively to “alpha isomethyl ionone (gamma-methylionone), CAS # 127-51-5”, tested 5% pet. (13)<sup>21</sup>

It is a “top 100” substance (IFRA, pers. comm.2010) under the label of “alpha-ISOMETHYL IONONE (CAS # 127-51-5)”.

The results of the Heisterberg study<sup>22</sup> may be added: No positive case was observed. In almost 3.000 patients tested in the IVDK, there was 1 “+” case. PR and RI were very unfavourable. In the Groningen study<sup>20</sup> there were 2 “+” reactions and one additional case with an irritant reaction.

<sup>20</sup> van Oosten E J, Schuttelaar M L, Coenraads P J. Clinical relevance of positive patch test reactions to the 26 EU-labelled fragrances. *Contact Dermatitis* 2009; 61: 217-223.

<sup>21</sup> An S, Lee A Y, Lee C H, Kim D W, Hahm J H, Kim K J, Moon K C, Won Y H, Ro Y S, Eun H C. Fragrance contact dermatitis in Korea: a joint study. *Contact Dermatitis* 2005; 53: 320-323.

<sup>22</sup> Heisterberg MV, Menne 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; 65: 266-75.

In the Korean study<sup>21</sup>), 9 patients (2.1%) showed a “positive reaction”. Neither reaction strength (+/++/+++) nor the number of irritant/doubtful reactions were reported, especially when considering that the patch test concentration was 5% as opposed to the other studies. With such sparse data presentation validity and reliability cannot be assessed.

So, with three “+” cases out of 4 large studies from Europe, involving > 4000 patients, together with an unfavourable reaction profile and the possibility of false positives, the notion of an established allergen was confirmed ?

### **Methylheptine carbonate (METHYL 2-OCTYNOATE)**

Cited from Appendix I (of the SCCS opinion)

Since the last SCCNFP-opinion of 1999, the IVDK 2007 study yielded 0.3% (95% CI: 0.1 – 0.49%) positive reactions in 2401 consecutively PTested patients (1% pet.) (4). The IVDK 2010 study, n=1 weak positive reaction was observed in 988 patients tested with the compound (7). In the Groningen 2009 study, n=1, i.e. 0.3% (95% CI: 0.01 – 1.7%) had positive reactions to this allergen, tested at only 2% pet. (6). In a previous case report of a fragrance laboratory assistant with work-related ACD both methyl heptin and methyl octin carbonate had been found sensitizers – probably due to their very similar chemical structure (172). In a recent bi-centric study with 350 eczema patients who were consecutively tested with 1% and 2% M2O in pet.; 0.8% positive reactions were observed. However, in 3 additional cases active sensitization, with first reactions appearing 2 to 4 weeks after the patch test, and prompt reactions in the 2 cases repeat patch tested, was observed (174).

Although the number of cases reported is very low (probably due to low exposure) the classification of an established allergen is justified because of its high sensitizing potency (considered in the opinion). This example (active sensitization included) demonstrates that thorough interpretation of clinical data together with additional data can result in a well founded judgement.

This example may demonstrate as well, that very few “cases” of doubtful evidence and without further supporting data are not suitable to declare a chemical an “established allergen”.

#### **In summary:**

Substances which are obviously devoid of a sensitizing potential should certainly not be labeled as an “established allergen” (Example: Benzyl benzoate).

Established allergens should be labeled. Above all, those classified as of “concern” (SCCS) or “(very) important” (IVDK). However, the notion “established” is generously used, with sometimes rather poor evidence (Examples: Anisyl alcohol, Methyl Ionone, further examples

see Appendix I of this paper. Whether such compounds (the 'likely allergens' included) were all to be labeled is certainly a controversial issue. An alternative could be the entry in a publicly accessible data base.

**It is noteworthy that 19 out of 54 “established allergens” are based on not more than “up to 10 positive test reactions reported”** (table 7.1). The validity of the reactions is often not considered (e.g. The Korean study results <sup>21)</sup>; see above) and not critically commented on.

“Positive reactions” (not further specified) were obviously regarded by the SCCS as endowed with unequivocal “face evidence” not to be questioned. Criticism on such an approach is put forward in the above chapters.

Data evaluation may be further questioned with the case of camphor (table 7.1.). Three publications were cited to classify camphor as an “established allergen”. However, in 2 cases, not camphor, but the camphor oil<sup>23</sup> (*Cinnamum camphora* oil) was tested, containing a number of well-known allergenic compounds such as cinnamaldehyde, geraniol, eugenol and terpenic compounds. The positive reactions observed are of no surprise. A 3<sup>rd</sup> case reacted to a product containing sensitizing essential oils. Camphor was not tested and thus sensitization to camphor was not shown and its designation as an “established allergen” not substantiated.

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<sup>23</sup> The main chemical components are  $\alpha$ -pinene, camphene,  $\beta$ -pinene, sabinene, phellandrene, limonene, 1,8-cineole,  $\gamma$ -terpinene,  $p$ -cymene, terpinolene, furfural, camphor, linalool, bornyl acetate, terpinen-4-ol, caryophyllene, borneol, piperitone, geraniol, safrole, cinnamaldehyde, methyl cinnamate and eugenol.

## Appendix I

Substances classified as „established allergens“ (table 13.1. of the opinion) with “human evidence” and impact category “+” (1 to 10 cases) re-evaluated on the basis of data of Appendix I of the opinion. Of 54 substances classified as “established”, 19 belonged to impact class “+”. Of these, 12 were re-evaluated. In 8 /12 evidence for classification as established could be considered poor taking into account a) the number of cases relative to use volume, b) the possibility of false positives c) the quality of data presentation.

Substance	Cases probable	Less probable	RI/ PR	Reaction pattern 1)	Top 100	Original data 2)	Classif. as “established”	Comment
Acetylcedrene	4	1	RI= - 0.5 / PR= 100%	Bad	+	+	?	+ only / many “?-irrit” / very few cases / high exposure /
Amyl salicylate	4		RI= - 0.25 /PR= 100%	Bad	+	+	?	+ only / many “?-irrit” / very few cases / high exposure /
trans anethole	3		n.calc	good	+	+	(+)	Stronger reactions/ high exposure / rarely tested/ very few cases
Anisyl alcohol §	1	2	RI:-0.7 PR=66.6% 4)	(Bad)	-	+	?	Probably only 1 unequivocal case /
Benzaldehyde	6	3	RI= - 0.52 /PR= 100%	Bad	-	+ and ?	(+)	+ only / many “?-irrit” / very few cases /
<b>Camphor</b>	<b>0</b>	See comm.	n. calc	n. appl.	+	???	???	Not a single documented case. In 2 cases the camphor oil ( <i>Cinnamum camphora</i> oil) was tested, containing a number of well known allergenic compounds such as geraniol, eugenol and terpenic compounds A 3 <sup>rd</sup> case reacted to a product containing sensitizing essential oils. Camphor was not tested and thus sensitization to camphor was not shown.
Hexadecanolactone		6 + 1	N calc	n. appl	-	?	?	1 case reported by Larsen (2001) ( <sup>7</sup> ) 6 cases from a Korean study (Footnote 21). Rarely tested.



Methyl 2-octynoate (Methylheptine carbonate) §	9		RI:-0.5 PR: 87,5% (8)	Bad	-	+	+	1 +++ reaction / active sensitisation. Additional evidence: "strong sensitiser"
Alpha.iso Methyl lonone §	3	9	RI:-0.8 PR:100% (7)	Bad	+	+ and ?	??	+ only / many "?-irrit" / very few cases in > 4000 tested/ high exposure / 9 cases from a Korean study poorly documented (Footnote 21)
Propylidene Phthalide		4 <sup>(6)</sup>	N calc	n. appl	-	?	?	4 <sup>(6)</sup> only poorly documented cases. 3/25 positive in human maximisation test
Sclareol							??	No clinical cases.
TETRAMETHYL ACETYLOCTAHYDR ONAPHTHALENES	8		RI:+0.1 PR: 87.5	medium	-	+ and ?	+	Few cases but not Top 100; 1 stronger reaction. Medium reaction profile

§ since 1999

1) "bad": **neg RI / PR= 100% / good= strong reactions /**

2) + = sufficient / ? insufficient

3) ? "poor evidence"

4) cases from 3 studies joint for calculation.

5) A **rubefacient** is a substance for topical application that produces redness of the skin e.g. by causing dilation of the capillaries and an increase in blood circulation. Reaction was very probably an irritant /false positive

6) "2.6% in 182 patients tested" Malten K E, van Ketel W G, Nater J P, Liem D H. Reactions in selected patients to 22 fragrance materials. *Contact Dermatitis* 1984; 11: 1-10.

7) Larsen W. et al Fragrance contact dermatitis: a worldwide multicenter investigation (Part II). *Contact Dermatitis* 2001; 44: 344-346.

8) cases from 4 studies joint for calculation