Extended Fragrance Ingredients Surveillance Study (EFISS) - Surveillance Study to Monitor the Frequency of Contact Allergy to a Defined Group of Fragrance Ingredients with a View to Providing Reliable Information onTrends

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Primary Objective:Identify trends in the incidence of skin contact allergy with particular reference to fragrance materials that have not hitherto beentested on a systematic basis.Secondary Objective(s):A subsidiary objective is to gather data on...

Ethical review	Approved WMO
Status	Pending
Health condition type	Administration site reactions
Study type	Observational invasive

Summary

ID

NL-OMON56979

Source
ToetsingOnline

Brief title
Extended Fragrance Ingredients Surveillance Study (EFISS)

Condition

- Administration site reactions
- Allergic conditions
- Epidermal and dermal conditions

Synonym
allergie contact dermatitis, contact eczema

Research involving
Human

Sponsors and support

Primary sponsor: IFRA (International Fragrance Association)
Source(s) of monetary or material Support: IFRA Perfume industry

Intervention

Keyword: allergie contact dermatitis, Epicutanous patch-testing, fragrance ingredients, surveillance study

Outcome measures

Primary outcome

The results of the epicutaneous patch test which are assessed according to

international guidelines, International Contact

Dermatitis Research Group (ICDRG). The reactions are qualified as -, positive

(+), strongly positive (++), extremely positive

(+++), negative (-), doubtful (?), irritation (ir)

Secondary outcome

Data on intra- and inter-clinical variations with the aim of reducing them.

Study description

Background summary

Background of the study:
Fragrance contact allergy (CA) is frequently associated with allergic contact dermatitis, which is a well-known health problem. For
example, it has been estimated that 1-4% of Danish adults drawn from the general population may have CA to fragrance
substances, while the frequency of CA among European and American dermatitis patients has been shown to be between about
6.5% and 10.4%. In general, CA or dermal sensitization to a given substance will not be observed until an individual has been

exposed to a concentration of a given substance that exceeds the induction threshold, thus sensitizing the individual.
The prevention of contact allergy and subsequent potential allergic contact dermatitis has been recognized to be critical to industry governance by The International Fragrance Association (IFRA) and the Research Institute for Fragrance Materials, Inc. (RIFM).
These groups have worked together to develop a quantitative risk assessment (QRA) and later refined via the QRA 1 (2008) into QRA2 (2017). The key steps of the QRA comprise: 1) determination of the *no expected sensitization induction lever (NESIL); 2) application of sensitization assessment factors (SAF); and 3) consumer exposure level (CEL) calculated from product use data. This process allows one to set an acceptable exposure level (AEL), a level at which sensitization is not likely to take place, which can then be compared to the CEL. Provided that the AEL is less than the CEL, allergic sensitization leading to subsequent CA should not occur for the vast majority of the population.
The QRA is achieving recognition and credibility among regulators and critical stakeholders, for example the SCCS (Scientific Committee for Consumer Safety) and is well regarded by the Joint Research Centre (JRC). However, it has been criticised by some as not yet demonstrating reduced incidence of skin CA in populations, i.e., no demonstration in real people. Similarly, the credibility of the QRA relative to regulators and regulatory scientists requires that industry commit to efforts to demonstrate its effectiveness over time.
As part of the overall effort to address CA issue, the IDEA project (International Dialogue for the Evaluation of Allergens, www.ideaproject.info) was set up. It is designed to provide a broadly agreed and transparent framework for assessing fragrance sensitizers globally. It presents an opportunity to build partnerships between the international fragrance industry and its stakeholders in order to improve the risk assessment of those fragrance ingredients, identified as relevant skin allergens with a view to achieving better consumer protection. As part of this stakeholder partnership initiative, there is a need to make the post-market monitoring more relevant and up-to-date, to provide greater insights into potential trends in skin contact allergy, which specifically addresses induction of dermal sensitization. In order to address these questions, a number of potential options for studies were developed and discussed extensively in a series of workshops (April 6, 2016, February 15, 2017 and December 7, 2017) with representatives of industry, IFRA and RIFM plus dermatologists, epidemiologists, biostatisticians from academia and observers from the SCCS.
The following three major possibilities for a study, as summarised below, were identified and examined at length in these workshops.
The first option was an intervention study using a fragrance ingredient that is

a known dermal sensitizer that has never been marketed and where there are no intentions of marketing the material. The study would involve calculating the NESIL, using QRA 2 and testing it via participant exposure to selected products containing the target material, at the calculated levels, over a period of 6 months. This would be followed by a patch test. A control group using the same products without the target material would also be run and similarly tested at the end of the 6-month period. This proposal was considered and rejected on ethical grounds. Also, it only served to demonstrate the QRA 2 in the context of a single material.

The second option was a study In which a naïve cohort was followed versus a baseline over a period of at least 10 years, with testing every 3 years, supported by a well-designed questionnaire, e.g., LEHC (Life Events History Calendar), to determine exposure. This study presented problems in identifying a genuinely naïve population and how the baseline would be established. A further problem was the cohort size. With up to 30% loss to follow-up predicted due to the length between each round of testing, a starting cohort of in excess of 12,000 subjects was estimated to be necessary. Finally, it was concluded that despite the study population size and substantial costs, there was little certainty that the study would return meaningful results as to the effectiveness or not of the QRA.

Finally, in conjunction with the various stakeholders and experts, it was decided that a surveillance study, testing for additional fragrance materials in addition to the existing Standard sets and individual substances, run over an extended period, provided the best and most workable approach. The limitations of such a study in terms of producing a definite conclusion on QRA effectiveness, in the short or even medium term, were recognized and discussed at length.

A key issue for successful monitoring in trends has been that testing has relied on a set of patch test substances, i.e., the screening Fragrance Mix 1 and Fragrance Mix 2 (FM 1 and FM 2), their component materials and the so-called non-fragrance mix materials.

FM 1 and FM 2 that have remained unchanged for over 35 and 15 years respectively. with no additional materials being added to these or the other materials in this "Standard set*.

More recently, there have been a number of developments including the evolution of the QRA as described above, two relevant (2012 & 2017) opinions of the SCCS (Scientific Committee on Consumer Safety) and the Regulation (2023/1545) on labelling of allergens. Further, there is an ongoing process of updating of IFRA Standards with regard to QRA2.

In addition, there has been the ongoing challenge of intra- and inter-clinic variations in patch test results (See Annex I for a review of the literature in relation to this issue). Additionally, there are number of materials of varying potency, which hitherto have not been

tested on a systematic basis and which are in use in product types with high consumer exposure.
Consequently, it is opportune to design an industry-sponsored surveillance study incorporating both additional and Standard
materials that has the possibility of identifying trends in the incidence of skin contact allergy. It is also the case that, as a first step, by
adding seven (7) selected additional materials to the existing Standard series mixes and individual materials (Annex II), which will be
provided for free to the participating clinics (Annex lil), new insights may be gained and the likelihood of identifying trends increased.
It should be noted that these materials are all currently in use with moderate to high levels of use (approximately 8,000-280,000
kg/year based on 2015 data - See Annex II) in personal care products but not currently tested in a systematic manner. A further
refinement is that by conducting such a study with a comprehensive protocol and quality coordination, there is potential to reduce
intra- and inter-clinic variations. Hence important and relevant Information on trends in patch test reactions to fragrance ingredients
and markers can be obtained.
In preparation for this main EFISS study, a pilot was conducted in 2022 with the following objectives:
• Carry out range-finding and determination of patch testing concentrations for use in the main EFISS study;
• Gain familiarisation with the ad

Study objective

Primary Objective:
Identify trends in the incidence of skin contact allergy with particular reference to fragrance materials that have not hitherto been
tested on a systematic basis.
Secondary Objective(s):
A subsidiary objective is to gather data on intra- and inter-clinic variations with a view reducing these.

Study design

Observational, non-invasive study with the application of additional epicutaneous patch test series on the back. Without the use of
medicinal product, non-blinded and non- randomized.
Duration:
The duration for an individual participant is one week during which there will be three visits of variable time durations.
Visit 1, day 0:
A short interview will be held to reconfirm basic Information about the subject and to check the inclusion and exclusion criteria.

Informed consent will be signed. This visit also includes the preparation of material, the application of the patch test on the back.
This visit will take about 15 minutes. The actual patch test needs to be in situ for 48 hours.
Visit 2, day 3, 72 hours after application:
The visit will take about 10 minutes and includes reading and photographing of the (possible) skin reactions at the sites of
application.
Visit 3, day 7,168 hours after application:
Subjects might benefit directly from participation in this study. If a positive reaction to one of the seven additional tested substances is observed, subject will know he/she is allergic to this allergen which is included in cosmetic products in daily life
This visit includes the final reading and photographing of the (possible) skin reaction at the sites of applications and will take about
15 minutes. It may be longer if the treating physician sees a positive result to any of the materials (Standard and test materials) and this precipitates a discussion with the patient on the meaning of the results..

Study burden and risks

It is important to note that included subjects are already scheduled for routine diagnostic patch test investigation because of
dermatitis. Therefore, subjects do not have to Schedule additional visits for study participation. For the routine diagnostic patch test
investigation three visits will be planned. At During the first visit, after inclusion, subjects will be asked to answer questions
concerning medical history and concomitant medication.
Subjects are at risk for developing an allergic skin reaction on the test sites. This skin reaction is self-limiting in nature, but can be
treated with a local corticosteroid cream if the reaction is inconvenient.
Subjects might benefit directly from participation in this study. If a positive reaction to one of the seven additional tested substances is observed, subject will know he/she is allergic to this allergen which is included in cosmetic products in daily life

Contacts

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Scientific
IFRA (International Fragrance Association)

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CH

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

Dermatitis patents, 18 years or older who are eligible for a diagnostic patch test

Exclusion criteria

Apart from excluding children and adolescence below 18 years of age at 4 weeks before testing, no specific exclusion criteria other than those covered by the ESCD guidelines (European Society of Contact Dermatitis guideline for diagnostic patch testing - recommendations on best practice, 2015) are to be considered.

Study design

Design

Study type: Observational invasive
Masking: Open (masking not used)

Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-10-2024
Enrollment:	900
Type:	Anticipated

Medical products/devices used

Registration:	No

Ethics review

Approved WMO

Date:	26-08-2024
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL87080.042.24