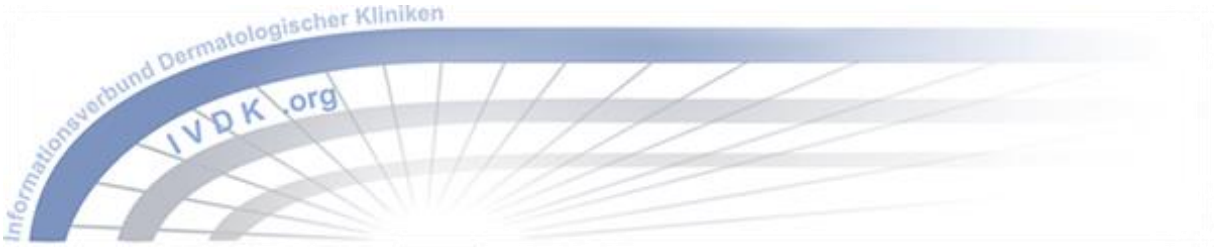

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Comment on the SCCS Opinion SCCS/1632/21 of 7 May 2021

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Comment on the SCCS Opinion SCCS/1632/21 of 7 May 2021

On 7 May 2021, the Scientific Committee on Consumer Safety (SCCS) published a scientific advice on the threshold for the warning 'contains formaldehyde' in Annex V, preamble point 2 for formaldehyde-releasing substances. Their conclusions were:

"The SCCS considers that the present threshold does not sufficiently protect consumers sensitised to formaldehyde from exposure to free formaldehyde from formaldehyde releasers."

"Reducing the present threshold by a factor of 50, that is, to 0.001% (10 ppm), will protect the vast majority of consumers sensitised to formaldehyde. This threshold applies to the total free formaldehyde irrespective of whether a product contains one or more formaldehyde releaser(s)."

From my point of view, this opinion is not well founded. A reduction of this magnitude is not necessary and will in practice cause unnecessary restrictions for most formaldehyde-sensitive individuals and possibly initiate an increasing use of other preservatives in cosmetics with unforeseeable allergological risks.

In detail:

SCCS Opinion SCCS/1632/21, Page 8, paragraph 2:
"A number of different ROAT studies using different FRs *[formaldehyde releasers]* trying to elicit ACD *[allergic contact dermatitis]* in formaldehyde allergic individuals have been reviewed in 2010 by de Groot et al. (4). These studies illustrate that on normal skin, concentrations of free formaldehyde of 130-370 ppm, as released by different FRs, are clearly capable of eliciting ACD in formaldehyde-sensitised individuals (5-8)."

Quotation from de Groot et al. (4), referring to Zachariae et al. (6): "On the basis of this investigation, the amount of formaldehyde that does *not* elicit dermatitis in formaldehyde-sensitive subjects should be between 130 and 370 p.p.m."
Herbert and Rietschel (5) did not define any threshold based on their own study, but they cited a publication by Jordan et al. (J Am Acad Dermatol 1979; 1: 44-48) who performed threshold patch tests in formaldehyde-sensitive individuals in an unusual setting: "Patch tests to 0, 30, 60, and 100 ppm aqueous formaldehyde in a vehicle consisting of 12% methanol in water were applied in nine subjects … The tests were applied on Friday and reapplied on the following Monday (72 hr) and Wednesday (120 hr) … The last reading was done on Friday (168 hr)." Altogether, 6 of 9 individuals reacted to 100 ppm formaldehyde in the course of the study. Five of them also reacted to 60 ppm, and 4 to 30 ppm. In addition, 13 formaldehyde-sensitive subjects took part in a use test. For 2 weeks, they sprayed a spray containing 28.86 ppm formaldehyde in a 12% methanol-in-water vehicle twice daily into one axilla, and the same spray without formaldehyde into the other axilla. Methanol is a skin irritant. Four participants complained about itching and burning at the vehicle side, and another 2 at the formaldehyde side. Two of the individuals who complained about itching and burning at the vehicle side "developed a very mild perifollicular dermatitis to the formaldehyde side that color

photography could not adequately reproduce" at day 7 and day 11, respectively.
Flyvholm et al. (7) concluded from their study that "the threshold concentration for occluded patch test to formaldehyde in formaldehyde-sensitive patients was 250 ppm". Definite positive reactions in a ROAT with a leave-on preparation containing 300 ppm of free formaldehyde were not seen.
The aim of the study by Isaksson et al. (8) was to find out if preservation of a corticosteroid cream (Flutivate® cream) with a formaldehyde releaser negatively affects therapeutic efficiency in formaldehyde-sensitive dermatitis patients. The study clearly proved that it does. As part of the study, patch tests with formaldehyde at different concentrations were performed. One of the 7 patients reacted to formaldehyde at a concentration of 0.0312% (312 ppm); for the remainder, the threshold for a clear-cut positive patch test reaction was at least 0.125% (1250 ppm). And "there was no correlation between the FA [formaldehyde] reactivity and the tendency to healing in the FA-allergic patients treated with Flutivate® cream".

Summing up, the cited studies do *not* illustrate that on normal skin, concentrations of free formaldehyde of 130-370 ppm, as released by different FRs, are clearly capable of eliciting ACD in formaldehyde-sensitised individuals.

SCCS Opinion SCCS/1632/21, Page 8, paragraph 3:
The ROAT study with application of a formaldehyde-containing moisturizer on pre-irritated skin in 15 formaldehyde-sensitive individuals by Hauksson et al. (9) is regarded as key study. In this study, an experimental irritant contact dermatitis was provoked in the study participants by applying filter papers with sodium lauryl sulfate (SLS) for 24 hours. After removal of the SLS-patch, a ROAT was performed in the corresponding areas using three moisturizers preserved with DMDM hydantoin containing > 40 ppm, 20-40 ppm, 2.5-10 ppm of free formaldehyde. A control ROAT was performed using the same moisturizer without formaldehyde. A closer look at table 1 of the corresponding publication reveals the poor reliability and reproducibility of formaldehyde patch tests and the poor correlation of ROAT and patch test results. Patch tests with formaldehyde at different concentrations could be reproduced with similar reaction intensities in not more than 7 out of 15 sensitized participants. Six of these 7 individuals, all of whom had strong patch test reactions to formaldehyde, reacted in the ROAT. (The seventh was excluded from the analysis because of mistakes when performing the ROAT.) Of the remaining 8 formaldehyde-sensitive participants, only 2 (with weak positive patch test reactions to formaldehyde) had a positive ROAT. Among those 6 subjects who did not show any reaction in the ROAT, there were 4 with strong patch test reactions to formaldehyde.

No doubt – there are individuals with a high-grade contact allergy to formaldehyde who react to even traces of formaldehyde in cosmetics. But very probably these are only very few patients. From this study, one cannot extrapolate that 60% (9 / 15) of the formaldehyde-sensitive individuals will react to 40 ppm formaldehyde in a cosmetic product, or 40% (6 / 15) to 20-40 ppm.

SCCS Opinion SCCS/1632/21, Page 8, paragraph 4:
In this paragraph, elicitation thresholds under use condition (or at least in ROATs) are extrapolated from patch test results. Based on the assumption that the "ED_{10} for formaldehyde has been estimated to be 20.1 µg/cm² (95% CI: 4.09-43.9 µg/cm²) (11)" in patch tests, the ED_{10} in the ROAT is calculated by division by an adjustment factor of 10, resulting in a threshold of "around 2 µg/cm² (95% CI: 0.41-4.4 µg/cm²)". The SCCS admits that this approach has two limitations: "As a limitation, this approach relies on (i) one single patch test study (7), and (ii) a hitherto unvalidated putative "adjustment factor" of 10 for volatile compounds not based on results with formaldehyde, but with the fragrances isoeugenol and hydroxyisohexyl 3-cyclohexene carboxaldehyde (12)."

It is remarkable that these calculations are based on a study from 1997 (7), and the models used were developed and published in 2009 (12) and 2011 (11), but none of these models has been validated for formaldehyde, although ten years have passed since then.
As mentioned above, in the study by Flyvholm et al. (7) (which is the only experimental base for these calculations), no definite positive reactions in a ROAT with a leave-on preparation containing 300 ppm of free formaldehyde were seen. Therefore, doubts are justified as to whether these threshold calculations are really valid. Further studies are needed in order to define a valid ED_{10} under use conditions for formaldehyde-sensitive individuals, stratified by reaction intensity in the patch test. Any recommendation based on current data seems premature.

In conclusion, SCCS recommends reducing the threshold for labelling free formaldehyde from 0.05% to 0.001% (from 500 ppm to 10 ppm) because this "will protect the vast majority of consumers sensitised to formaldehyde". The "vast majority" referred to here is 90%.
However, it has to be considered how this threshold was derived.

1) The above mentioned "adjustment factor" of 10 when comparing patch test thresholds and ROAT thresholds is not sufficiently proven for formaldehyde.
2) In addition, the lower limit of the extrapolated dose per area (0.41 µg/cm², corresponding to about 50 ppm) was taken as a first step.
3) Finally, the results of the study by Hauksson et al (9) which cannot be regarded representative for every day cosmetic use (see above) were considered because it "provides compelling, directly usable evidence that concentrations of 20-40 ppm still elicit a large share of formaldehyde-allergic subjects, while a concentration of up to 10 ppm was safe in this regard."

Taken together, there are several steps when deriving this threshold which are not sufficiently validated, leading to a too low threshold. Ten ppm is definitely not an ED_{10} under cosmetic use conditions. Very probably, far less than 10% of the formaldehyde-sensitive individuals will experience an adverse reaction when using a cosmetic product containing 10 ppm of free formaldehyde.

The question is: Is there any definition of "vast majority" for legal purposes? What part of the sensitized individuals should be protected or warned by regulations? If you wish to protect almost 100%, then you have to declare even traces of every contact allergen because you will always find at least one patient with an extremely high degree of sensitization / an extremely low elicitation threshold. In the context of life-threatening immediate-type allergies, this may make sense, but in case of allergic contact dermatitis, this "over-protection" will lead to unnecessary restrictions for most of the allergic patients, considerably lowering their quality of life.

Very probably, lowering the threshold for labelling formaldehyde in cosmetic products from 500 ppm to 10 ppm would have two consequences. First, patients with a moderate or weak degree of sensitization to formaldehyde would avoid such products which narrows their choices in an unnecessary way. Second, cosmetic producers would switch to other preservatives in order to avoid the formaldehyde labelling. Considering the well-known “Dillarstone effect” (101), we would then face an increased use of preservatives with a higher or an unknown allergenic potential.

From the epidemiological point of view, there is no need to lower the labelling threshold. There is no evidence for an increasing incidence of formaldehyde sensitization. Sensitization frequencies observed in the Information Network of Departments of Dermatology (IVDK) or in the European Surveillance System on Contact Allergies (ESSCA) have remained stable for years (102,103). Also, the frequency of positive patch test reactions to formaldehyde releasers in the IVDK is stable at a very low level (104), indicating that the formaldehyde released is not a major problem.

References

SCCS (Scientific Committee on Consumer Safety), Scientific advice on the threshold for the warning 'contains formaldehyde' in Annex V, preamble point 2 for formaldehyde-releasing substances, final version of 7 May 2021, SCCS/1632/21.
https://ec.europa.eu/health/sites/default/files/scientific_committees/consumer_safety/docs/sccs_o_254.pdf

References from the SCCS Opinion SCCS/1632/21:

4. de Groot A, White IR, Flyvholm M-A, Lensen G, Coenraads P-J. Formaldehyde-releasers in cosmetics: relationship to formaldehyde contact allergy. Part 2. Patch test relationship to formaldehyde contact allergy, experimental provocation tests, amount of formaldehyde released, and assessment of risk to consumers allergic to formaldehyde. Contact Dermatitis. Januar 2010;62(1):18–31.

5. Herbert C, Rietschel RL. Formaldehyde and formaldehyde releasers: how much avoidance of cross-reacting agents is required? Contact Dermatitis. Juni 2004;50(6):371–3.

6. Zachariae C, Hall B, Cottin M, Cupferman S, Andersen KE, Menné T. Experimental elicitation of contact allergy from a diazolidinyl urea-preserved cream in relation to anatomical region, exposure time and concentration. Contact Dermatitis. November 2005;53(5):268–77.

7. Flyvholm MA, Hall BM, Agner T, Tiedemann E, Greenhill P, Vanderveken W, u. a. Threshold for occluded formaldehyde patch test in formaldehyde-sensitive patients. Relationship to repeated open application test with a product containing formaldehyde releaser. Contact Dermatitis. Januar 1997;36(1):26–33.

8. Isaksson M, Gruvberger B, Goon AT-J, Bruze M. Can an imidazolidinyl urea-preserved corticosteroid cream be safely used in individuals hypersensitive to formaldehyde? Contact Dermatitis. Januar 2006;54(1):29–34.

9. Hauksson I, Pontén A, Gruvberger B, Isaksson M, Engfeldt M, Bruze M. Skincare products containing low concentrations of formaldehyde detected by the chromotropic acid method cannot be safely used in formaldehyde-allergic patients. Br J Dermatol. Februar 2016;174(2):371–9.

11. Fischer LA, Menné T, Voelund A, Johansen JD. Can exposure limitations for well-known contact allergens be simplified? An analysis of dose-response patch test data. Contact Dermatitis. Juni 2011;64(6):337–42.

12. Fischer LA, Voelund A, Andersen KE, Menné T, Johansen JD. The dose-response relationship between the patch test and ROAT and the potential use for regulatory purposes. Contact Dermatitis. 2009;61(4):201–8.

Additional references:

101. Dillarstone A. Cosmetic preservatives. Contact Dermatitis 1997; 37: 190.

102. Uter W, Gefeller O, Mahler V, Geier J. Trends and current spectrum of contact allergy in Central Europe: results of the Information Network of Departments of Dermatology (IVDK) 2007-2018. Br J Dermatol. 2020; 183: 857-865

103. Uter W, Bauer A, Belloni Fortina A, Bircher AJ, Brans R, Buhl T, Cooper SM, Czarnecka-Operacz M, Dickel H, Dugonik A, Geier J, Giménez-Arnau AM, Gonçalo M, Johansen JD, Johnston GA, Mahler V, Rustemeyer T, Sanchez-Perez J, Schuttelaar MLA, Simon D, Spiewak R, Valiukevičienė S, Weisshaar E, White IR, Wilkinson M; ESSCA Working Group. Patch test results with the European baseline series and additions thereof in the ESSCA network, 2015-2018. Contact Dermatitis 2021; 84: 109-120

104. Kreft B, Geier J. Dauerbrenner Konservierungsmittelallergie – Was geht, was kommt, was bleibt? Hautarzt 2020; 71: 190-196

Conflicts of Interests:

I don't have any personal conflicts of interests. The IVDK, maintained by the IVDK e.V., of which I am an employee, is sponsored by the chemical, cosmetic and fragrance industry (associations) as well as by public funds. For details, see http://ivdk.org/en/sponsors/.