

Letter to the Editor

Fragrance mix I: TRUE Test™ versus pet.-based patch test

doi:10.1111/cod.12352

Dear Sir,

I read with interest, if somewhat belatedly, the paper by Mortz and Andersen (1) comparing the diagnostic performance of fragrance mix I (FM I) provided by TRUE Test™ (MEKOS Laboratories A/S, Hillerød, Denmark) with the allergen preparation provided by Trolab™ (Almirall Hermal GmbH, Reinbek, Germany). This study is based on patch test data of 5006 patients tested with both allergen preparations in the Odense department. Of these patients, 187 reacted to both allergen preparations, 31 only to the TRUE Test™ material and 277 only to the Trolab™ material. The difference in contact allergy prevalence (4.4% versus 9.3%, $p < 0.0001$) is very evident. Hence, the question arises of whether one material is too insensitive (resulting in false negatives) or the other is too non-specific (yielding false positives) – or whether both possibilities apply.

A look at the dose per area delivered by the allergen preparations, namely, $450 \mu\text{g}/\text{cm}^2$ in the case of the TRUE Test™ material and $5.6 \text{ mg}/\text{cm}^2$ (with the small Finn Chambers® loaded with 20 mg) (2) in the case of the Trolab™ material, shows a dose of the pet.-based allergen that is higher by approximately one order of magnitude. Matrix effects of the different vehicles, and in particular allergeo-kinetic effects of the 5% sorbitan sesquiolate (SSO) added to the Trolab™ material, must also be considered. The different doses may explain the vastly differing prevalence of patch test reactions that appear morphologically 'positive' (at least infiltrated erythema). Although patch testing is the gold standard method for diagnosing contact allergy, such diverging results call for the assessment of patch test results against other, 'external' criteria.

One way to assess the diagnostic performance is to consider clinical relevance, as also employed in the study by Mortz and Andersen, notwithstanding difficulties with the consistent application of this assessment, which is conceptually appealing, but difficult to use in practice. For

instance, regarding a positive patch test reaction to FM I, clinical relevance could easily be overdiagnosed, owing to the ubiquitous presence of fragrances – especially as ingredient labelling for 26 fragrances, including the 8 contained in FM I, only became available during the study period (1988–2009). Hence, a more specific assessment has been possible only since 2003, when the 26 fragrances were introduced to Annex III of the Cosmetics Directive (now: Cosmetics Regulation) by the seventh amendment (2003/15/EC). Conversely, a lack of recall or awareness on the part of the patient or insufficient exposure analysis on the part of the doctor will always lead to under-recognition of clinical relevance.

With this quite important limitation in mind, the following question can be addressed: what is the proportion of patients with a non-positive reaction to the TRUE Test™ material who have a clinically relevant positive reaction to the Trolab™ test material? The table below shows some data extracted from the original publication, except for the rightmost column, which has been calculated on the assumption that patients in whom relevance had been assessed constituted a random sample of all patients (with positive patch test reactions) in whom this would have normally been performed.

Material	n (positive) to publication	Clinical relevance		
		n (actual, according to publication)	% of those with positive reactions assessed	n (hypothetical, extrapolated)
TRUE Test™	218	130/178	73.0	159
Trolab™	464	222/345	64.3	298

With different assumptions, the following total numbers of 'clinically relevant' reactions missed by the TRUE Test™ material can be calculated:

- Conservatively assuming that all 130 relevant positive reactions to the TRUE Test™ material were also relevant positive reactions to the Trolab™ material, and that it was never the case that a positive

reaction to one mix was considered to be relevant while a positive reaction to the other test was considered to be not relevant, $222 - 130 = 92$ missed reactions would result, including 48 patients with doubtful reactions to the TRUE Test™ material. This corresponds to 1.8% of all consecutively patch tested patients.

- Furthermore, assuming that the proportions of relevant positive reactions among all positive reactions to either mix were representative in the subsample assessed for relevance, the difference would be $298 - 159 = 139$ missed reactions (including the above-mentioned 48 patients). This would correspond to 2.8% of all consecutively patch tested patients.
- If it is assumed that some relevant positive reactions to the TRUE Test™ material occurred with non-positive reactions to the Trolab™ material, which is rather unlikely in view of the > 10 times higher dose per area of the Trolab™ material, the above numbers/proportions would be higher. At the same time, this would indicate that some relevant reactions are missed by the Trolab™ FM I.

Although the number of false negatives may be overestimated to some extent by the above calculations in relation to clinical relevance as discussed above, it seems clear enough that the use of FM I with the TRUE Test™ alone will result in a marked underdiagnosis of contact allergy to the eight ingredients of the mix. As a compensation, the pet.-based FM I can additionally be tested, as suggested by the authors. Alternatively, a redesign of the TRUE Test™ FM I should be considered. However, the problem of the addition of SSO in the currently used pet.-based FM I should also be addressed. As a straightforward possibility for excluding at least one particular type of 'false-positive' reaction, additional testing with SSO along with FM I in the baseline series is suggested.

The improvement in diagnostic accuracy of FM I in either test system is of importance in view of its role both in a clinical setting and in population-based studies (3).

Wolfgang Uter

IMBE, University of Erlangen-Nuernberg, Waldstr. 6, Erlangen 91054, Germany

Accepted for publication 16 December 2014

References

- 1 Mortz C G, Andersen K E. Fragrance mix I patch test reactions in 5006 consecutive dermatitis patients tested simultaneously with TRUE Test™ and Trolab™ test material. *Contact Dermatitis* 2010; **63**: 248–253.
- 2 Bruze M, Goossens A, Isaksson M. Recommendation to increase the test concentration of methylchloroisothiazolinone/methylisothiazolinone in the European baseline patch test series – on behalf of the European Society of Contact Dermatitis and the European Environmental and Contact Dermatitis Research Group. *Contact Dermatitis* 2014; **71**: 35–40.
- 3 Uter W, Johansen J D, Börje A, Karlberg A-T, Lidén C, Rastogi S, Roberts D, White I R. Categorization of fragrance contact allergens for prioritization of preventive measures: clinical and experimental data and consideration of structure–activity relationships. *Contact Dermatitis* 2013; **69**: 196–230.