"Approach followed by the SCCS to characterize fragrance allergens"

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General definition of a contact allergen

A substance which is capable of . . .

- inducing contact sensitisation in man after penetration and binding to epidermal proteins (“micro level”)
- eliciting allergic contact dermatitis after sufficient exposure, “sufficient” varying inter-individually (“clinical level”)

Clinical definition of a contact allergen

A substance, or a natural mixture of substances,

- to which the patient has (undoubtedly/probably/possibly) been exposed, areas of contact (perfectly/partly) corresponding to areas of dermatitis, with plausible time course,
- which elicited a (weak/strong/extreme) allergic patch test reaction to a (too low/adequate/too high) patch test concentration, in a (suboptimal/adequate) vehicle,
- the avoidance of which will ensure the patient is (mostly/perfectly) free of recurrences in the future

Operational definition of a fragrance contact allergen in the SCCS opinion

A fragrance substance, or a natural mixture of substances (extract), which (after

bio–

activation),

- based on several published reports of sufficient quality, has caused contact sensitisation in patients, or
- according to a historical human max. test / HRIPT is a sensitiser, or
- has been identified as contact allergen in guideline animal methods (effectively, only the LLNA), or
- can be categorised as likely allergen if *limited* human or experimental data is combined with structure activity considerations

Sources of Evidence

- Manual search of the journal "Contact Dermatitis" (Oct. 2010)
- Medline search of CAS numbers identified in reviews and clinical studies already retrieved
- Manual search of all RIFM reviews published in "Food Chem. Tox." (last 20 years)
- "top 100" substances in terms of volume used (as supplied by IFRA)
- "top 101-200" substances if R43
- Animal test data (GPMT, LLNA, Buehler test) requested from IFRA – eventually, LLNA protocol summaries regarding 59 fragrances were presented and considered along with two published reviews

Grading of Evidence

Human data overrules other data

- HMT / HRIPT: predictive value positive: OK; ...
  negative: doubtful
- Case reports: detailed (exposure, relevance), but no "profile" of reactions to allergen preparation used
- Clinical series: (very) many patients tested, reaction profile, but little detail (albeit "epidemiological relevance"; A. Schnuch)
- It is possible (and has been done) to set up various rigid "quality criteria" against which most published evidence may appear poor
- The SCCS working group used published evidence which did not raise *reasonable doubts* on compliance with international guidelines

Aggregation of Evidence

A step-wise 'hierarchical' process was used; once categorisation as contact allergen (CA) was achieved, further steps were omitted.

- *Estd. CA in humans*: reports/series from ≥ 2 independent centres or positive human induction test
- *Estd. CA in animals*: positive result(s) of (a) guideline study/ies
- *Likely CA*: limited human and/or animal evidence and/or other evidence, including SAR considerations (≥ 2 criteria must be met)
- *Possible CA*: Only one of above criteria for 'likely CA' is met ('Possible' CAs are not considered further, except for stating a need for further data).

Further characterisation of fragrance allergens

For "estd. CA in humans" only, the absolute number of *reported* cases was taken to identify levels of suggested preventive action:

- $>$ 100 reported cases: restriction (table 13-5)
- $>$ 1000 reported cases and inconclusive time trend: withdrawal (HICC)
- persistingly high prevalence of CA and futile attempts to reduce concentration of (chloro-)atranol: withdrawal (*E. prunastri* and furfuracea)

Validity of (published) Patch Test Results

- Commonly used PT concentrations may be too low (Bruze et al., COD 2012;66:131-6)
- Use of non-oxidised material in PTing where oxidation products are the (much more important) allergen gives false-negative results
- Not PTing a substance at all (because it is unknown it is contained in a culprit product) will inevitably yield a "false-negative" result . . . which is why labelling/ingredient information is an important step not only in individual secondary prevention, but also in epidemiological surveillance based on clinical data

Sensitivity of "Estd. CA in humans"

- Requirement of (i) peer-reviewed publications from (ii) at least two groups believed to reduce the impact of aberrant PT reading standards (e.g., false-positive results)
- The low minimum number required has to be related to the fact that many substances have yet been rarely tested
- . . . and also to the fact that only a fraction of all positive test results are published at all,
- . . . and also to the fact that only a fraction of patients with skin reactions to a cosmetic products seeks dermatological care
- Additional criteria (number and time trend of published cases) considered for suggested measures beyond labelling

Thank you for your attention!