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Review

Criteria for the evidence-based categorisation of skin sensitisers

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1. Introduction

The question whether a substance is a skin sensitiser (a contact allergen) (Johansen et al., 2011) and thus poses a risk to humans, and to what extent, is decided by hazard identification and risk assessment. The outcome of this is relevant for a number of regulatory issues, i.e., risk management. One basic step in risk management relies on exposure information such as *ingredient*

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labelling: the consumer or user of a product needs to be aware of the presence of a certain substance because it is possible that this substance may negatively affect health – in this case in terms of either inducing contact allergy or eliciting allergic contact dermatitis (the clinical disease) in those already sensitised.

Full ingredient information is hitherto not mandatory for any type of consumer or occupationally-used product, although in the EU cosmetic products come close to this ideal in terms of compulsory labelling of all ingredients (except for the majority of fragrance substances) using the International Nomenclature of Cosmetic Ingredients (INCI, http://ec.europa.eu/growth/tools-databases/cosing/, last accessed 21 November 2016). Until full ingredient information for all products is eventually achieved, science-based criteria are needed for the identification of those substances which, due to a documented skin sensitisation hazard, should be listed in/on those products containing them. From this background, an *ad hoc* expert group constituted by the European Commission within the Scientific Committee on Consumer Safety (SCCS) to evaluate "Fragrance Allergens in Cosmetic Products" developed a set of criteria for the grading of available information and for classification as contact allergen, which are presented here.

2. Identification and grading of evidence

In order to base decisions on the best available evidence – which may change over time with increasing knowledge and make re-assessment necessary – a structured approach of identifying, grading and aggregating available information should be used. As one of the initial steps of their work, the above-mentioned expert group reviewed existing approaches for their suitability for the task of sensitively identifying scientific hazard information.

A number of previous suggestions on the classification of substances as allergens have been made (Basketter et al., 1999; Flyvholm et al., 1996; Schnuch et al., 2002). One expert group developed a proprietary categorisation for evaluating and ranking 244 substances (Schlede et al., 2003). The categorisation of skin sensitisers according to experimentally derived sensitising potency has also been proposed (Basketter et al., 2005). The European implementation of the Global Harmonized System (GHS) is the CLP regulation EC 1272/2008, which also includes criteria for the classification and subcategorization of skin sensitisers, based on human and animal data (EC, 2011; ECHA, 2015). For the purpose of categorisation of fragrances as contact allergens, these discussions were extended to reconcile different perspectives and to arrive at a strategy that is both consistent and practically applicable (SCCS, 2012; Karlberg et al., 2013; Uter et al., 2013). Prospectively, the quality criteria outlined here can be regarded also as a guidance for the future presentation of clinical skin sensitisation data, in addition to guidelines already published [e.g., (Uter et al., 2016, 2004; Johansen et al., 2015)] as well as for the evaluation of existing scientific results, as during their initial application. The criteria presented here do not cover the classification of substances causing immunological contact urticaria, which was out of scope for the task performed, and for which separate suggestions by a WHO working group (Flyvholm et al., 1996) and by CLP (EC, 2008) (EC, 2011) exist.

2.1. Quality of evidence – general considerations

A basic requirement for a structured literature search for relevant information is an appropriate and sensitive search strategy which should be outlined in the review of the substance for classification. Adherence to procedures of data extraction used in the preparation of a Cochrane Systematic Review are considered optimal (http://handbook.cochrane.org/ last accessed 23 September 2016). The CAS number is the most suitable single identifier of a substance; its use in scientific papers, to aid indexing in bibliographic repositories and retrieval by researchers, should be encouraged. However, it has to be noted that, for historical reasons, more than one CAS number may exist for the same substance or natural mixture. Hence, all possibly relevant CAS numbers must be included in the search. To increase sensitivity of the search, not only the preferred chemical name, but also variants and synonyms or other names of the substance, or even trade name(s) – although the use of the latter should be discouraged in scientific papers – should be integrated into the search strategy. As important resources, Medline®, Embase®, Web of Science™ and other comprehensive databases should be consulted. In general, scientific reviews, letters to the editors without data presentation or duplicate publications should be excluded, except possibly for the discussion of the classification result. The observational unit of a systematic review is clearly a study, and not a publication: Occasionally there may be several publications providing important observations based on a single study, which thus all need to be considered, but avoiding numerical multiplication (Huston and Moher, 1996).

However, particularly regarding experimental studies, important data may not be publicly available. If the evaluation process is set within a legal framework, such a framework should enable provision of relevant results from the files of industry or contract research institutes (so-called 'grey material' is required, for example by the SCCS when assessing the safety of cosmetic ingredients). Even greater transparency of the evaluation process could indeed be achieved if such material is made publicly available.

Assembled evidence has to be graded in two steps: (i) the quality of each single study, and (ii) the strength of evidence underlying the eventual classification as an allergen. Generally, studies (published or not) which are eligible for consideration will contribute to the final overall judgement to different degrees.

- Positive human data, if sufficiently demonstrated (see below), will always overrule negative experimental (animal or *in vitro)* or *in silico* data of similar internal validity, as they provide direct evidence on sensitisation risk in humans.
- Small study groups will contribute less precise information than larger studies of otherwise similar quality. Effect estimates such as proportions of sensitised animals or individuals, or stimulation indices for dose groups and other derivations should ideally be accompanied by an interval estimate (confidence interval) to address precision. As a minimum requirement, the size of the study groups and the numbers of events must be given in the report.

The following subsections will address special aspects of human, animal and other studies, respectively.

2.2. Quality of human (clinical) evidence

Two major types of clinical studies must be distinguished because they provide a different scope of human evidence (Uter et al., 2016):

- Case reports or small case series, focusing on patients with positive (test) reactions to the target substance, sometimes including a set of non-exposed, possibly non-diseased "control patients"; these should present a concise summary of relevant aspects of the patient's history, diagnostic procedures and possibly further outcomes.
- Clinical series in which results of a potentially large group of patients patch tested with the target substance, often