Critical Comment

on

Evaluation of selected sensitizing fragrance substances

A LOUS follow-up project

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Summary and Conclusion

The LOUS report selected 11 fragrance compounds for classification in sub-category 1A (strong sensitizer) according to the CLP regulation and the ECHA 2015 guidance[1]. The selected compounds were the following: Citral, Cinnamaldehyde, Cinnamyl alcohol, Coumarin, Eugenol, Farnesol, Geraniol, Hydroxycitronellal, Methyl octynoate, *Cinnamomum cassia leaf oil / Cinnamomum zeylanicum, ext. , Evernia prunastri, ext.*

When using non-human data, the compounds would have been allocated to sub-category 1B, with the exception of cinnamaldehyde and methyl-octynoate (sub-category 1A) (LOUS p.52). By contrast, for the remaining 9 compounds a classification as a skin sensitizer in sub-category 1A was considered justified, solely based on human patch test data.

In ECHA 2015 (Annex I: 3.4.2.2.4.2) it is stated that "evidence from animal studies is usually much more reliable than evidence from human exposure". It is our opinion, that in such a situation, where human data shall overrule non-human evidence*, the quality and reliability of evidence derived from human data must be unequivocally strong*. Several issues shall be raised:

1. Frequencies of sensitization possibly giving rise to concern

One important question refers to the criteria for sub-categorisation 1A ("relatively high and substantial incidence") which is set by ECHA 2015 and LOUS arbitrarily at "≥ 1% for routinely tested patients[2], whereas authors of the EECDRG think that "A sensitivity rate of 1% or under is normally regarded as acceptable". With 2% there would be some concern, and with 3% there would be a problem (Wilkinson et al 2002).

Therefore we would set the benchmark for unselected patients at 2%.

As for the general population, a benchmark of ≥ 0.2% was set for subcategory 1A. Thyssen et al (2009)): considered the 'acceptable risk' and suggested: " When either 1/1000 …or 1/10,000 subjects in the general population become sensitized, the contact allergy epidemics should rather be categorized as ''concentrated" and ''low-level", respectively.

One might agree on 0.2% to 0.4% which would still be in the epidemic category of "concentrated", anyway not of concern.

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[1] The supplemental hazard statement EUH208 ("Contains <name of sensitising substance>. May produce an allergic reaction") will be required at concentrations ≥ 0.01% for strong sensitisers (sub-category 1A) according to the CLP Regulation

[2] "The figure of 1% for consecutive (i.e. unselected) dermatitis patients is based on the generally agreed consideration that a contact allergy frequency of ≥ 1% in such patients is of high concern".(ECHA 2015, p. 336)

As for selected patients, a benchmark of 2% (higher than in unselected patients by a factor of 2) was set by ECHA 2015. We disagree. The selection processes are quite heterogeneous and no meaningful benchmark can be derived. Comparing baseline and selected testing, Uter et al (2014) found differences in sensitization frequencies by a factor up to 3.6. Even more worrying is the fact that the LOUS report referred to the results of breakdown testing in fragrance mix positives (Patients were classified as "selected", without giving details on the selection itself). It is to no surprise, that many patients reacted to one or more of the ingredients and easily exceeded the benchmark of 2%, e.g. isoeugenol with 20% (For details see fig. 2 a).

Data from selected patients should not be used at all for hazard or risk assessment [3]

2. Frequencies of sensitization to fragrances

One recent publication of the IVDK with data up to 2013 demonstrates the rising and falling trends of FM I, FM II and the single ingredients which cover the 11 compounds (except *cinnamomum cassia* leaf oil and methyl-octynoate). (Fig 1 to 4). As the CLP and the ECHA 2015 guidance give no clue as to choosing the suitable period to be considered, we additionally analysed data from a most recent period (2014/2015) and calculated the prevalence in the general population. Oak moss absolue, isoeugenol, HICC (Lyral ®) and (marginally) cinnamic aldehyde can be considered as allergens of concern. *The remainder, namely Hydroxycitronellal, Cinnamic alcohol, Eugenol, Geraniol, Citral, Farnesol, and Coumarin rank below 1% in patients and ≤ 1/1000 in the general population, and do not fulfill the criteria for sub-category 1A*. This assessment is corroborated by two recent and reliable studies in unselected patients form the UK and from Denmark (Mann et al 2014; Heisterberg et al 2011)

3. Hazard versus Risk: The Role of Exposure

- *The LOUS and ECHA Guidance approach*

Hazard and risk are not clearly distinguished, neither in the LOUS report nor in the ECHA Guidance 2015. The result of a LLNA indicates hazard, i.e. the intrinsic properties (potency of the chemical), whereas the number of cases can be regarded as the resultant of risk. They "reflect, in addition to the intrinsic properties of the substances, factors such as the exposure situation" etc (CLP 3.4.2.2.2.2.). "When considering human evidence, it is necessary to take into account the size of the population exposed and the extent of exposure and frequency…." ECHA 2015 (p. 334), i.e. *a)* high or low exposure per product (in %) and *b)* high or low exposure per population (in numbers). The LOUS report used the IFRA standard limit, i.e., if the IFRA standard limit is < 1.0 % the exposure is thus considered as being relatively low (LOUS p. 54). Using the IFRA standard limit, all compounds were categorized in sub-category 1A, because the exposure was considered "low".

[3] Exceptions: occupational subgroups.

It should be mentioned that there is no scientific basis for such a distinction (“low” vs “high”). More importantly, a quantitative relation of exposure and allergy prevalence is missing, meaning that the risk is not sufficiently quantified. The above requirement “take into account the size of the population exposed” is not met.

- *The sensitization-exposure quotient (SEQ) of fragrances (Indicator of risk)*

The SEQ is calculated by relating frequencies of sensitization and exposure frequencies. It is a dimension-less value. The SEQ indicates high and low risk, respectively, ranging from *Evernia prunastri* (SEQ 44), methyl-octynoate (15) and cinnamal (10) to citral (0.9), geraniol (0.2), linalool (0.09), gamma-Methylionone (0.08). Interestingly, there was a good correlation between hazard (LLNA) and risk (SEQ), showing that hazard is usually the driving force of risk. There were exceptions:

The EC3 value of HICC is rather high (i.e. potency rather low), in the range of geraniol. However, the risk is relatively high, more than 10x higher than that of geraniol, probably, because former use concentrations of HICC were much too high. The driving force for risk was not hazard but exposure.

Methyl-octynoate was found to be a rare allergen (0.2%). The SEQ, however, revealed a very high risk. The EC3 value of < 0.5% indicates a very potent allergen. The driving force of risk was shown to be hazard.

The classification of 11 compounds evaluated by LOUS as being allocated to sub-category 1A is mainly based on frequencies of sensitization (exception: methyl-octynoate). Based on IVDK and other data from Europe, this classification cannot be confirmed, except for *Evernia prunastri*, cinnamaldehyde and methyl-octynoate. (together with isoeugenol and HICC, both not evaluated), compounds rightly considered as “of high concern”. This assessment is supported by the SEQ (risk) approach: There was a good correlation between hazard, risk (SEQ) and (our) classification in sub-category 1A. And for the remainder namely *hydroxycitronellal, cinnamic alcohol, eugenol, geraniol, citral, farnesol, and coumarin*, sub-category 1B is justified, according to an overall view of findings.

In summary: The allocation of these substances to sub-category 1A (strong sensitizer) by LOUS is refuted.

1. Introduction

The project "Evaluation of selected sensitising fragrance substances" with the authors Lea Bredsdorff and Elsa Nilesen was initiated as a LOUS[4] follow-up project by the Danish EPA. The objective of the study was to evaluate selected fragrance substances in relation to the classification criteria for strong sensitisers (Category 1A sensitisers) according to the CLP Regulation on classification, labelling and packaging of substances and mixtures (EC no. 1272/2008). The authors referred further to the updated version (COMMISSION REGULATION (EU) No 286/2011 of 10 March 2011) and to the ECHA (2015). Guidance on the Application of the CLP Criteria. Version 4.1.
The project was carried out from July to November 2015 at the National Food Institute, Technical University of Denmark.

In the past, certain fragrance compounds have been unequivocally identified as skin sensitizers, with various impacts on human health (SCCS 2012, Johansen & Lepoittevin 2011). Many fragrances are already classified as skin sensitisers (Skin Sens Cat 1) according to the CLP Regulation (EC no. 1272/2008). The CLP criteria for classification of skin sensitisers were revised in 2011 and now provide possibility for sub-categorising skin sensitisers in two sub-categories, sub-category 1A (strong sensitisers) or 1B (other skin sensitisers). The question was if some of the fragrances that are already classified. as skin sensitisers in Category 1 fulfil the CLP criteria for classification as strong sensitisers in sub-category 1A[5]. Such a classification implies that classification of mixtures containing the substance is required at a lower concentration (factor 10) compared to skin sensitisers in Category 1.

In the LOUS project 11 compounds were selected as candidates for subcategory 1A for further evaluation mainly referring to a list of compounds considered to be "of special concern" (i.e. > 100 reported cases) by the SCCS (2012). The selection process itself shall not be commented on. For evaluation of the 11 compounds the LOUS project referred to the CLP regulation and in particular to the ECHA guidance, (ECHA 2015), which set certain criteria for allocation of a compound to subcategory 1A using animal data (in particular LLNA) and data from human observation (Patch test data, information on exposure, number of reported cases)

[4] LOUS: List of Undesirable Substances
[5] The supplemental hazard statement EUH208 ("Contains <name of sensitising substance>. May produce an allergic reaction") will be required at concentrations ≥ 0.01% for strong sensitisers (sub-category 1A) according to the CLP Regulation

The 11 compounds further evaluated were the following

Citral,
Cinnamaldehyde
Cinnamyl alcohol
Coumarin
Eugenol
Farnesol
Geraniol
Hydroxycitronellal
Methyl octynoate
Cinnamomum cassia leaf oil / Cinnamomum zeylanicum, ext.
Evernia prunastri, ext.

HICC and isoeugenol were, however, not considered further as a harmonised classification in sub-category 1A already had been proposed, i.e. the purpose of the project had already been fulfilled.

For all 11 substances selected for detailed assessment, a classification as a skin sensitiser in sub-category 1A was considered justified based on the available data.
For nine of the substances, sub-category 1A was considered justified based on human patch test data. For methyl octynoate, sub-category 1A was considered justified primarily based on non-human data. For *Cinnamomum cassia leaf oil/Cinnamomum zeylanicum, ext*.), sub-category 1A was considered justified based on their constituents by read across to the major compounds such as cinnamaldehyde and eugenol.
However, referring to the results of animal tests (mainly LLNA) these nine substances would have been allocated to subcategory 1B, with the exception of cinnamaldehyde (21/22 LLNAs showed an EC3 value <2% and thus, justifying sub-category 1A).

Thus, classification of compounds as a skin sensitizer in sub-category 1A was considered justified mainly based on human patch test data. The compounds would have been allocated to 1B, if non-human data were given priority (with 2 exceptions: Cinnamaldehyde and methyl-octynoate).

In such a situation, where human data shall overrule non-human evidence, the evidence derived from human data must be unequivocally strong.
In the following the evaluation process is questioned and alternative results are presented.

2. Frequencies of sensitization possibly giving rise to concern

In the following chapter, the thresholds for “frequent” given by the ECHA 2015 guidance and used by the LOUS report (Bredsdorff & Nielsen (2016) are critically discussed.

The LOUS report referred to the CLP criteria for classifying an allergen in subcategory 1A (“relatively high and substantial incidence of reactions in a defined population in relation to relatively low exposure”).

2.1. **In patch test populations** (consecutive patients)

The ECHA (2015) Guidance considered ≥ 1% as “frequent”. “The figure of 1% for consecutive (i.e. unselected) dermatitis patients is based on the generally agreed consideration that a contact allergy frequency of ≥ 1% in such patients is of high concern”.(ECHA 2015, p. 336) “General agreement” was, however, not substantiated. According to a publication from authors of the EECDRG (Wilkinson et al 2002) “A sensitivity rate of 1% or under in patients attending a patch test clinic is normally regarded as acceptable (1). When sensitivity rates exceed 2% there are concerns, and when the rate exceeds 3% there is usually a problem”.

The assertion (“≥ 1% is of high concern”) is not generally agreed on.
We would rather set the benchmark for unselected patients at 2%.
ECHA 2015 and LOUS as well as the SCCS 2012 regarded ≥ 100 reported cases as a reason of “concern” or allocation to sub-category 1A. This benchmark is quite arbitrary and was nowhere substantiated. It is not supported by epidemiological data (see below). Exposure considerations are missing.

2.2. In the general population

With regard to the general population the ECHA 2015 guidance considered ≥ 0.2% as “frequent” based on the observation that the frequency of contact allergy in dermatitis patients is approximately 5 (range 2-10) times higher than in the general population.

Thyssen et al considering the ‘acceptable risk’suggested that in case more than 1/100 subjects in the general population are contact sensitized…one should categorize the epidemic as ‘‘generalized”.
When either 1/1000 …or 1/10,000 subjects in the general population become sensitized, the contact allergy epidemics should rather be categorized as ‘‘concentrated” and ‘‘low-level”, respectively (see table 1)

Table 1: Epidemic categories and number of persons affected (from Thyssen et al (2009)):

Number of contact sensitized subjects in the general population	Epidemic category
>1/20	Outbreak
>1/100	Generalized
>1/1000	Concentrated
>1/10,000	Low
>1/100,000	–
>1/10,000,000	–

Based on the relation of a 2% benchmark in patients and a factor of 5 to 10 lower in the general population one might agree on 0.2% to 0.4% which would still be in the epidemic category of "concentrated".

2.3. Selected dermatitis patients (aimed testing, usually special test series)

The threshold for "frequent" given by ECHA 2015 for frequencies found in selected PT populations is set at ≥ 2% (i.e. higher than in unselected patients by a factor of 2), but was again not substantiated. In fact, it seems quite arbitrary. Due to the high heterogeneity of the selection process, figures from such studies can rarely be used for hazard or risk assessments (with some exceptions: e.g. sensitization to hair dyes in female hairdresser clients (Uter et al 2014)).

a). "As the prevalence of (positive) reactions in consecutive patients is not comparable to the prevalence when only selected patients are tested (expected to be higher in the latter case), ….results are presented separately" (Uter et al 2010. The differences between routine testing and selected testing varies by factors from 1.9 to 3.6 (> 3: 3x), in any case higher than the factor of 2 (ECHA 2015) (Table 2)

Table 2: Comparison of frequencies of sensitization (stand for age and sex) after testing with baseline series (consecutive patients) versus special series (fragrance series; aimed testing) (Uter el al (2010) modified)

Substance	Baseline	Special	Factor
Oak moss absolue	1.81	5.59	3,1
Isoeugenol	1.62	3.41	2,1
Cinnamic aldehyde	1.43	2.64	1,9
Hydroxycitronellal	1.17	2.95	2,5
Cinnamic alcohol	0.73	2.36	3,2
Eugenol	0.44	1.57	3,6
Geraniol	0.39	0.87	2,2
α Amylcinn aldehyde	0.26	0.61	2,4

Factor (average): 2,6 (range: 1.9 – 3.6) > 3: (3x); >2 - < 3 (4x); < 2 (1x)

b) One striking example of selection can be found in the LOUS report (p 164). The results of breakdown testing the single ingredients of FM I in FM I positives were taken from a study of the IVDK (Schnuch et al 2015; table 2), where 3.8% of FM I positives reacted to geraniol. This was cited as "31/806 (3.8%) patients were positive". It was only mentioned that patients were "selected", without giving details on the selection process. There were even more "break down studies" referred to (e.g. Nardelli et al (2013); Santucci et al (1987).

These two examples illustrate the high heterogeneity of studies in selected patients (with quite different selection processes). The mere figure as "%" does not mean anything. The reference population should always be included. The characterization by "selected" is much too vague. It is impossible to set a meaningful threshold for concern. To juxtapose figures from such studies as was done in the LOUS report is misleading and general conclusions cannot be drawn regarding hazard or risk[6].

Data from selected patients should not be used at all for hazard or risk assessment [7]

[6] Example: Hydroxycitronellal: For unselected/consecutive dermatitis patients, positive reactions range between 0.9 and 2.6% (4 studies) and for selected dermatitis patients positive reactions range between 0 and 55% (35 studies) (p. 196)

[7] (Exceptions: occupational subgroups).

3. Frequencies of sensitization to fragrances

Frequencies of sensitization change over time (Fig1 to 4.). The CLP and the ECHA 2015 guidance give no clue as to choosing the suitable period to be considered. Therefore we present IVDK data from a longer period and most recent data (2014/2015)

3.1. Recent study from the IVDK (1998–2013 (FM I) and 2005–2013 (FM II)) (Geier et al 2015)

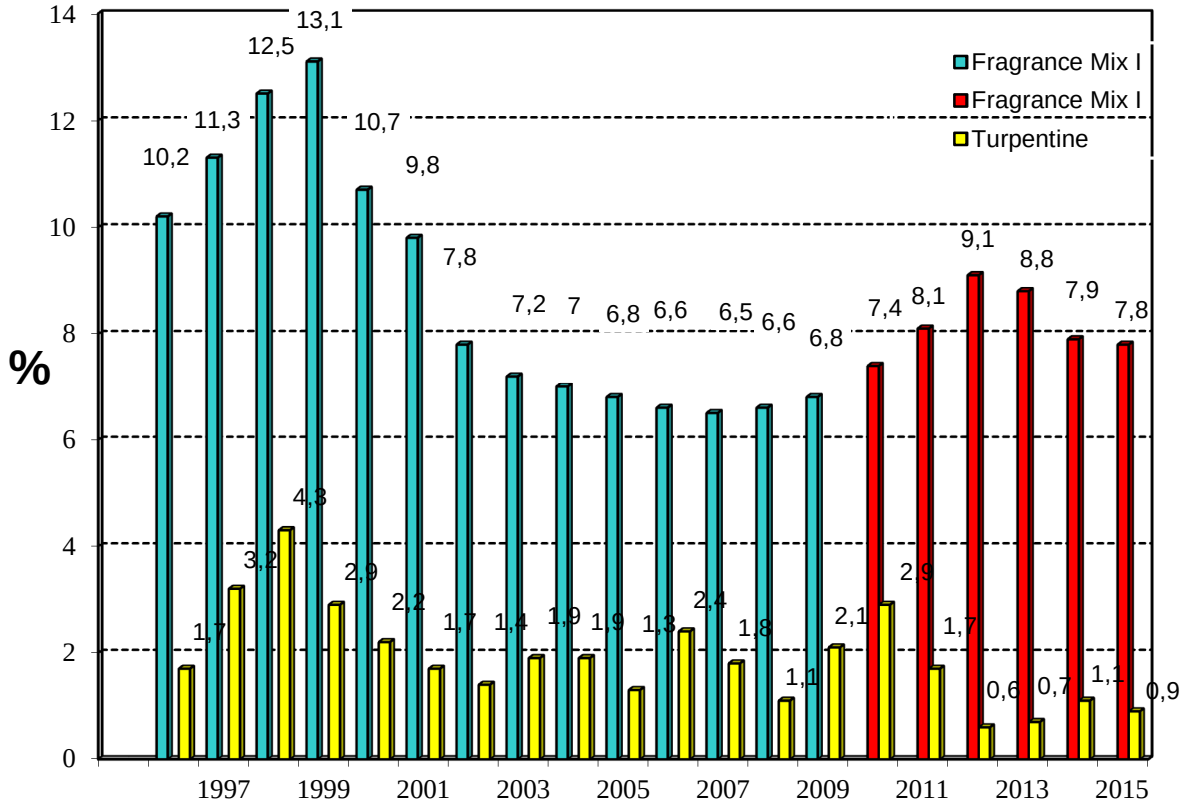

Fig. 1: Time trend of prevalences of sensitisation to the fragrance mix I, and oil of turpentine in IVDK patients. The ever-increasing prevalence of contact allergy to substances of the fragrance mix in the late nineties was worrying. It might have been partly caused by an increased use of essential oils at that time leading to an increase of sensitization to oil of turpentine (Schnuch et al 2004) . The decline of reactions to FM I from 1999 to 2007 was not only noted in the IVDK, but also in other countries. Danish data showed a similar time trend (Thyssen et al 2008). Regarding the recent increase in 2010 It may be speculated that an inadequate use of cinnamic compounds played a role (Geier et al 2015), supported by data from the UK (Mann et al (2014).IVDK data for 2014 and 2015 unpublished.

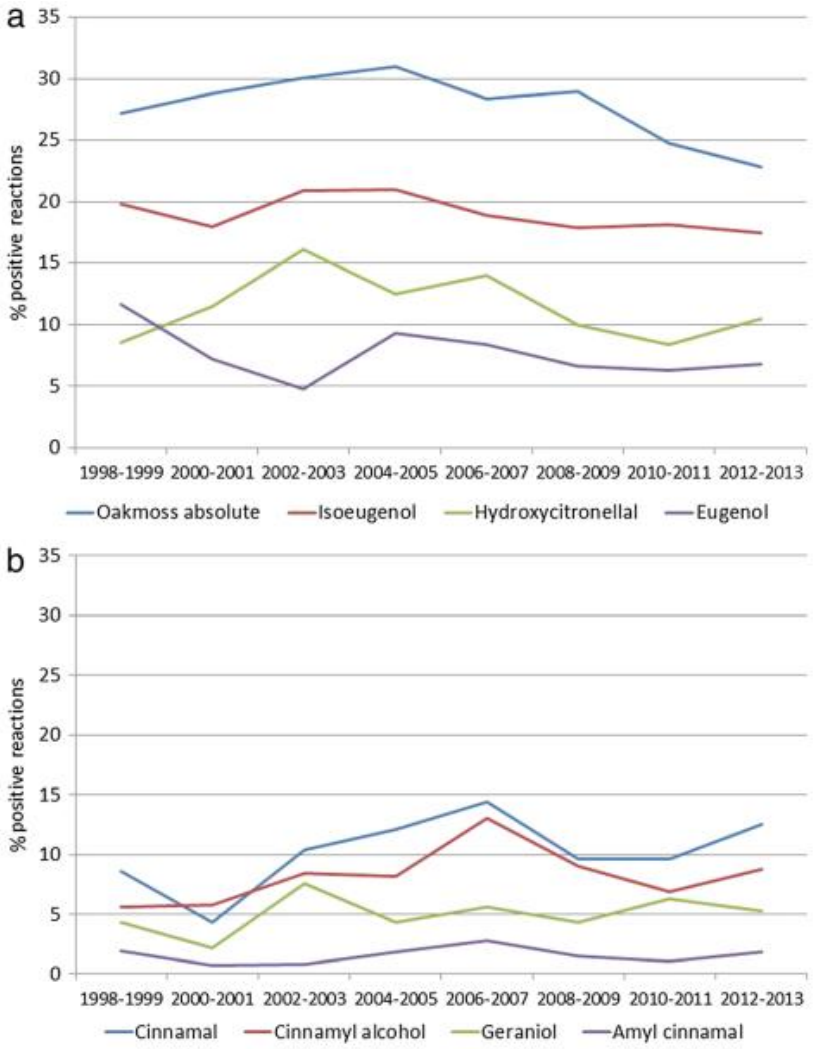

Figure 2. (a) Reaction frequencies to four components of fragrance mix (FM I) *in patients reacting to FM I*. (b) Reaction frequencies to the other four components of fragrance mix (FM I) in patients reacting to FM I (Geier et al 2015)

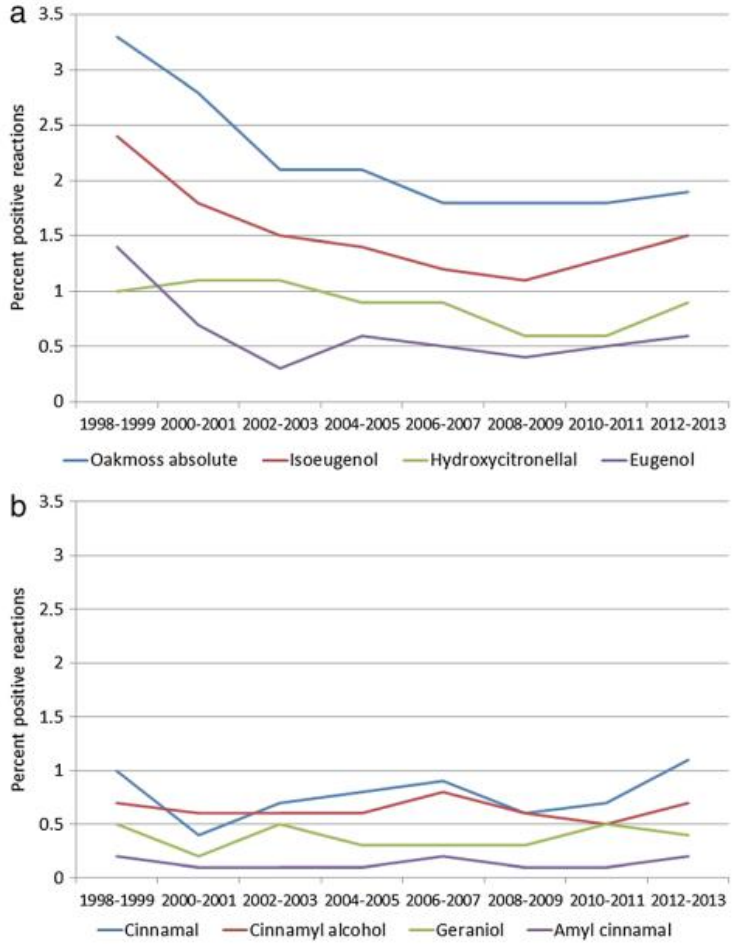

Figure 3. (a) Extrapolated reaction frequencies to four components of fragrance mix (FM I) in the test population. (b) Extrapolated reaction frequencies to the other four components of fragrance mix (FM I) in the test population. Two substances (oak moss and isoeugenol) are clearly above 1%, and one (cinnamal) can be considered marginally increased. All other substances remained below 1% over time.

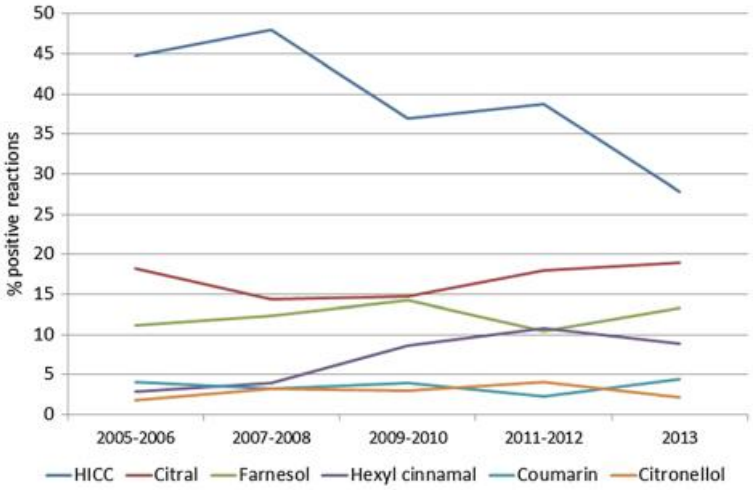

Figure 4. Reaction frequencies to the components of fragrance mix II (FM II) *in patients reacting to FM II.* There was a relative decrease of reactions to HICC and an increase of reactions to hexylcinnamal. Reactions to the FM II itself remained rather stable (4% to 5%) between 2005 and 2013 (Geier et al (2015).

3.2. Frequencies of sensitization to fragrances (IVDK 2014 – 2015) in patients and the general population

Substance	% pos. [95%-KI] in breakdown testing	patients (%)	CE DUR 10 years	% population
Oak moss absolue	23,7 [20,0 - 27,7]	1,79	258475	0,32
Isoeugenol	18,6 [15,3 - 22,3]	1,41	203040	0,25
Cinnamic aldehyde	12,4 [9,7 - 15,7]	0,94	135360	0,17
Hydroxycitronellal	10,6 [8,0 - 13,7]	0,80	115200	0,14
Cinnamic alcohol	10,2 [7,7 - 13,2]	0,77	110880	0,14
Eugenol	10,0 [7,5 - 13,0]	0,76	109440	0,13
Geraniol	6,9 [4,9 - 9,6]	0,52	74880	0,09
α Amylcinn aldehyde	2,2 [1,1 - 4,0]	0,17	24480	0,03
Sorbitansesquioleat	4,3 [2,7 - 6,5]			

Table 3: Results of breakdown down testing in 490 patients positive to FM I, extrapolation to routine testing as described in Geier et al 2015 on the basis of FM I positives (7.9% out of 21,634 tested standardized for sex and age) and calculation of the prevalence in the general population using the “worst case” model (see annex 1). Oak moss absolue, isoeugenol and (marginally) cinnamic aldehyde can be considered as allergens of concern. The remainder rank below 1% in patients and ≤ 1/1000 in the population, and could hardly be considered as “of concern” (See also Fig 2 to 4 and Thyssen et al (2009)

Testsubstanz	% pos. [95%-KI] in breakdown testing	patients (%)	CE DUR 10 years	% population
HICC (Lyral)	37.3 [31.1- 43.8]	1,60	230400	0,28
Citral	19.1 [14.5 - 24.4]	0,82	118080	0,14
Farnesol	12.1 [8.3 - 16.7]	0,52	74880	0,09
Citronellol	4.3 [2.1 - 7.5]	0,19	27360	0,03
Cumarin	4.3 [2.1 - 7.5]	0,19	27360	0,03
Alpha-Hexylzimtaldehyd	3.9 [1.9 - 7.0]	0,17	24480	0,03

Tab 4: Results of breakdown testing in 258 patients positive to FM II, extrapolation to routine testing as described in Geier et al 2015 on the basis of FM II positives (4.3% out of 21,657 tested standardized for sex and age) and calculation of the prevalence in the general population using the “worst case” model (see annex 1). Only HICC (Lyral) must be considered as allergen of concern. The remainder rank below 1% in patients and ≤ 1/1000 in the population, and could hardly be considered as “of concern” (See also Thyssen et al (2009) (above)

3.3. Comparison with recent and reliable studies in unselected patients

Study and study period Substance	IVDK (unpublished) 2014/15	IVDK (Schnuch 2007) 2003/4	IVDK (Uter 2010) 2005-2008	Heisterberg (2011) (DK) 1/2008 – 7/2010	Mann (2014) (UK) 2011/12
Oak moss absolue	1,79	2,0	1,8	2,5	1,7
Isoeugenol	1,41	1,1	1,6	1,1	2,1
Cinnamic aldehyde	0,94	1,0	1,4	1,3	1,4
Hydroxycitronellal	0,80	1,3	1,2	0,9	1,0
Cinnamic alcohol	0,77	0,6	0,7	0,7	2,5
Eugenol	0,76	0,4	0,4	0,3	0,62
Geraniol	0,52	0,4	0,4	0	0,46
α Amylcinn aldehyde	0,17	0,1	0,3	0,2	0,15

IVDK data standardized for sex and age

Table 5 Frequencies of sensitization the FM I compounds found in different studies. Oak moss and isoeugenol could be considered as substances of concern, together with (marginally) cinnamic aldehyde. Cinnamic alcohol, which had never been at the top of FM allergens, could be regarded as an outlier probably due to a temporarily limited inadequate exposure to cinnamic compounds (see comment to Fig 1)

Study and study period Substance	IVDK 2014/15	IVDK 2003/4	Heisterberg (DK) 1/2008 – 7/2010	Mann (UK) 2011/12
HICC/ Lyral	1,60	2,3	2,3	1,3
Citral	0,82	0,6	0,3	1,0
Farnesol	0,52	0,9	0,4	0,41
Citronellol	0,19	0,5	0,1	0,31
Cumarin	0,19	0,4	0,2	0,41
Alpha-Hexylzimtaldehyd	0,17	0,1	0,6	0,46

Table 6 Frequencies of sensitization the FM II compounds found in different studies. Only HICC / Lyral ® must be considered as a substance of concern.

4. Hazard versus Risk: The Role of Exposure

4.1. The LOUS and ECHA Guidance approach

The CLP regulation and the ECHA guidance (2015) provide the framework and the criteria for *hazard* categories. Yet, hazard and risk are not clearly distinguished. The result of predictive animal testing, e.g. LLNA, indicates hazard, i.e. the intrinsic properties (potency of the chemical). However, the number of clinical cases are also used for 'hazard" categorization, whereas strictly speaking, the number of cases observed indicate a hazard present *and* the risk. In paragraph 3.4.2.2.2.2.(CLP) it is stated

"Positive effects seen in either humans or animals will normally justify classification. Evidence from animal studies is usually much more reliable than evidence from human exposure…. " "positive human data on skin sensitisation are usually derived from case-control or other, less defined studies. Evaluation of human data must therefore be carried out with caution, as the frequency of cases reflect, in addition to the intrinsic properties of the substances, factors such as the exposure situation, bioavailability, individual predisposition and preventive measures taken" .

In other words: The number of cases reflect risk as a resultant of hazard and exposure (and other). The *hazard* classifications 1A and 1B (based on human data) are derived from different *risks* characterized by the number of cases in relation to exposure. There are attempts to operationalize frequency and exposure (Tab 3.4.2.b- d), but that seems less founded from a scientific point of view (frequency was critically discussed above).

There are 2 aspects of exposure:

a) High or low exposure per product (in %) and

b) High or low exposure per population (in numbers)

This is expressed in the ECHA Guidance (p. 334) as follows:

> *"When considering human evidence, it is necessary to take into account the size of the population exposed and the extent of exposure and frequency…."*

However, the ECHA guidance and the LOUS report refer mainly to exposure per product (a) saying that < 1.0% is to be considered as “low exposure” and ≥ 1 as “relatively high exposure” (ECHA 2015; p. 337). The LOUS report used the IFRA standard limit, i.e., if the IFRA standard limit is < 1.0 % the exposure is thus considered as being relatively low (LOUS p. 54)[8]. It should be mentioned that there is no scientific basis for such a distinction. Furthermore, the IFRA limits are set basically referring to the potency of the chemical. Most of the 11 substances evaluated by LOUS qualify for sub category 1B, according to the LLNA results, but using the proxy (IFRA-limits derived from animal tests) the substances are categorized in sub-category 1A. There seems to be a lack of consistency.

The second aspect (the size of the population exposed) is only marginally considered further in the categorization process, although it is obvious (and evident from our calculation of the sensitization-exposure quotient (SEQ; see below) that all frequencies of sensitization are put into perspective by exposure, both per product and per population exposed (see ECHA, above).

4.2. The sensitization-exposure quotient (SEQ) of fragrances (Indicator of risk)

As an estimate of sensitization risk, the sensitization exposure quotient (SEQ) was calculated as the quotient of the relative frequency of sensitization (IVDK data) and the relative frequency of use (in terms of volume (IFRA data)) and labelling (INCI) documented by the CVUA (Chemisches und Veterinär- Untersuchungsamt Karlsruhe/Germany), The total products (n=5451) and leave-on products (n = 3541) were considered for analysis. The SEQs (the risk) varied greatly. (Tab 7 to 10).

Interestingly, there was a good correlation between hazard and risk, showing that hazard is usually the driving force of risk (table 11). But there are exceptions to the rule:

The EC3 value of HICC is rather low, in the range of geraniol. However, the risk is relatively high, more than 10x higher than that of geraniol. The increased risk can easily be explained. In the nineties and the first years of the new century there were products containing > 3% of HICC (Schnuch 2009), which is much too high (by a factor of 1.000) compared with the actual recommended IFRA limit of 0.02% !

[8] A scoring system proposed by ECHA including not only the benchmark of < 1.0 % but also repeated exposure < once/daily (score 1) versus ≥ once/daily (score 2) and number of exposure (< 100 (score 0) versus >100 (score 2) was not further considered.

Methyl-octynoate was found to be a rare allergen (0.2%) and thus was not under critical observation, far from being an allergen of concern. Only the SEQ revealed a very high risk (table 7). Further search for information revealed that methyl-octynoate confers a very high hazard (EC3 value < 0.5%), thus supporting the SEQ approach. Again, the driving force of risk was shown to be hazard.

Frequencies of sensitization *may* or may not indicate hazard or risk. In the case of HICC they did not indicate hazard but only (high) risk. In the case of Methyl-octynoate, they indicated neither hazard nor risk.

As a general rule, mere frequencies of sensitization alone are not ideal indicators for hazard or risk. They should be evaluated against further information (exposure, animal studies), in particular, if there are discrepancies between human observations and animal studies (as was the case with HICC and methyl-octynoate).

Table. 7 SEQs ≥ 10

Tree moss (Evernia furfuracea)	73.16
Oak moss absolue (Evernia prunastri)	44.03
Methyl 2-octynoate (Methyl heptine carbonate)*	15.5
Cinnamal	9.95
Isoeugenol	9.75

Table 8 SEQs > 1.0 and <10

HICC	3.86
Farnesol	3.25
Anise alcohol	3.1
Cinnamyl alcohol	2.46
Benzyl cinnamate	1.84
Hydroxycitronellal	1.49
Eugenol	0.96

Tabl 9 SEQs < 1 and ≥ 0,1

Citral	0.9
Amyl cinnamal	0.7
Butylphenyl methylpropional (Lilial ®) *	0.44
Hexyl cinnamal	0.38
Cumarin	0.28
Geraniol	0.21
Benzyl salicylate	0.18
Benzyl alcohol	0.18

Tabl 10: SEQs ≤ 0,1

Citronellol	0.1
Linalool	0.09
Alpha-Isomethyl ionone (gamma-Methylionone)*	0.08
D,l-Limonene	0.05
Benzyl benzoate	0

Tab 11 Correlation between SEQ (risk) and hazard
(low EC3 values indicate high potency; high SEQs indicate high risk). For comment: see text.

fragrance	SEQ	EC3%	
limonene	**0.05**	30%	Low potency and low risk
linalool	**0.09**	46.2%	
citronellol	**0.1**	43.5%	
benzyl alcohol	**0.18**	>50%	
geraniol	**0.21**	22.4%	
HICC	**3.86**	17.1%	Low potency higher risk
cinnamal	**9.95**	0.2%	High potency and high risk
isoeugenol	**9.75**	0.54%	
methyl 2-octynoate	**15.5**	< 0.5%	
Oak moss (chloroatranol)	**44.3**	0.4%	

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ANNEX I

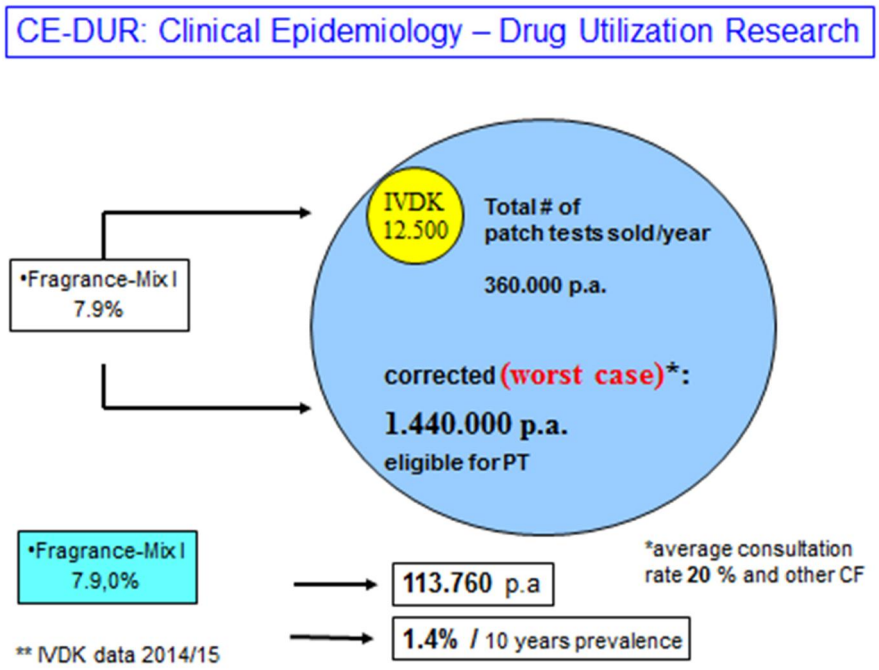
The CE-DUR approach [1-6]

The CE-DUR approach estimates the frequency of sensitization in the general population.

Two data sources are used:
i) Patch test results of patients attending the IVDK dermatological departments. The IVDK patients represent approximately 2–3% of all patients patch tested in Germany. Characteristics such as gender, age, disease pattern or suspected causal exposure and the frequency of positive patch tests are considered to be largely representative of all German patients patch tested and

ii) sales of patch test material in Germany, the latter representing a starting point for the estimation of the number of persons ‘eligible’ for testing at the population level because of a suspected contact sensitization.

The sales of PT material used in the original publication [1, 2] (~600.000 p.a.) had to be corrected to ~360.000 [3], which is the basis of the actual calculation (see below)



Frequency of sensitization to FM I according to a “worst case” model, with a consultation rate of 20% [2, 7]. The 10-years prevalence would be 1.4%. According to a “medium” model with a consultation rate of 25% (and other correction factors) the 10-years prevalence would be 0.9%. For comparison: In the year 2006, the prevalence of FM I allergy was 1.6% (95% CI: 1.2-2.1%) according to a study from Denmark [7], and between 0.9% (95% CI: 0.6 - 1.3%) and 1.8% (95% CI: 1.4- 2.3%) in a European study [8]

It can be concluded that the CE-DUR approach is a good estimation of the prevalences of contact allergies in the general population. The “worst case” model is used in the calculation of single fragrances (see table 3 + 4).

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