



Adding sorbitan sesquioleate to the European baseline series: Necessary, reasonable, or unavoidable?

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Abstract

Positive reactions to fragrance mix I (FM I) are frequent in consecutively patch tested patients suspected of having allergic contact dermatitis. However, the FM I test preparations contain 5% of the emulsifier sorbitan sesquioleate (SSO), and it is well known that SSO can cause contact allergic reactions in its own right. Indeed, the available data show that some patients with contact allergy to SSO react to FM I but are not allergic to fragrances. When SSO is not tested, this situation may go unnoticed, a wrong diagnosis of fragrance allergy may be given to the patient, and unjustified advice to avoid fragrances and fragranced products will be given in such cases. To avoid such sub-optimal patient care, we postulate that testing with SSO in all patch tested individuals is mandatory. As it is well known that only a minority of FM I-reactive patients will undergo a breakdown test with the ingredients and SSO, testing with SSO in all patients can only be achieved by adding it to the European baseline series. Not testing with SSO may also result in misinterpretation of patch test reactions to *Myroxylon pereirae* resin and 2-hydroxyethyl methacrylate in the baseline series, as both (may) contain SSO, and, for the same reason, of reactions to several other hapten test materials.

KEYWORDS

contact allergy, European baseline series, fragrance mix, *Myroxylon pereirae* resin, patch test interpretation, perfume allergy, sorbitan sesquioleate

1 | INTRODUCTION

Positive reactions to fragrance mix I (FM I) and *Myroxylon pereirae* resin (MP) are frequent in consecutively patch tested patients suspected of having allergic contact dermatitis. However, the FM I test preparations from both Chemotechnique Diagnostics (Vellinge, Sweden), SmartPractice Europe (Barsbüttel, Germany) and SmartPractice Canada (Calgary, Canada) contain 5% of the emulsifier sorbitan sesquioleate (SSO) in order to ensure a stable, homogeneous distribution of the chemicals. It is well known that SSO can cause contact allergic reactions

in its own right, and therefore, in SSO-allergic individuals, a positive patch test reaction to FM I may lead to an incorrect diagnosis of fragrance allergy, and unjustified, and unnecessary, advice to the patient to stop using fragrances and fragranced products.

We postulate that this problem can, at least partly, be overcome by testing with SSO as part of the European baseline series. This suggestion is not new. Indeed, in 1995, the members of the European Environmental and Contact Dermatitis Research Group (EECDRG) firmly stated that “this emulsifier should be added to the European standard series. Otherwise, a positive reaction to fragrance mix cannot adequately be interpreted.”¹ In 2001, Orton and Shaw recommended “that all patients tested with the fragrance mix should have concomitant

[Correction added on 3 July 2019, after first online publication: The corresponding author's surname was previously wrong and has been corrected in this version.]

testing with SSO", because "it is clear that patients may be falsely attributed as having an allergic reaction to fragrance mix."² In 2015, the Information Network of Departments of Dermatology (IVDK) concluded: "Our results indicate that reactivity to SSO markedly affects the outcome of patch testing with FM I and its single constituents. SSO must be an obligatory part of the full FM I breakdown test, and should ideally be included in the baseline series."³ Finally, in 2016, Bennike and Johansen in Denmark, despite finding a low prevalence of 0.2% positive reactions to SSO in a 5-year period, commented that "in order to correctly diagnose the individual patient, concomitant patch testing with FM I and SSO should be performed, and baseline testing with SSO will remain part of the standard procedure at our department."⁴

However, in spite of the clear conclusions and recommendations of all of these authors, SSO was not mentioned in the 2019 article of the European Society of Contact Dermatitis (ESCD) with recommendations on changes in the European baseline series.⁵ We have learned that the topic was discussed briefly in the working party recommending the changes on behalf of the ESCD,⁵ but it was felt that contact allergy to SSO was too infrequent to consider it for inclusion (Uter W, email communication, February 2019). With this contribution, we intend to stimulate discussion on this topic and show that inclusion may be necessary, at least reasonable, and possibly unavoidable.

2 | FREQUENCY OF CONTACT ALLERGY TO SSO IN ROUTINE TESTING

There are few recent data on routine testing with SSO in European countries. In Denmark, in the period 2010 to 2014, 4637 patients were tested at one centre with SSO 20% pet., and there were nine (0.2%) positive reactions.⁴ The German Contact Dermatitis Research Group (DKG) included SSO 20% pet. in the baseline series in September 2015, and there were 0.8% positive reactions in 2016, 0.9% in 2017, and 0.6% in 2018; the average for this 3-year period was 0.8% (203/25752)⁶ (Geier J, unpublished data, May 2019). In Belgium, in the period January 1, 2002 to December 31, 2011, 77 of 5284 routinely tested patients had positive reactions to SSO 20% pet., that is, 1.5% (Gilissen L, Goossens A, unpublished data, April 2019). Before that period, in the same country, two studies from different centres had reported 2.9%⁷ and 5.2%⁸ positive reactions to SSO in routine testing in the second half of the 1990s. In 1995, an EECDRG study reported a 0.7% prevalence of positive reactions to SSO.¹ In older European studies, prevalences ranged from 0.2% to 0.7%.⁹ In The Netherlands, 9 of 339 children (2.7%) routinely tested with SSO 20% had positive patch test reactions to the emulsifier; they had been selected on the basis of their age (0-17 years) only.¹⁰

In the United States, in two studies from the same centre performed in the periods 2006 to 2007¹¹ and 2008 to 2010,¹² high prevalences of 10.7% positive reactions in a very small series of 112 consecutive patients¹¹ and 3.9%¹² positive reactions were observed, respectively. The frequency of 10.7% positive reactions seems excessively high, although all patients were reported as using products containing "sorbitan derivatives or sorbitol" (mostly in topical corticosteroid or antifungal

preparations), and follow-up indicated improvement in nearly all individuals after avoidance of suspected products.¹¹ In China, in the year 2014, 481 healthy student volunteers were patch tested with SSO 20% pet., and 2.3% had positive reactions (2.7% in men; 1.5% in women).¹³

From these data, we conclude that there are insufficient data in European countries to decide whether inclusion of SSO in the European baseline series is justified, based on the primary criterion of a frequency of sensitization exceeding 0.5% to 1%.¹⁴ However, the 1.5% positive reactions to SSO in Belgium would warrant its inclusion (it has indeed been included there in 2018) and, if "exceeding 0.5% to 1%" is not interpreted as ">1%", current data from Germany (0.6%-0.9%) would also suggest inclusion in Germany. Indeed, the DKG added SSO to its baseline series in 2015. For comparison, several haptens that have been present in the baseline series for decades show comparable frequencies of sensitization, namely, mercapto mix, sesquiterpene lactone mix, *p*-tert-butylphenolformaldehyde resin, *N*-isopropyl-*N'*-phenyl-*p*-phenylenediamine, paraben mix, or even lower prevalences, such as primin, clioquinol, and benzocaine.¹⁵ Data from other countries, such as the United States^{11,12} and China,¹³ suggest that contact allergy to SSO—at least in those countries—is not infrequent. We suggest that the European Surveillance System on Contact Allergies (ESSCA) considers starting a study into the prevalence of SSO sensitization in the participating European countries.

3 | RELATIONSHIP BETWEEN CONTACT ALLERGY TO SSO AND CONTACT ALLERGY TO FM I

In the Danish study mentioned above,⁴ sensitization to SSO was identified in nine (0.2%) patients; the proportion of FM I-positive patients with concomitant positive reactions to SSO was 1.4%.⁴ Eight of the nine SSO-positive individuals were also tested with FM I; six (75%) had positive reactions (+/++) to FM I, and the other two (25%) had doubtful reactions (?+) to FM I.

In recent IVDK data covering the period 2016 to 2018, among 1669 FM I-positive patients, 92 (5.5%) also reacted to SSO. Among patients with negative, doubtful or irritant reactions to FM I, the percentage of SSO-positive patients was only 0.5%. Conversely, in the group of 206 SSO-positive individuals, 92 (45%) also reacted to FM I, whereas, among patients without positive reactions to SSO, only 6.2% had positive reactions to FM I (Geier J, unpublished data, May 2019). The difference was statistically significant, with an odds ratio (OR) of 12.2.

In Belgium, in the period January 1, 2002 to December 31, 2011, among 529 FM I-positive patients, 47 (8.9%) also reacted to SSO. In the entire group (FM I-positive patients and FM I-negative patients), the percentage of SSO-positive patients was 1.5%. Conversely, in the group of 77 SSO-positive patients, co-reactivity to FM I was seen in 47 patients, that is, 61%, whereas, in the total group of patch tested patients, only 9.9% reacted to FM I (Gilissen L, Goossens A, unpublished data, April 2019). The difference was statistically significant, with an OR of 15.4.

In a study from the United States, performed in the period 2008 to 2010, 23 patients had positive reactions to SSO 20% pet.¹² Of this

group, apart from one patient reacting to sorbitan oleate, 12 (50%) also reacted to MP (containing 5% SSO) and 11 (46%) to FM I.¹² In a previous study from the same clinic, performed in 2006 to 2007, the data of 12 patients reacting to SSO and one patient reacting to sorbitan oleate were analysed. Eight of 13 (62%) also reacted to FM I, and 7 of 13 (54%) also reacted to MP.¹¹ In the United Kingdom, in the period 1982 to 2000, Orton and Shaw, in their hospital, investigated 14 patients with positive patch test reactions to SSO 20% pet. (total number tested and mode of selection not mentioned), and all of them co-reacted to FM I.²

These data may be summarized as follows. In the studies from Denmark, the IVDK and Belgium, 1.5%, 5.5% and 8.9% of FM I-positive patients co-reacted to SSO, whereas the percentages were 0.2%, 0.5% and 1.5% in the entire patch tested population or in SSO-negative individuals. Conversely, of SSO-positive patients, 45% to 100% co-reacted to FM I, whereas the percentages of reactivity to FM I in consecutively patch tested patients or in SSO-negative individuals in the Danish, Belgian and IVDK studies ranged from 6.2% to 9.9%. Generally, the percentage of reactivity to FM I in SSO-positive patients was six to eight times higher than in SSO-negative individuals. From these data, we conclude that contact allergy to SSO markedly affects (ie, increases) reactivity to FM I and that the 5% SSO present in FM I may, in a number of cases, be responsible for the positive patch test reactions to FM I.

4 | RESULTS OF FM I BREAKDOWN TESTING IN PATIENTS WITH AND WITHOUT ALLERGY TO SSO

In the Danish study,⁴ three of the six patients with concomitant positive reactions to SSO and FM I had no positive reactions to any of the eight single constituents of FM I, containing 1% SSO. The remaining three patients had three or more positive reactions to the single constituents of the mix.⁴ The eight SSO-positive patients with either concomitant positive or doubtful reactions to FM I were further evaluated. Six (75%) of eight patients did not react to a perfume mix 6% pet. (containing no SSO and the same ingredients as FM I, except for amyl cinnamal and *Evernia prunastri* extract), and two patients with ++ reactions to FM I had doubtful reactions to the perfume mix not containing SSO.⁴

In a retrospective study from the IVDK, in the period 1998 to 2013, 2952 FM I-positive patients had full breakdown tests in a second patch test round with its eight ingredients (all 1% pet. and containing 1% SSO) and SSO 20% pet.⁴ Among these, 154 (5.2%) had positive reactions to SSO 20% pet. Positive reactions to one or more of the single fragrances contained in the mix were significantly more common (83% vs 57%) in SSO-positive patients, who also had more multiple reactions than FM I-positive patients with negative SSO results (62% vs 21% patients with reactions to two or more fragrances).⁴ The authors concluded that contact allergy to SSO markedly affects reactivity to FM I and its ingredients.⁴

In Belgium, in the period January 1, 2002 to December 31, 2011, 529 FM I-positive patients were patch tested with its eight ingredients, in

concentrations of 2% and 1% pet. (in the case of cinnamal). Of these ingredients, only *E. prunastri* extract (oakmoss absolute) contained SSO (5%). Of 482 patients reacting to FM I but not to SSO, 207 (43%) had positive reactions to one or more of the seven ingredients not containing SSO, indicating fragrance sensitization. However, of the 47 patients who reacted to FM I and SSO, only seven (15%) had positive reactions to one of the seven ingredients, indicating that the reaction to FM I in the other 85% was attributable to SSO allergy (or *E. prunastri* sensitization). The difference (43% vs 15%) was statistically significant (χ^2 test, $P = 0.0002$; OR = 4.3).

In a study from the United States, performed in 2006 to 2007, among eight patients reacting to both FM I and SSO, six patients also reacted to at least one of the eight individual components of the mix emulsified with 1% SSO. The eight FM I-positive individuals were also tested with several fragrances and essential oils not containing SSO, but none showed definitive positive reactions to other fragrance chemicals that were not part of FM I.¹¹ Nevertheless, the authors stated that their results suggested that at least six of eight FM I-positive patients had a true fragrance allergy and were not just reacting to the SSO in FM I.¹¹ This conclusion was largely based on co-reactivity to MP and the assumption that MP did not contain SSO.¹¹ However, as MP did contain 5% SSO (email information from Chemotechnique Diagnostics, March 2019), this conclusion was incorrect.

In the United Kingdom, in the period 1982 to 2000, Orton and Shaw tested 14 SSO-positive individuals (of whom all co-reacted to the FM I) with the eight constituents of FM I obtained from Chemotechnique Diagnostics, tested at 2% pet. and not containing SSO. Twelve (86%) had negative results with all constituents, indicating reactivity to SSO in the FM I. The remaining two individuals (14%) had positive reactions, both to *E. prunastri* (which at that time did not yet contain SSO), and one of them also showed positive reactions to isoeugenol and geraniol (2% pet.).²

The results of these studies can be summarized as follows. The breakdown testing data from Denmark, the IVDK and the United States are difficult to interpret, because the constituents all contained 1% SSO themselves. Nevertheless, positive reactions to one or more of the single fragrances contained in the mix and multiple positive reactions were significantly more common in SSO-positive patients, indicating that the 1% SSO in the ingredients is probably the allergenic chemical in a number of SSO-positive individuals.⁴ More interesting are the data from Belgium and the United Kingdom, as patients were tested with ingredients not containing SSO. In the Belgian study, 43% of SSO-negative individuals showed positive reactions to at least one of seven ingredients vs 15% of SSO-positive patients, the latter indicating that far fewer SSO-positive and FM I-positive patients are fragrance-allergic. Unfortunately, data from patients reacting to *E. prunastri* had to be excluded, as it contains 5% SSO (Gilissen L, Goossens A, unpublished data, April 2019). The most convincing evidence for the role of SSO allergy in positive reactions to FM I is from the UK study²: 12 of 14 (86%) SSO-positive individuals had negative results with all eight ingredients not containing SSO, indicating that the large majority of the reactions to FM I in SSO-positive patients were, in fact, caused by SSO and did not indicate contact allergy to one or more of its fragrance ingredients.

Chemotechnique Diagnostics		SmartPractice Europe/ SmartPractice Canada	
Hapten	Concentration of SSO (%)	Hapten	Concentration of SSO (%)
Decyl glucoside 5% pet.	2	Cinnamal 1% pet.	1
DMDM hydantoin 1% pet.	1	Fragrance mix 8% pet. ^a	5
Ethylene urea, melamine formaldehyde 5% pet.	5	Fragrance mix (B) 8% pet.	1
Formaldehyde 1% pet.	1	Hydroxycitronellal 1% pet.	1
Fragrance mix I 8% pet. ^a	5	Isoeugenol 1% pet.	1
Glutaral 0.5% and 0.2% pet.	5	<i>Evernia</i> <i>prunastri</i> extract 1% pet.	5
Hydroxyethyl methacrylate 2% pet. ^a	1	<i>Evernia</i> <i>furfuracea</i> extract 1% pet.	5
MCI/MI 0.01% and 0.02% pet.	1	-	-
Melamine formaldehyde 7% pet.	1	-	-
MI 0.2% pet.	1	-	-
<i>Myroxylon pereirae</i> resin 25% pet. ^a	5	-	-
<i>Evernia prunastri</i> extract 2% pet.	5	-	-
Perfume mix 6% pet.	1	-	-
Toluene-2,5-diamine 1% pet.	1	-	-

Abbreviations: MCI, methylchloroisothiazolinone; MI, methylisothiazolinone.

^aPresent in the European baseline series.

TABLE 1 Patch test materials containing sorbitan sesquioleate (SSO) (2019)

5 | PATCH TEST PREPARATIONS CONTAINING SSO

Information supplied by Chemotechnique Diagnostics, SmartPractice Europe and SmartPractice Canada shows that several patch test materials from both companies contain 1% to 5% SSO (Table 1). Three haptens in the European baseline series, that is, FM I (both suppliers), *M. pereirae* resin (balsam of Peru) (Chemotechnique Diagnostics), and 2-hydroxyethyl methacrylate (HEMA) (Chemotechnique Diagnostics), contain SSO. Thus, without testing with SSO separately, positive reactions to not only FM I, but also to MP and HEMA, may be interpreted incorrectly, and patients may be given the wrong advice.

6 | ETHICAL CONSIDERATIONS

As physicians, it is our obligation to provide optimal patient care. This includes *primum non nocere*, the primary importance of doing no harm to the patient. One may well argue that, by not testing with SSO, we run the risk of doing harm to patients when we tell them that they are fragrance-allergic (mostly resulting in the advice to avoid fragrances and fragranced products), when, in fact, this may not be the case (and we are, or at least could be, aware of this). Avoiding fragrances is difficult, may lead to financial cost (more expensive non-fragranced alternatives), and not using perfumes, deodorants and other fragranced

products may decrease quality of life and could have a negative impact on social life when patients avoid circumstances in which they can have contact with fragrances, for example, at social gatherings. In other words, by not testing with SSO, we may actually harm our patients, which could easily be avoided.

Some may argue that testing with SSO in the baseline series is unnecessary, as a positive reaction to FM I should always be followed by breakdown testing with the eight constituents and SSO. There is no doubt that this is very useful, and should preferably be done. However, it is common experience that this is not always done. In the departments of dermatology joining the IVDK, that is, centres particularly interested in contact allergy, for example, a full breakdown test is achieved in only 25% FM I-positive patients. In some cases, the dermatologist may not perform breakdown testing, but also patients may refuse a second patch test round for reasons of cost, lack of time or distance to the clinic. With inclusion of SSO in the baseline series, the consequences of this shortcoming could be minimized. Thus, in our view, a decision of the ESCD to include SSO in the baseline series will lead to improved patient care.

7 | CONCLUSIONS

1. Several researchers have, in the recent or more distant past, argued that SSO should be included in the baseline series; so far, this has not been implemented by the ESCD.

2. In some countries in Europe, such as Belgium and Germany, the prevalence of sensitization to SSO in routine testing is high enough to warrant its inclusion in the European baseline series, based on the criterion of a "frequency of sensitization exceeding 0.5%-1%".¹⁴
3. It has been well demonstrated that patients with contact allergy to SSO may react to FM I but are not allergic to fragrances.
4. When SSO is not tested, this situation may go unnoticed, a wrong diagnosis of fragrance allergy may result, and an unjustified advice to avoid fragrances and fragranced products will often be issued, which is not only suboptimal patient care, but may, in fact harm, the patient; thus, testing with SSO in all patients is mandatory.
5. As it is well known that only a minority of FM I-positive patients will undergo a breakdown test with the ingredients and SSO, testing with SSO in all patients can be achieved only by adding it to the European baseline series.
6. Not testing with SSO may also result in misinterpretation of patch test reactions to MP and HEMA in the baseline series, as well as of those to several other haptens (Table 1).

8 | RECOMMENDATIONS

1. We suggest that the ESSCA considers starting a study into the prevalence of SSO sensitization in the participating European countries.
2. We encourage the ESCD to (re-)open the discussion on adding SSO to the European baseline series
3. We suggest that the manufacturers of commercial patch test materials investigate the possibilities of replacing SSO with a less allergenic or, preferably, non-allergenic emulsifier, or of developing production methods that do not require the use of emulsifiers.
4. We particularly request manufacturers of commercial patch test materials to make the eight ingredients of FM I SSO-free as soon as possible. Currently, even with breakdown testing, correct and definitive interpretation of the patch test results in SSO-positive individuals is impossible, as one ingredient (*E. prunastri* extract) of one manufacturer contains 5% SSO, and four ingredients of the other provider contain 1% to 5% SSO (Table 1).

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