IDEA
International Dialogue for the Evaluation of Allergens

Report on the IDEA Workshop on

Characterization and Categorization of Fragrance Allergens

September 23-25th, 2014

Château du Lac
Avenue du Lac, 87
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This report is based on the formal presentations and discussions that took place. It is intended to be a balanced report of what took place. Bias in the selection of speakers and interests of the other workshop participants affect the proceedings. The rapporteur (Ian R. White) had copies of the presentations and comprehensive notes taken during the meeting when preparing this report. Participants had the opportunity of commenting on the draft report. **Only items headed 'Agreed Conclusions' are such.**

1. Objective of Workshop

"To lay the foundation for an allergen characterization and categorization procedure which feeds risk management steps towards reduction of allergic contact dermatitis and which can be subject to continuous review, correlation, and improvement."

2. Definition of a Contact Allergen (Workshop Aug 27-29, 2013) for the purposes of IDEA

"A contact allergen is a substance that is capable of inducing delayed type sensitization in humans, which may manifest as allergic contact dermatitis.
The elicitation of allergic contact dermatitis requires sufficient exposure and is subject to significant inter-individual variability".

3. Relationship between contact allergy and allergic contact dermatitis

Contact allergy may be induced by skin contact with low molecular weight haptens and may evolve to allergic contact dermatitis if the exposure exceeds the individual elicitation threshold in sensitized individuals.

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Contact allergy is an altered immune status induced by a specific substance; it is demonstrated by a positive patch test and identifies the population at risk of developing allergic contact dermatitis.

Once sensitised (induction has occurred), allergic contact dermatitis occurs when the exposure to the allergen exceeds the individual threshold of elicitation. When exposure to an allergen is causing/has caused clinical symptoms (disease) of dermatitis (allergic contact dermatitis) the allergen is considered to be of current/old relevance, respectively. It may be the case that there is no obvious history of exposure or dermatitis relevant to the allergen and in such circumstances the individual's allergy is considered to be of unknown relevance. However, should sensitised individuals have appropriate exposure at some time in the future they will be at risk of developing allergic contact dermatitis. In this respect, contact allergy can have life-long implications for the individual.

Most knowledge about contact dermatitis is derived from clinical case reports, clinical studies of in- and out-patient groups, statistical compilations of patch test reports, and from studies of small outbreaks of dermatitis.

Dose-response thresholds are important to consider in both the induction of contact allergy and its expression in the elicitation of allergic contact dermatitis. In general, more individuals will become sensitised with higher doses or repeated lower doses (exposure) of the allergen and similarly for the elicitation of reactions.

Dinitrochlorobenzene (DNCB) has been used as an experimental model to show the effects of dose on induction. Repeated open application tests (ROAT) with a number of fragrance allergens and preservatives illustrate the important of frequency of applications for the elicitation of allergic contact dermatitis in the clinical setting. A ROAT may mimic consumer exposures.

Patch testing (performed according to the International Contact Dermatitis Research Group (ICDRG) guidelines) is the gold standard to determine the presence of contact allergy.

Patch test concentrations should cause a minimum of irritant/doubtful and a maximum of allergic reactions and are determined accordingly (the highest non-irritant concentration that will cause the fewest false-negative reactions). The clinical technique, allergen preparation, application, reading and interpretation is presently under review by the European Society of Contact Dermatitis (ESCD) who are writing a guideline. Considering fragrance allergens, however, they should be applied to test chambers immediately before application to the skin to reduce evaporation which could lower the dose.

For fragrance substances there are now two mixes of fragrance allergens (**fragrance mix I** containing *Evernia prunastri* (Oak moss abs.), isoeugenol, cinnamal, cinnamyl alcohol, eugenol, hydroxycitronellal, geraniol and α-amyl cinnamal; **fragrance mix II** containing hydroxyisohexyl 3-cyclohexene carboxaldehyde

(HICC), citral, farnesol, citronellol, hexyl cinnamal and coumarin) and **Balsam of Peru** (*Myroxylon pereirae*) used in routine diagnostic patch testing as indicators (screening agents) with varying specificity and sensitivity regarding contact allergy to fragrances.

Current data from the National Allergy Research Centre in Denmark show that (*circa*) 8% of eczema patients undergoing patch testing have contact allergy to fragrance mix I, 5% to fragrance mix II, 4% to Balsam of Peru and 2% to the specific fragrance chemical HICC. Of females tested, some 14.5% of women have contact allergy to the fragrance markers and 10% of men with an overall rate of 13% in the tested population. In the years 2005 to 2008 the prevalence of fragrance mix I in Germany was 6.58% (standardized for age and sex) (Uter W et al. Contact Dermatitis 2010: 63; 254-261). In 2010: 7.4% ; in 2011 : 8.1% ; in 2012: 9.1% (all standardised) (Mahler V, Geier J, Schnuch A. Deutsche Dermatologische Gesellshaft. DOI: 10.111/ddg.12371; 2014). For 2013 (not yet published) 8.8% (Schnuch, personal communication). There are temporal variations but the current overall trend appears to be upwards.

Determining clinical relevance of a positive patch test reaction can be difficult and time-consuming. In essence it depends on:

a) History of the patient (including information on exposure and (subsequent) rashes/eczema);

b) Re-exposures with the suspected allergen patch test preparation and, if needed, patch testing with own products and use testing with a suspected product;

c) Exposure analysis which involves the expert knowledge of the investigating dermatologist, review of product ingredient labels, material safety data sheets (MSDS) and (when available) chemical analysis and, if available, information from the manufacturer of the consumer product.

The reading of patch test reactions is a standardised (?+, +, ++, +++) system to show the 'severity' of the reaction (allergic contact dermatitis) elicited by the standardised allergen preparation. Weak (+), strong (++), and extreme (+++) reactions, classified according to the respective morphology are considered as positive reactions. At least a (+) reaction is considered as a proxy for contact allergy.

The industry-sponsored 'EDEN' study (Diepgen et al) has shown good reproducibility of fragrance mix patch test results for ++ and +++ reactions but poorer reproducibility of former patch test results for + reactions and excellent specificity for negative subjects.

In general, individuals who show stronger reactions will experience elicitation reactions with lower concentrations of the allergen. Studies have shown that up to 100% of patients with +++ reactions to fragrance markers have a positive history of fragrance intolerance but only a quarter of those with ?+ reactions. (Frosch PJ et al. Contact Derm 1995:32; Johansen JD et al. Acta Derm Venereol 1997:77).

For repeated exposures, as in the ROAT, smaller concentrations are sufficient for elicitation as compared to patch testing. The number of days (exposures) until elicitation occurs depends on the exposure

concentration. This is illustrated with isoeugenol where for 0.2%, 7 days of exposure (median) was required and for 0.05%, 15 days of exposure (Andersen KE et al. Toxicol Appl Pharmacol 2001:170:166-171). The individual's threshold dose needed for elicitation in patch testing affects the time required for elicitation in a ROAT (as sensitivity increases (the threshold dose decreases) the time until a positive ROAT decreases). Two applications per day for 14 days is recommended (Johansen JD, Frosch PJ, Svedman C, Andersen KE, Bruze M, Pirker C, Menné T. Contact Dermatitis 2003:48:310-316). When doing such elicitation tests it is important to appreciate that sensitivity depends on anatomical region: axilla > arm; face=neck> arm; upper back > lower back.

Perfumes for women were shown to have a mean content of 12 fragrance allergens (of the 26 required to be labelled) (Buckley DA.Br J Dermatol. 2007 :157; 295-30) as determined by examination of product labels. In the Uter et al study (Contact Dermatitis 2013: 69; 335-341) the median number of fragrance allergens labelled in products varied between categories, ranging up to 9 in perfumes. Such mixtures ('cocktails') of allergens reflect normal consumer exposure. In animal experiments it has been shown that mixtures enhance induction and elicitation (Bonefeld C et al. Contact Dermatitis 2011: 65; 336-42).

For 1790 patients with diagnosed fragrance allergy, the contact allergy was relevant in at least 60% of cases and in 753 (42.1%) a cosmetic product was identified as the cause of the dermatitis (Heisterberg M on behalf of DCDG, Contact Dermatitis 2011: 64; 258-64). Deodorants, scented lotions, fine fragrances, shampoos and liquid soaps and aftershaves were particularly responsible.

Clinical relevance provides information for the patient with a dermatitis (whether the allergen is causing or contributes to the dermatitis, or is of old relevance). Assessment is complicated and resource demanding and (usually) does not provide information about what induced the contact allergy. Information about presence of individual chemicals is critical.

Patch test data provides the first indication that sensitisation is occurring. Data from larger patch test populations may indicate that sensitisation is occurring in the general population (or specific subgroups), which is therefore of concern.

Although the dose required for induction of contact allergy is (usually) higher than required for the elicitation of an allergic reaction, regulations do restrict exposure based on elicitation concentration rather than induction concentration if the frequency of contact allergy is high in the general population. Examples of this are nickel and chromium (cement, leather). Clinical epidemiological data illustrate the benefits of this approach. Clinical epidemiological data has also been used as evidence of concern leading to ban (legal prohibition) allergens from the market to prevent any further exposure to the consumer. Clearly, consumer exposure to allergens should be such as to prevent the induction of contact allergy in the first place (primary prevention) and thereby prevent a proportion of the population from having to be protected from elicitation reactions (secondary prevention). To date, the only available method to achieve this has been by

restrictions based on elicitation data. This has direct relevance for humans and provides safe levels for both induction and elicitation. In the future, a scientifically valid and applied Quantitative Risk Assessment (QRA) may be utilised.

4. Differences in prevalence of skin sensitisation

Provided that patch testing has been done in a standardized way following the pertinent guidelines (to reduce uncertainties associated with patch testing due to e.g., non-standardised patch test material or inadequately trained personnel), regional variations in the prevalence of contact allergy to a particular allergen may be due to:

1) variation in product usage and. allergen exposure,
2) differences in proportion of occupational cases seen,
3) inter-individual variations in patch test readings and
4) access to care / patch testing.

Data from the United States of America (USA) show differences in prevalence which could be due to variations in product use and patterns, access to patch testing and the way patch test reading takes place. Interpretation of data is difficult as there is a huge geographical area with relatively few numbers (clinical data) from individual centres. There might also be selection bias based on health insurance. Further, the TRUE Test® is less sensitive than petrolatum-based allergens for fragrance mix I (Mortz CG, Andersen KA. Contact Dermatitis 2010: 63; 248-53).

Data from Europe also show geographical differences (Uter et al. Contact Dermatitis 2012: 67; 9-19 and Schnuch et al. Contact Dermatitis 1997: 37; 200-209).

An allergen may be rarely reported simply because it is not tested.

Agreed Conclusions

Properly conducted patch tests are the 'gold standard' for the clinical detection of contact allergy.

-Positive patch tests are the indication that exposure to a substance is causing contact allergy with a risk of allergic contact dermatitis and should trigger a re-evaluation of the risk.

-Epidemiological evaluation of patch test results allow a comparison of the relative importance of contact allergens in terms of frequency of reaction and indicate contact allergy trends over time.

-Positive patch test data represent the relevant endpoint in humans and are core data which assist in making decisions for preventive strategies in public health.

Proposal for additional conclusion, provided by Johansen and Diepgen on request of the workshop participants but not discussed or agreed at the Workshop

-Exposure information is crucial for diagnosing contact allergy and allergic contact dermatitis, for advising patients and for prevention. The most important source of exposure information concerning cosmetic products is ingredient labelling.

5. Data basis for characterisation and categorisation of allergens

Methods to determine sensitisation potential of a substance include:

- OECD[1] 429: Local lymph node assay (LLNA);
- OECD 406: Guinea pig maximisation test (GPMT), Buehler occluded patch test.

However, these are no longer permitted in Europe for new cosmetic ingredients where the information generated would be used solely for the purposes of risk assessment in the sector. Historical data, created before the legislative cut-off, can be used.

In silico tools (Weight of Evidence) with read-across and structural considerations (alerts) are utilised.

Human non-clinical studies (in that they are done on normal individuals and not as part of the investigation of a disease process) include human maximisation test (considered as unethical in Europe) and the human repeat insult patch test (to show that the substance does not induce contact allergy under the test condition).

Now, a series of *in vitro/ in chemico* methods are under varying degrees of development and for some (Direct Peptide Reactivity Assay (DPRA), keratinocyte activation (KeratinoSens), human cell-line activation test (h-CLAT)) – OECD guidelines are expected to be published. For these, however, they provide information on whether the substance is a sensitiser or not but not the relative potency. Additionally, they provide no or very limited capability to identify pro-haptens. These methods are not developed as stand-alone assays to replace the animal assays, but are meant to be used in combination under a testing strategy scheme.[2]

[1] Organisation for Economic Cooperation and Development

[2] If protein reactivity (DPRA) and keratinocyte activation (KeratinoSens) are both negative this is highly sensitive to predict that the substance is a non-sensitiser. If there is dendritic cell activation (e.g. h-CLAT) then this is highly sensitive to predict the substance is a sensitiser.
The so-called 'gold list' of substances spanning a range of sensitising potencies developed from LLNA and other data should be used with caution as original data may not be accessible and errors are known to be present.

Allergen classification for labelling and packaging (CLP) legislation originally has been developed for handling of substances in the workplace. There is scepticism among the dermatological community and others that it is of use for the prevention of contact allergy or the development of allergic contact dermatitis in the consumer.

An OECD guidance document under development aims to describe an Integrated Approach to Testing and Assessment (IATA) as a structured approach used for hazard identification (potential), hazard characterisation (potency) and/or safety assessment (potential/potency and exposure) of a chemical or group of chemicals, which strategically integrates and weights all relevant data. This approach considers metabolism, biological availability, covalent binding, cellular response, organ response (T cell proliferation), outcome (clinical, challenge) applied in a matrix to inform weight of evidence. This general framework guidance for skin sensitization:

1) anticipates sufficient flexibility in the use of the individual information sources to cover multiple regulatory needs within OECD member countries;
2) provides generic guidance on the evaluation and application of IATA;
3) provides consistent description of the information sources that can be used within an IATA for skin sensitisation and
4) includes a template for describing IATA so that the same documentation format for describing and evaluating IATA can be used by member countries.

Although significant progress has been made on *in vitro* methods for hazard identification, the challenge remains potency assessment. Additionally, identification of weaker allergens remains a problem. A Weight of Evidence approach to No Expected Sensitisation Induction Level (NESIL) needs to be developed.

Agreed Conclusion

Non-clinical methods including non-animal approaches (e.g. those with OECD guidelines) have the potential to allow for the identification of a contact allergen. However non-animal test systems require further refinement for characterization and categorization.

6. Characterisation and categorisation of allergens

For allergic hazard potential of substances, the 'sensitivity' is:

- Clinical diagnostic capability > limit of predictive toxicology > regulatory limits

After a hazard has been identified, the next step is to examine the dose response and use it to characterise the relative potency of the substance. For the local lymph node assay (LLNA), this is well recognised as the

EC3[3] value, now widely used as a potency marker. For *in vitro* methods, some methods or IATA may provide some information on potency, but they do not achieve the graded response of the LLNA. Human data can play a role.

For nearly 50 years, there have been two categories: sensitiser/not classified. Recent "progress" advanced this to three: strong sensitiser/moderate sensitiser/not classified. The European Chemicals Agency (ECHA) Guidelines have taken a step further: extreme/strong/moderate/not classified. The Scientific Committee for Consumer Safety (SCCS) have also made category suggestions. A recent proposal has proposed 6 categories:

- Extreme/strong/moderate/weak/very weak/non-sensitiser.

Regulatory classification: human

Human evidence for sub-category 1A (under the CLP system, differentiating very strong and strong skin sensitisers in 1A and 1B) can include:

1) positive responses at ≤ 500 µg/cm2 (human repeat insult patch test (HRIPT), human maximisation test (HMT) – induction threshold);
2) diagnostic patch test data where there is a relatively high and substantial incidence of reactions in a defined population in relation to relatively low exposure;
3) other epidemiological evidence where there is a relatively high and substantial incidence of allergic contact dermatitis in relation to relatively low exposure.

Human evidence for sub-category 1B can include:

1) positive responses at > 500 µg/cm^2 (HRIPT, HMT – induction threshold);
2) diagnostic patch test data where there is a relatively low but substantial incidence of reactions in a defined population in relation to relatively high exposure;
3) other epidemiological evidence where there is a relatively low but substantial incidence of allergic contact dermatitis in relation to relatively high exposure.

The United Nations Globally Harmonized System of Classification and Labelling of Chemicals (GHS) may be used to split the classification of allergens as Extreme, Strong, Moderate, Weak, Very Weak, Non-sensitiser (Basketter et al, 2014; Dermatitis 25; 11-21) and could help by associating each category with a default NESIL and existing substances placed into these six categories could assist in the evaluation of *in vitro* methods for potency prediction.

[3] The EC3 value, interpolated from the dose response curve, is the effective concentration of the test substance required to produce a three-fold increase in the stimulation index compared to vehicle-treated controls.

Fragrance ingredients, as ordinary chemicals, are covered by chemical regulations and use of > 1 tonne per annum puts them within REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals).

To ensure that any actions (classification, exposure) are meaningful for prevention of contact allergy there must be measurement focused on consumers and workers.

7. Genetic factors

For certain drugs there is very clear and strong evidence of genetic determination of susceptibility to sensitisation. For certain contact allergens genetic linkage has been shown controlling reactivity to various metals, dinitrofluorobenzene (DNFB) and other allergens in various strains of mice. Relevant linkage is almost all within H2 and Ia regions (Homologues of human HLA Class I and II). Most mice cannot be sensitised to nickel because of a lack of key histidine residues in the toll-like receptor (TLR)-4– nickel binds to histidine, hence in humans, TLR-4 is activated. Guinea pigs of strain II can be made allergic to dichromate and beryllium but not mercury. Guinea pigs of strain XIII are the reverse (Polak, Barnes & Turk (1968) Immunology, 14: 707-711).

The role of TLR-4 in sensitisation to nickel in mice was recently challenged. The allergic response to nickel following epicutaneous exposure is MYD88-dependent (an element of the innate immune system) and interleukin (IL)-1 receptor dependent, but independent of TLR-4 (Vennegaard et al. Contact Dermatitis 2014: 71; 224-231).

In considering the situation in man, we may consider 1) genetic control of general susceptibility to sensitisation by anything – non-specific susceptibility (high/low responders) and 2) specific susceptibility to sensitisation by the allergen(s) of interest where single gene products may be critical – HLA molecules, TCR, specific proteins that get haptenated etc.– as in drug allergy. Susceptibility may be acquired.

In general, there is a normal (Gaussian) distribution of reactivity in humans. Polysensitised individuals have a stronger response on challenge, i.e., a lower elicitation threshold. (Moss C, Friedmann PS, et al. Clin Exp Immunol 1985; 61: 232-4; Schnuch A, Westphal G, et al. Contact Dermatitis 2011; 64:2-23). Polysensitisation can be regarded as a clinical sign of increased susceptibility.

It was presented that genetics/polymorphisms may play a role in sensitization to moderate/weak allergens or in lower exposure conditions in combination with further risk factors.

The HRIPT enrols ‘normal’ individuals. Testing ‘at risk’ populations would increase sensitivity. Increasing age appears to be a risk factor for polysensitisation.

Whatever the influence of genetic susceptibility on sensitisation, the relative influence is considerably lower than exposure (dose) and sensitising potency of an allergen. In general, exposure is critical, not susceptibility. However, in cases of contact allergy, where the chemical is i) a very rare sensitiser and ii) a very weak sensitiser, susceptibility could be the driving force compared to the above 'normal' situation.

Agreed Conclusion

The role of genetic factors in susceptibility to contact allergy is yet to be defined.

8. Improving Dialogue between Industry and the Dermatology Community

There is a complex communication interchange between the dermatologist – patient – industry with regards to information on the presence of an allergen, availability to test the substance and mechanisms for the patient (consumer) to avoid exposure.

An industry-led task force has been mandated to establish a process for obtaining diagnostic data.

1) Working process to identify (fragrance) allergens that is well-publicized to both industry and dermatology communities (global)
2) Easy way to identify individual(s) in consumer product companies for the dermatologist to contact on a worldwide basis
3) Standardized method of supplying properly identified samples to dermatologist
4) Formal mechanism for obtaining results from the dermatologist
5) Agreement on information needed to help improve the risk assessment
6) Formal mechanism to review data on (fragrance) allergens
7) Identifying potential pro-active surveillance fragrance materials for dermatologists to test

It is central that feedback be established so that:

- Industry → Dermatologists: provide reference materials to help the diagnosis of contact dermatitis
- Dermatologists → Industry: provide results of clinical testing as feedback into risk assessment/management process

Full ingredient labelling is seen as essential by the dermatological community. However, in the absence (at present) of full ingredient labelling of fragrance substances, there is a requirement to develop a strategy to inform the consumer of the presence of non-labelled fragrance substances to which they have a contact allergy. Additionally, there should be a single point of contact.

Agreed Conclusion

Readily accessible product ingredient information including labelling is critical for evaluating exposure, reliable diagnosis and prevention.

9. Break out reports

9.1. Studies

Retrospective studies are problematic as data from different centres may involve different samples, methods, readings etc. as well as competence of local dermatologists.

For new materials early studies are of dubious benefit as it can take time before consumer exposure to the material is established.

However, there is a need for accurate baseline data for prevalence to assess the effectiveness of QRA and to develop a procedure for dealing with clinical alerts.

A common protocol for patch testing, with a high degree of standardization and calibration for the preparation, application, reading and interpretation of the test material(s) is critical for the establishment of baseline data from different clinics.

Fragrance mixes I and II and the 14 individual ingredients should be monitored, together with *Evernia furfuracea* (Tree moss) and oxidised linalool and limonene. For oxidised linalool and limonene they must be adequately standardised as patch test ingredients. The relevance assessment of these oxidation products is taking place in the context of the IDEA workshop on pre- and pro-haptens.

For other substances, routine testing of groups of substances over blocks of time would provide information on the prevalence and relative importance of them as allergens (information on consumer exposure is required).

Synchronous application of patch ingredients and on consecutive patients is required from a range of dermatology centres with the necessary competences and clinic loads.

Use of a detailed questionnaire is required to obtain quantitative and qualitative information on exposures (to fragrance allergens), occupation, consumer habits, past and present topical drugs used, product types presented by the patient, body site of initial and present dermatitis, etc.

Primary readout is the prevalence of contact allergy (endpoint of concern) and the secondary readout is the prevalence of allergic contact dermatitis.

The studies should be overseen by an independent organization (e.g., European Commission services/Joint Research Centre (JRC) of the European Commission).

9.2. Suggested criteria for ranking the relative concern of fragrance allergens

Although many reactive chemicals will qualify as a 'contact allergen', this does not necessarily mean that adverse reactions will occur in practice. Therefore, an appropriate question is what are the criteria that qualify a substance as contact allergen of concern?
It is important to consider allergens with human data. *In vitro* / *in silico* / animal data are helpful but by themselves insufficient.

Some substances are assumed to be contact allergens only in a specific context. Mixture effects, presence of skin penetration enhancers and patch test concentration may have importance in the elicitation process.

In clinical practice, the routine surveillance of contact allergy to fragrance substances covers only a few such substances (those in fragrances mixes I and II, *Myroxylon pereirae* and, from some centres, those fragrance allergens required to be labelled in the European Union (EU)); this is insufficient.

Concerns result from the multiplication of several factors, the most important being: individual cases of allergic contact dermatitis, clinical epidemiology demonstrating contact allergy (including data from cosmetovigilance networks) and population-based studies of contact allergy, including occupational subgroups.
Exposure assessment may be difficult where there is a lack of appropriate information. Presently, the presence of only 26 fragrance allergens is required on the ingredient labels of cosmetic products and household detergents. No other meaningful labelling or consumer information tool exists currently.

At least some indication of the exposure levels to all suspect substances in the general population is essential.

It is suggested that the relative concern regarding fragrance allergens could be considered as:

Major concern
- Many reported cases (at least 100) of contact allergy or,
- Few reported cases (at least 10) where there is low and/or infrequent exposure or,
- Some cases of very severe allergic contact dermatitis.

Potentially major concern

•There are cases but there is no existing epidemiological survey to confirm the frequency in the general population or in a subgroup.

•Non-clinical data (*in vitro*, *in silico*, animal) indicates a risk, but there is no clinical or epidemiological data to confirm it.

Moderate concern

•More than minor but does not fit criteria for major.

•*Definitio per exclusionem*.

Minor concern

•Isolated sporadic case reports where there is large and/or frequent exposure and,

•Large epidemiological data demonstrates/confirms rarity of contact allergy.

No current concern[4]

(This remains to be formally discussed and fully considered).

9.3. Communication

Ideally, samples for patch testing should be diluted according to de Groot. If not listed in de Groot, the raw material (with Certificate of analysis of all ingredients) should be provided.

For larger companies there is usually no problem with this, but this may not be so for small and medium sized enterprises (SMEs).

On line resources are needed that provide information to dermatologists (e.g. guidelines for sample preparation/who to contact, etc.) to help diagnosis.

Diagnosis allows identification of causative agents and a means to avoid. Full ingredient labelling is central to providing the consumer (patient) a means to avoid future exposures that are detrimental to their health (elicitation of allergic contact dermatitis). The construction and maintenance of lists of products that do not contain the material of concern and list of safe alternatives would be helpful for the consumer.

Ingredient information must be available at the time of assessment. Although full product ingredient labelling is central to this and fragrance substances are no different than other chemicals/substances), 'apps' and similar digital resources are considered important supportive systems.

[4] This was not fully discussed at the IDEA meeting but a suggestion post-meeting was: "Many people have been extensively exposed to the substance over a long time (a minimum of 7 years), but where the chemical has been sufficiently tested, and in particular surveyed by an epidemiological surveillance system, contact allergy has been shown to be extremely rare."

The key to monitoring the safety of a cosmetic ingredient, including a fragrance substance, is good feedback form clinician/patient and industry. Stakeholder meetings to discuss new and emerging allergens are necessary.

10. Overall Discussion and Conclusions:[5]

Risks to human health presented by contact allergens must be rigorously assessed and properly managed.

Patch testing performed by appropriately trained individuals (necessary competencies with frequent and direct patient involvement) fits the criteria for which the testing has been designed, to be sensitive and specific as a diagnostic tool. The relevance of a positive patch test for an individual (patient or consumer) is a matter for the trained dermatologist investigating the patient.

A positive patch test (demonstrating contact allergy) is the first indication that exposure to a substance is causing allergy in the population. Data from individual clinics and regions may be used as a means of comparing the relative importance of contact allergens in terms of the frequency of reactions and allows contact allergy trends to be followed over time.

A positive patch test reaction does not:

- prove what exposures caused the induction of contact allergy;
- give any dose-response information for the causal exposure;
- inform on what types of exposure may be tolerated, either for induction or elicitation.

Some non-experts may believe that a positive patch test result is not relevant for “real life” exposures. This is a fallacy, based on the failure to understand that the elicitation of contact allergy under diagnostic patch test conditions is intended to show only one thing, whether an individual patient has contact allergy to a substance. Those real life exposures have culminated in an adaptive immune response. A test material may not represent the “labelled allergen” but rather the “actual allergen” to which the consumer (or worker) is exposed (e.g. linalool, oxidised linalool). Thus, pre- /pro-hapten activities must be considered.

Positive patch test data should inform those who produce and/or use the substance that:

- it is a skin sensitiser;
- consequently, a potential cause of contact allergy….
- and, therefore, of allergic contact dermatitis.

[5] These are produced by the rapporteur.

Exposure information is crucial for diagnosing contact allergy and allergic contact dermatitis, for advising patients and for prevention. To date and in practice, the most important source of exposure information concerning cosmetic products is ingredient labelling.[6]

QRA must be evaluated by its impacts in minimising the frequency of contact allergy to fragrance substances in the population (eczema patients undergoing routine patch testing may be considered an at risk group and, therefore, suitable for study). However, it is also critical to the evaluation that sources of exposure to the substance can be easily identified. It is accepted by dermatologists[7] that full ingredient labelling is pivotal to this; on-line and other resources should be considered a desirable addition and not a substitute for ingredient labelling.[8]

Classification and potency sub-categorisation of allergens may be useful in prioritising work on consumer protection only. They are not substitutes for primary and secondary preventive strategies.

In order to progress the IDEA project, studies are now required to examine the effectiveness of QRA and the frequency of contact allergy to fragrance substances in eczema patients (as a proxy for the general population). As well as monitoring the frequencies of contact allergy to the substances present in Fragrance mixes I and II, oxidised limonene and oxidised linalool are a good starting point for the other SCCS-identified materials to be assessed. These lists are, however, indicative and not exhaustive and other substances identified as potential allergens in humans from *in vitro* or *in silico* methods should be monitored for contact allergy.

Such studies will permit feedback into the QRA model as a tool to prevent induction of contact allergy (primary prevention).

Protocols for the necessary studies should be drawn up independently of industry or its advisers. Although the Joint Research Centre (JRC) of the European Commission could be involved, a suggestion is that the IDEA Supervisory Group takes on the responsibility. Monitoring and evaluation should also be independent.

[6] The 6th Amendment of the Cosmetics Directive (93/35/EEC, June 1993) introduced full ingredient labelling apart from fragrance substances. The preamble to the Directive stated that labelling would allow consumers with an identified contact allergy to avoid exposures harmful to them. The 7th Amendment introduced labelling (with pragmatic limits of 10 ppm and 100 ppm for leave-on and rinse-off cosmetic products, respectively, determined by the European Parliament) of 26 fragrance substances identified in the 1999 Opinion of the SCC-NFP (SCCNFP/0017/98 Final). The 2012 Opinion of the SCCS (SCCS/1459/11) on contact allergy to fragrance substances identified 54 simple chemicals (12 high risk) and 28 natural extracts (8 high risk) that are established contact allergens in man. The consumer is presently unaware of the presence of many fragrance substances identified as allergens.

[7] This has been stated by national associations (dermatology) in Europe and the ESCD.

[8] In the agreed Conclusion of the first IDEA meeting on QRA, March 2013, it is stated "Labeling and Provision of information on ingredients as an important complement to QRA and in-market validation."

Priorities for other activities to progress the IDEA project also need to be identified and an action plan established to enable them.

Dr. Ian R. White

Workshop Rapporteur

Appendix 1 – Workshop Participants:

- European Commission and European Scientific Committees: Dr. Gaetano Castaldo (EU Commission, DG Sanco B2 Unit), Dr. Federica De Gaetano (EU Commission, DG Sanco B2 Unit), Prof. Pieter-Jan Coenraads (University Medical Centre Groningen and member of the SCCS).

- Academic community and national Authorities: Prof. Klaus Andersen (Odense University Hospital), Dr. David Basketter (Consultant), Prof. Donald Belsito (Columbia University Medical Center and RIFM Expert Panel Member), Prof. Magnus Bruze (Lunds Universiteit and RIFM Expert Panel Member), Prof. Thomas Diepgen (Ruprecht-Karls University), Prof. Jeanne Duus Johansen (University of Copenhagen), Prof. Peter Friedmann (University of Southampton), Prof. Tony Gaspari (University of Maryland), Prof. David Gawkrodger (University of Sheffield, former SCCS member), Dr. David Lovell (University of Surrey), Prof. Stefan Martin (University of Freiburg), Prof. Hans Merk (Universitätsklinikum Aachen), Prof. Jean-François Nicolas (University of Lyon), Prof. Marc Pallardy (Université Paris-Sud), Prof. Axel Schnuch (IVDK / University of Göttingen).

- Industry: Dr. Anne Marie Api (RIFM), Dr. Peter Cadby (Chanel), Mr. Graham Ellis (Givaudan), Dr. Nicola Gilmour (Unilever), Dr. Peter Griem (Symrise), Dr. Etje Hulzebos (I.F.F.), Dr. Petra Kern (Procter & Gamble), Dr. Sylvie Lemoine (AISE), Dr. Linda Loretz (PCPC), Dr. Florian Schellauf (Cosmetics Europe), Dr. Scott Schneider (Firmenich).

- IDEA Staff: Dr. Hans-J. Bender (Moderator), Dr. Cécile González (IFRA), Dr. Fred Lebreux (IFRA), Dr. Matthias Vey (IFRA).

- Supervisory Group members: Prof. Jim Bridges (University of Surrey), Dr. Ian R. White (Guy's & St Thomas' NHS Hospitals, Rapporteur)