IDEA
International Dialogue for the Evaluation of Allergens

Final Minutes from the IDEA Working Group meeting on the

Feasibility of a study to assess the effectiveness of QRA

April 6th, 2016

Martin's Klooster Hotel
Onze Lieve Vrouwstraat 18,
3000 Leuven

Participants: Anne Marie Api, David Basketter, Don Belsito, Shawn Blythe, Magnus Bruze, Graham Ellis, Nicky Gilmour, Karl-Heinz Jöckel, Petra Kern, Gerd Kallischnigg, Boris Müller, Benjamin Smith, Wolfgang Uter, Bob Safford, Maya Krasteva, David Rich, Axel Schnuch, Ian White.

Observers: Pieter Jan Coenraads (on behalf of SCCS), Jeanne Duus Johansen

IDEA Management: Cecile Gonzalez, Joe Huggard, Amaia Irizar, Pierre Sivac (introductory note), Matthias Vey

Moderator: Hans Bender

The SCCS Opinion on fragrances in 2012 provided the backdrop to the meeting as it led to the generation of the IDEA project and the associated workshops on key themes. Arriving now at the point where quantitative risk assessment (QRA) has been thoroughly reviewed and updated, its functionality in reducing the clinical problem of fragrance allergy needs to be demonstrated. The aim of the workshop was to discuss how far this could be done by monitoring studies in the clinical population or whether complementing or additional studies would be required. In parallel, the continuing need for dialogue so that we understand the different perspectives of interested parties remains essential, including of the European Commission who have an ongoing and particular interest in progress on this topic.

Previous meetings within the QRA project have discussed the matter of how to assess the effectiveness of what is generally referred to as QRA2. Based on those discussions, it had been requested that a clinical study plan was drafted, including details on allergens to be monitored, patient data to be recorded and the nature of the testing centres likely to be included. This had been done and was presented to the current meeting as a basis for the future work programme. It was pointed out that the proposal tried to address one criticism of monitoring studies in different centres, which is that of missing uniformity. The proposal presented would involve the recruitment of a

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number of centres of excellence that currently undertake extensive diagnostic patch testing. These centres would monitor the frequency of contact allergy to fragrance, probably via rates of reaction in consecutive eczema patients tested with fragrance mixes 1 and 2, 2 grades of Oakmoss, the 26 individual labelled fragrance allergens and other common markers of fragrance allergy such as Balsam of Peru as well as sorbitan sesquioleate. This would be done 3 – 6 month over a period of at least 5 years. Discussion also included whether it was important at the outset to agree "success criteria"; here the meeting did not clearly speak with one voice as a lot of concern was expressed with regard to confounding factors (life cycle of products, historic sensitization, variation in overall exposure) that might make such a goal impossible, such that it was concluded that this discussion should be continued once a fragrance allergy baseline in the first two years of the study had been established and a better understanding of the natural variability in results is available.

Several members present felt that such a work programme should not be the only option. All recognised that the longer term monitoring of contact allergy via diagnostic patch testing in dermatology clinics was an essential component of a work programme. However, the primary purpose of such testing will always remain the treatment of the individual patient. Furthermore, it rarely (at least for fragrances) is able to identify the specific sources of exposure which are likely to be responsible for the induction of contact allergy. This means that relating the evidence generated back to specific risk assessment successes as well as failures is extremely difficult – the approach cannot deliver more than a broad view of trends. Because of this limitation, the meeting began preliminary discussion on what additional work might be proposed which would generate a more focused evaluation of a specific risk assessment. For example, specific groups could be closely monitored before and after being provided with individual products subjected to QRA2. However, all agreed that it was not appropriate at this meeting to complete such a discussion and recommended that the IDEA Supervisory Group consider convening a separate meeting with the delineation of this additional work programme as its sole objective. With this agreed, the meeting then focused on the existing study plan and came to the following conclusions and recommendations:

1. It was recognised that collation of clinical data from routine diagnostic patch testing with a range of fragrance allergens will continue and therefore it was agreed that active involvement with this to enhance the information on trends that is generated thereby is necessary. The current study plan is directed towards this end.

2. It was also recognised that the collated clinic data carries a number of confounding factors which make its interpretation subject to some uncertainty. Nevertheless, past experience with more precise exposure patterns and or target population, e.g. with metal allergens and preservatives with relatively high prevalence rates, shows that such clinic data can provide a good read out demonstrating the impact of interventions.

3. The group agreed that it was important that whatever clinical work was done to evaluate QRA2, the highest ethical standards must be applied. For example, repeated patch testing (>2) was to be avoided.

4. The group also agreed that, at its most basic level, simple surveillance of fragrance contact allergy rates would not suffice adequately to evaluate QRA2. Thus, additional information to stratify individuals and documentation of exposure would really help to provide a more robust analysis. However, the extra activity involved needs to be limited to avoid being burdensome, and therefore impractical.

5. Evaluation of synthetic substances used exclusively by IFRA members would help to limit the uncertainty around other sources of allergy induction. Such materials would be of particular value in both the general monitoring study as well as in other work – to be agreed at a subsequent IDEA meeting (see point 9).

6. Consequently, the group supported the draft proposal for surveillance in a number of European clinical centres of excellence, subject to reassurance concerning the numbers needed and the nature/purpose of the questionnaire.

7. The study would be repeated, probably for 3-6 months per year, perhaps for up to a decade, thereby providing a quality set of data on the frequency of fragrance allergy.

8. The next steps require finalising the study protocol, including all the substances and their patch test concentrations, recruitment of suitable centres of excellence, establishment of training meeting and amendment of the patient questionnaire to incorporate aspects such as aromatherapy and patient hobbies as well as documenting the location of the "first rash" (Action – IRW) to collect as much relevant information about exposure as possible.

9. The group agreed that a complementary controlled cohort study should be designed, with the aim of testing (a) defined fragrance allergen/s at its maximum allowed use level/s in (a) defined product/s whose use could be carefully monitored. Only this type of approach really has the power to assess whether QRA2 is functional and effective.

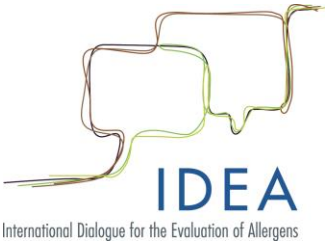
10. Finally, all agreed that the information from studies should be freely available and generated via an entirely open and transparent process.

Further the following key conclusions were worked out jointly by all participants in the meeting:
The WG supports the surveillance system to assess prevalence of contact allergy in eczema patients as recommended by the dermatologists. Key additions to the proposed protocol are documented separately.
The WG points out that the surveillance system alone may not verify whether the QRA is effective due to confounding factors. Complementary work is therefore recommended and will be subject to a separate meeting.

Next steps include:

- Finalizing the protocol and discussing the logistics in undertaking this surveillance system, which is intended to be repeated annually for at least 5 years.
- Having the SG define a group which will agree on the operational aspects of the surveillance system.
- Ensuring that data will be analyzed independently and are accessible to all stakeholders.
- IDEA Management Team calling a meeting to define complementary work focused on evaluating the effectiveness of QRA.

David Basketter: 27-04-2016



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