IDEA
International Dialogue for the Evaluation of Allergens

Rapporteur's Progress Report on the 2nd IDEA Working Group meeting on the

Feasibility of a study to assess the effectiveness of QRA

February 15th, 2017 from 9:00 to 16:00

Martin's Klooster Hotel
Onze Lieve Vrouwstraat 18, 3000 Leuven
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1. Opening:

This comprised an overview of the IDEA history, rationale and projects during the last 4 years. We have progressed to a revised quantitative risk assessment (QRA2) which is now entering the process of final consideration by the European Commission. To this work we have added considerations of pre and pro haptens and an addendum dealing with the topic is being annexed to the QRA2 dossier. However, this remains "theory", such that the need to monitor the clinical situation to try to confirm that QRA2 delivers. That formed the basis of the discussions during the one day workshop.

A tour de table of the participants (listed in Annex I of this report) was organized.

2. Surveillance Study – status update and plans:

The workshop was updated on what has happened since April 2016. Central to this was the protocol already prepared by a sub-group (White, Uter and Johansen). However, the April WG did voice concerns, including over the interpretation of the clinical data. To help address the concerns, meetings have taken place in Malmo and in Erlangen (x2). It is clear that there is both interest in doing the clinical surveillance via routine patch testing, but also a degree of reluctance to commit to it.

One critical part of discussion is what materials to test in addition to FMI and FMII and/or the SCCS 26 fragrance materials. What is really needed are one or more "new" allergens, i.e. new to the market fragrances which are not already used or cross reactive with other existing allergens.

Several key criteria for material selection were suggested – see below. In the subsequent discussion, it was re-emphasized that "new" could include fragrance allergens from the 2012 SCCS opinion that are not currently being patch tested. It was likely to be of most help if the substances were at least moderately potent sensitisers.

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Criteria to be considered for new materials, to increase the chance of drawing conclusions on the effectiveness of QRA:

- QRA2 based company policy or IFRA Standard available since introduction of the molecule to the market
- No structural similarity to materials in use
- No presence in nature
- No use as or presence in flavours
- Low likelihood of material being used outside of the fragrance industry applications (and therefore outside the control of the fragrance industry's QRA)
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Information relevant to have:

- Robust NESIL (preferably a moderate to strong sensitiser, and not a weak sensitizer), based on LLNA, HRIPT, etc.
- Exposure info
- Volume of Use

However, these criteria and a number of other restrictions/additions have made some clinics reluctant to participate. Dermatologist opinion at the present workshop demonstrated that there was a willingness to participate and offered the perspective that quality of patch test data was as important as quantity.

Finally, it was noted that any surveillance represents a long term study – we need to think in terms of a decade.

What would we expect to see in routine clinical testing (with "known" allergens) assuming QRA2 works as expected? You might see a change, but it would be hard to understand the drivers of change. This led to wider discussion of these issues. For example, even a ban on a substance does not lead to the elimination of contact allergy entirely – it can take many years to "wash out" the effects in a sensitised population.

Surveillance work should focus on tracking patch test results to individual substances (i.e. not to fragrance mixes). Nevertheless, industry will have to face dermatologist commentary on changing rates to FMI and FMII. The dermatologists within the WG generally agreed that it was always going to be challenging to identify particular fragranced products responsible for the induction of contact allergy. Prompted by these concerns, it was suggested that it might be more helpful in terms of surveillance to repeat an EDEN type of study as this would eliminate some of the biases associated with patient studies.

All agreed that, whatever the challenges, engaging with the surveillance data from FMI, FMII and the 26 labelled fragrance allergens was important both for the data generated AND the goodwill that should be generated.

With regard to monitoring "new" materials, this was considered meaningful from several points of view. Whether new to the market, or as a new patch test material to the dermatologist, a surveillance system will provide valuable information, even if it does not allow drawing conclusions on the effectiveness of the QRA. If the monitoring can further include materials new to the market, these by definition are also new to the dermatologist.

A break out group addressed the challenge of new materials.

3. Complementary work - status update and plans

Separation was made between maintaining "a license to operate" versus demonstrating that QRA2 functions as expected. In addressing this, various questions were raised, including who are "the dermatologists", i.e. defining the stakeholders is important. Literature review identified several points: women are more likely to have fragrance contact allergy, therefore they should not be under-represented in any study; age is not relevant. The list of key conclusions were these:

Based upon a detailed review of some 40 papers examining the role of sex, age, prevalence by population (sensitive and general), prevalence variations with time and reproducibility of testing:

- Findings:
  - Incidence of skin CA is higher in women than men, possibly attributable to greater exposure.
  - Incidence of fragrance-related skin CA only declines in very old age but does increase as young population ages.
  - Sensitive populations exhibit approximately 6 times the prevalence of that of the general population.
  - The evidence as to prevalence changes over time is ambiguous
  - Lack of inter-and intra-clinic reproducibility is a major challenge to evaluating data.

Of course, some aspects of these conclusions were subject to discussion; it was noted too that the underlying data shows great variability, such that none of the conclusions were intended to be adopted as general rules.

Also presented were additional considerations relating to any study design:

- Ethics committee approvals
- On market issue
  - Roll-out time from substance assessment to bathroom shelves
    - e.g., for elements of the QRA1 implementation started in 2008, the changes in the marketplace might only have taken place recently
- Costs
- Time to results
- Addressing "Absence of evidence not evidence of absence"

Controlled study (Prospective study):
A detailed set of proposals for the construction of an additional controlled study was then presented, in which a newly sensitising substance is introduced. Dimethyl citraconate fitted a lot of the selection criteria mentioned earlier. Debate centred on whether the patient population is actually more likely to be sensitised to such a substance and thus on the necessary size of the test population. The assumptions necessary led to test group sizes of at least 3000. It was agreed that a tabulation of groups sizes, stats etc. should be incorporated into the meeting notes (ACTION).

Rather than the weak allergen dimethyl citraconate, it was suggested that it would be better to use a strong sensitiser such as diphencyclopropenone (DPCP) as a marker allergen and replace the 'control group' by knowledge of the ability of the material to sensitize people. There was both concern and debate generally about the ethics of inducing contact allergy in this study, even though doing so would be essential for the study to be meaningful.

Discussion continued with a consideration of the best products which could contain this test allergen, with a recommendation to use deodorant, liquid hand soap and a moisturizer as the exposure vehicles as they are amongst the most commonly used by consumers and are known to be associated with contact allergy.

Practical concerns were raised again about using a weak sensitizer for such a study – size of the group or formulation and stability of products needing to contain very high amounts of the weak sensitizer. The option of using a much stronger marker skin sensitiser like DPCP was noted.

The possibility of a cohort study was suggested, one which would run for 10 years and follow (at least) 3000 young volunteers, mirroring the work published by Buckley et al, 2003. These would be patch tested at 0, 3, 6 and 9 years. Buckley showed a doubling of the incidence rate in the 20-29 group compared to the 10-19 group. This type of change could be tracked and used as a point of comparison with the new population. This study has several advantages, including being non-interventional, but was subjected to some criticism since the robustness/repeatability of the Buckley et al observations was felt to be open to question.

The group was reminded that the focus of any study(ies) must be on demonstrating that QRA2 works, not that the earlier version of QRA does not work! This impacts study design markedly.

A further option offered some points to consider in an enhanced surveillance study. (USE slide 12).

Finally, a hybrid study design was presented.

4. Feedback from the breakout groups:

a) Breakout group on the intervention study:

One break out group focused on matters of size and logistics. The group addressed first DPCP as an alternative to dimethyl citraconate. Concern was expressed regarding the state of toxicology knowledge on this substance; this could easily preclude use in Germany. An alternative proposal suggested running a 6 month study focusing on a single current fragrance, hydroxycitronellal, having a test group using only products with this fragrance. However, there will always be criticism that the study is only 6 months; indeed, it would be criticised if it was 12 or 18 months! In contrast, use of DPCP could be for a shorter period, and it has no issues with pre-exposure etc. It would be necessary to confirm the DPCP NESIL in an HRIPT based on the LLNA EC3 value. Patch testing of the test group at the outset and at the end would be necessary. The DPCP would need to be in the complete range of personal care and household products.

Panel size considerations for a DPCP study might require a pilot investigation. The EC3 value (0.0003% to 0.05%) leads to NESILs in the range 0.1 to 10 µg/cm2. The possibility of synergies was discussed – this is already accommodated in QRA2; it was noted that even where strong positive reactions occurred to MI, they had no evidence that this had triggered the development of sensitivity to other allergens in the products. The diagnostic patch test concentration can likely be found from the Danish clinical study on induction and elicitation.

The group asked about potential exclusion criteria, e.g. drugs which may interfere with the development of contact allergy. It was noted that the likely adverse effect was ACD, readily treated by cessation of exposure

and topical steroids. A pilot study based on old risk assessment would be needed to determine what proportion of participants become sensitised and in what timeframe.

b) Breakout group on the surveillance study:

The second break out group dealt with aspects of the surveillance study – especially material selection and criteria for clinics. The agreed aims of the study were:

Inform overall risk assessment and management process
Good independant and reliable monitoring of the patch test system
Early alert system

These came with the caution that one should always interpret the result alongside indepth insight on product use.

The materials were as noted earlier, FMI, FMII and the 26 labelled fragrance allergens. However, additional points were raised. Considering practicalities of patch test routine, add a well defined number (5 – 6) of new materials. The criteria to apply to derive this subset should be:

Pooling from SCCS 2012 list and materials for consideration of getting new sensitization driven standards in the 49th Amendment
Focus on synthetics; best if these are not present in natural materials
Focus on the more potent sensitizers
Ensure use accross categories, with confirmed use in cosmetic products and focus on high exposure, both with regard to volume (EU) and to use in product types leading to high consumer exposure
Understanding other exposures is required and most relevant for data interpretation but not a criterion for excluding the material

It was proposed that the IDEA Management Team manage the process of critical data collection and material selection for approval by the WG and endorsed by the SG. The clinics should cover a good geographical scope, be balanced within Europe. They should have experience with routinely testing the 14 - 26 allergens on a minimum of 300 patients per year. Importantly, they need to agree to follow the protocol, including quality criteria, management and allow quality control. There also needs to be central data management with electronic data catchment suitable for a study that runs continuously for several years.

Annex 1: List of participants

Academia

Donald Belsito	Columbia University
Magnus Bruze	Lunds University
Thomas Diepgen	Ruprecht-Karls University
David Gawkrodger	University of Sheffield
Karl-Heinz Jöckel	Essen University
Hans Merk	Aachen University
Axel Schnuch	IVDK/University of Göttingen

SCCS Observer:

Pieter-Jan Coenraads	University Medical Centre Groningen

Industry:

Anne Marie Api	RIFM
David Basketter	DABMEB Consultancy
Graham Ellis	Givaudan
Nicola Gilmour	Unilever
Joe Huggard	Consultant
Petra Kern	P&G
Maya Krasteva	L'Oréal
Boris Müller	Symrise
Cian O'Mahony	Creme Global
Scott Schneider	Firmenich

Other Observers:

Florian Schellauf	Cosmetics Europe

IDEA Management Team:

Hans Bender
Cécile Gonzalez
Matthias Vey

IDEA Supervisory Group:

Rapporteur on behalf of the IDEA Supervisory Group: David Basketter