

IDEA Webinar of the Categorization Task Force

Monday, April 28th, 2014 from 3:00pm to 5:00pm (Brussels Time)

Final Minutes

Participants: Klaus Andersen (Odense University Hospital, University of Southern Denmark), Anne Marie Api (RIFM), David Basketter (Toxicology consultant), Hans Bender (Chairman), Peter Cadby (Chanel), Graham Ellis (Givaudan), Helmut Greim (IDEA Supervisory Group), Peter Griem (Symrise), Maya Krasteva (L'Oréal), Fred Lebreux (IDEA Management Team), Scott Schneider (Firmenich), Theodor Schumacher (Smart Practice), Benjamin Smith (Firmenich), Matthias Vey (IDEA Management Team).

1. Adoption of the agenda

The chairman welcomed the participants and went through the agenda, which was adopted such as provided.

2. Antitrust statement

The Chairman reminded the constraints of the antitrust law to the participants. All agreed that there shall be no discussions of agreements or concerted actions that may restrain competition. This prohibition includes the exchange of information concerning individual prices, rates, coverages, market practices, claims settlement practices, or any other competitive aspect of an individual company's operation. Each participant is obligated to speak up immediately for the purpose of preventing any discussion falling outside these bounds.

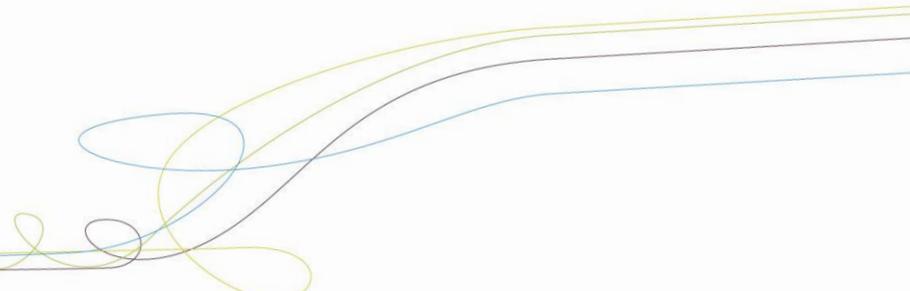
3. Objective

The group agreed that the remit of this task force is to arrive at a commonly accepted framework for the fragrance allergens characterization, which enables further categorization. This framework could be the basis for future effective and proportionate risk management procedures.

IDEA Management Team

Avenue des Arts, 6
1210 Brussels, Belgium
Tel: +32-2 214 20 61
Fax: +32-2 214 20 69

www.ideaproject.info





4. Characterization of allergens (“Yes/No”)

The participants agreed that the ECHA guidance on the application of the CLP criteria (att.01, section 3.4 from page 348 to 378) is an excellent basis for the characterization of allergens. This guidance describes which human and animal testing can be used but also how it should be interpreted to determine whether or not a substance is a skin sensitizer.

ACTION: The participants will review the ECHA guidance and provide feedback.

It was stressed that positive human data, and in particular the clinical experience resulting from patients examination, should take precedence over other negative data sources. The case of Methylisothiazolinone was reported as an illustration of toxicological studies refuted by post-marketing clinical data. A participant confirmed that human data (and its relative importance compared to other data sources) is comprehensively detailed in the ECHA guidance. However, only the substances already placed on the market can benefit of this clinical data and QSAR, in-vitro and animal data (although the regulatory context tends to discourage the latter) remains the basis for the characterization of newly introduced allergens. In effect, human testing such as HRIPT can only be conducted at concentrations not supposed to induce skin sensitization (tolerance studies) and are therefore of no help for the characterization of allergens.

The ranking of data by quality order was discussed as, for instance, a poorly conducted HRIPT (or conducted at too low level) cannot override a properly done LLNA. It was confirmed that all pieces of information should be considered and combined according to a well-thought weight of evidence approach. However, it was remarked that the weight of evidence approach is relatively subjective, like any other activities where expert judgment is engaged.

After consideration, it appeared difficult to define an objective and systematic process that non-experts could use to characterize allergens based on all available data. It was agreed that a workable solution in that case is to refer to the examples offered in the ECHA guidance. These examples ranging from elementary to complex help the decision-making process and allow non-experts to transpose usual weight of evidence techniques into their own cases.

The only drawback of the examples provided by ECHA is that they all lead to the substance classification while actually most of the reviewed substances do not qualify as skin sensitizer. Therefore the group recommended that these examples be complemented with a few cases where the data analysis leads to no classification.

However, these examples do not pretend to eradicate the subjectivity of the weight of evidence approach and it was recognized that two toxicologists analyzing the same data could potentially end up with

different conclusions. This difference of data interpretation can result from the complexity of cases (contradiction of testing data) and from biases inherent to toxicologists' organization (industry, regulators).

5. Categorization ("From low to high")

D. Basketter presented an article¹ recently published in *Dermatitis* and titled "Categorization of Chemicals According to Their Relative Human Skin Sensitizing Potency". The article, co-written by D.A. Basketter, N. Alépée, T. Ashikaga, J. Barroso, N. Gilmour, C. Goebel, J. Hibatallah, S. Hoffmann, P. Kern, S. Martinozzi-Teissier, G. Maxwell, K. Reisinger, H. Sakaguchi, A. Schepky, M. Tailhardat and M. Templier, proposes a new categorization system of skin sensitizers based on human data only.

The main objective of this article was to help the development of *in vitro* methods by optimizing their use for the definition of skin sensitizers' potency. In effect, current *in vitro* testing are more and more predictive for the characterization of allergens but remain of limited use for the determination of allergens potency or, at least, do not have the same predictability accuracy as traditional tools such as the LLNA. As of today, *in vitro* alternatives can qualitatively predict the potency category of an allergen ranging from non-sensitizing to extreme sensitizer.

Based on this observation, the authors created six categories (see Table 1) that result from the subdivision of the three GHS categories: SS 1A (strong sensitizer) led to categories 1 and 2, SS 1B (weak sensitizer) to categories 3 and 4 and no classification to categories 5 and 6. These categories were then populated with the main allergens found in commerce based on all existing human data (epidemiologic studies, clinical data, NOEL, results of HRIPT, etc.). The exposure criterion was also accounted in a qualitative way (expert judgment of substances used at low level and no very often vs. substances used very widely and in big quantities).

TABLE 1. Criteria for Categorization

Human Category*	Clinical Data (Benchmark Substances)	Human Test Data and NOEL
1	Extensive evidence of contact allergy in relation to degree of exposure and size of exposed population (MCI/MI, DNCB, <i>p</i> -phenylenediamine)	Where data were available, a best estimation has been made of the "NOEL" for the induction of skin sensitization in a HRIPT
2	A frequent cause of contact allergy, but of less significance compared with category 1 (formaldehyde, isoeugenol, methylidibromo glutaronitrile)	
3	A common cause of contact allergy, perhaps requiring higher exposure compared with category 2 (abietic acid, eugenol, imidazolidinyl urea)	Where a substance was nonsensitizing, this is indicated by "NS"
4	Infrequent cause of contact allergy in relation to level of exposure (benzocaine, hydroxycitronellal, resorcinol)	Where insufficient data were available, this is indicated as "ND".
5	A rare cause of contact allergy except perhaps in special circumstances, eg. use in topical medicaments (hexylcinnamal, isopropanol, parabens)	Key references are indicated for each substance
6	Essentially absent, with at least no systematic convincing evidence of contact allergy (xylene, glycerol, sodium lauryl sulfate)	

¹ <http://www.ncbi.nlm.nih.gov/pubmed/24407057>



Although expert judgment took an important place in the assignment of known allergens to categories (which could therefore lack objectivity), the result of this categorization is expected to help toxicologists convert in vitro testing data into a qualitative determination of skin sensitizers' potency. Motivated by the necessity to adapt risk management measures to allergens' potency, D. Basketter explained that default NESIL values could be attributed to each category. By doing so, in vitro testing data could feed the Dermal Sensitization QRA methodology and avoid resorting to other data sources. Furthermore, existing allergens should also be categorized within this new system to systematize the application of other types of risk management measures such as consumer information (although some participants felt that consumer information should not be conditioned by the categorization process but ensured for all types of sensitizers).

Most of the group agreed that this 6-category based approach is compatible with the recommendations made at the last IDEA workshop on fragrance allergens characterization. The work achieved through this article was regarded as a useful starting point and the recycling of GHS categories considered appropriate as it reflects current regulatory toxicology.

The group was not aware of any other sophisticated categorization approach that could compete with or be opposed to the article presented by D. Basketter. This work is apparently the first tentative to categorize 100+ allergens based on human data.

However the participants recommended that the model be further improved in light of the following information:

- The sensitization exposure quotient (SEQ), calculated as the quotient of the relative frequency of sensitization and the relative frequency of use. This concept developed by A. Schnuch is thoroughly described in the article "Risk of sensitization to preservatives estimated on the basis of patch test data and exposure, according to a sample of 3541 leave-on products", A. Schnuch, G. Mildau, E.-M. Kratz and W. Uter, 2011, *Contact Dermatitis*, 65, 167-174. However, it was remarked by the group that the relative frequency of use is not always easily accessible.
- The criteria published by the MAK Commission in the article "When should a substance be designated as sensitizing for the skin ('Sh') or for the airways ('Sa')?", A. Schnuch, H. Lessmann, K.-H. Schulz, D. Becker, T. Diepgen, H. Drexler, S. Erdmann, M. Fartasch, H. Greim, P. Kricke-Helling, R. Merget, H. Merk, D. Nowak, A. Rothe, G. Stropp, W. Uter and G. Wallenstein, 2002, *Human & Experimental Toxicology*, 21, 439-444. This article indicates when there are sufficient evidences, probable evidences or insufficiently documented evidences of an allergenic effect based on clinical and experimental data.
- The above quoted ECHA guidance which describes how human data should be analyzed, including in relation to potency determination. This ECHA guidance also proposes a categorization system in

four categories (three grades of skin sensitization potency and one category for non-sensitizing substances) which might be considered in the context of this development.

- The categorization system proposed by the SCCS in its opinion on fragrance allergens (SCCS/1459/11). The group agreed that it should be well understood how the SCCS established the relative importance of human fragrance allergens.
- More generally, the inclusion of all available information (including QSAR results, in vitro and animal testing data) was recommended. This is not a usual approach in toxicology to exclude non-human data and toxicologists usually try to collect all available information in order to make an informed decision. Such an improvement would make the system more robust and allow its use with new substances covered by little (or no) human data. It was mentioned that the LLNA predicts the NOEL in humans for about 90% of substances. For the ones it does not, the LLNA underestimates the NOEL in humans in the majority of cases. It confirms that the use of non-human data is important and should be included whenever this is available.

ACTION: The participants will read in detail the article of D. Basketter et Al. and make improvement proposals in line with the outlined above suggestions.

Additionally, it was stressed that the categorization of an allergen should be revisited every time new data (and in particular clinical data) become available.

It is noteworthy that a concern was raised about the categorization approach in general. Clinical reports show that some individuals tend to overreact to some very weak sensitizers either because they are particularly sensitive or due to an overexposure to the allergen. There was agreement by the participants that the way an individual reacts would not be the best descriptor for the property of an allergen. A strong reaction by one individual could happen to a weak sensitizer and a relatively weak reaction by another to a potent one. The group therefore agreed that the intrinsic sensitizing properties of a substance should not be confounded with the expression of the disease in an individual. Therefore, the categorization process should not be affected by this element of the contact allergy.

6. Next meeting

The group agreed to schedule a physical meeting end of June, potentially in Munich, Germany (to be confirmed). The IDEA Management Team will send a doodle poll to the participants in the next days.

Preparation, 09/05/2014 (F. Lebreux, IDEA Management Team)

First Review, 09/05/2014 (H. Bender, Chairman of the IDEA Categorization TF)

Final Review, 26/05/2014 (IDEA Categorization TF)