



Review

Criteria for the evidence-based categorisation of skin sensitisers



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Contents

1. Introduction	14
2. Identification and grading of evidence	15
2.1. Quality of evidence – general considerations	15
2.2. Quality of human (clinical) evidence	15
2.3. Quality of an animal study	16
2.4. Quality of alternative methods to <i>in vivo</i> tests	16
2.5. Quality of 'other' evidence	16
3. Aggregating evidence for a final conclusion	17
3.1. Established contact allergen in humans	17
3.2. Established contact allergen according to non-human evidence	18
3.3. Likely contact allergen, if human, animal and other evidence is considered	18
3.4. Possible contact allergen, if human, animal and other evidence is considered	18
3.5. "Non-classifiable"	18
4. Discussion	18
5. Conclusion	20
Conflict of interests	20
Acknowledgements	20
Supplementary data	20
References	20

1. Introduction

The question whether a substance is a skin sensitizer (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

concomitantly with other substances, are presented. In this type of report, usually only a minority of patients tested show a positive reaction to the test substance. This implies that the majority of patients can be used to illustrate the proportion of irritant, doubtful and negative reactions obtained with the allergen preparation used (concentration and vehicle). This information aids judgement on the appropriateness of the same allergen preparation as used in single cases. The degree of detail on the patients' histories is usually limited in such clinical epidemiological studies, compared to case reports.

Moreover, epidemiological studies of the general population or defined, e.g., occupational subgroups thereof may provide evidence on the prevalence or incidence of skin sensitisation, and on risk factors associated with sensitisation.

Some of the basic quality criteria which should be considered are tabulated below. Some of the quality criteria are more applicable to case reports, whereas others are more applicable to larger clinical series (Uter et al., 2016), which is specifically mentioned.

- Adherence to international patch test guidelines (Johansen et al., 2015).
- Material(s) tested should be characterised.
- Total number of patients tested (in case reports: the number and reactions of non-exposed and/or non-diseased controls possibly tested) must be given.
- Selection in terms of patch testing patients consecutively or in an aimed fashion, or selection of individuals in epidemiological studies, and the test period should be mentioned in clinical series and epidemiological studies, respectively.
- The grading of patch test reactions, including the proportions of doubtful or irritant reactions and the distribution of the strength of positive reactions (+, ++ and +++) should be given (Brasch and Fartasch, 2009; Johansen et al., 2015) in clinical series.
- 'Clinical relevance' means the finding on an individual level that an allergen had certainly, probably, or possibly, caused allergic contact dermatitis either in terms of the current episode, or a previous episode of allergic contact dermatitis (Johansen et al., 2015). In case reports, clinical relevance is, or should, always be evident. In clinical series, 'relevance' may be given on an aggregate level and may be derived from the epidemiological analysis of patch test data in terms of significant associations found to certain clinical or demographic factors, including age, sex, occupation, causative product types, etc. In general, relevance data may be of value to determine (currently) relevant exposures causing allergy, but is not crucial for a quality evaluation of patch test data except for single cases.
- Given a clear history of elicitation and proven contact with the substance later diagnosed as sensitiser which is typical for case histories, use-related tests [Repeated Open Application Test (ROAT), Provocative Use Test (PUT)] following the patch test are not deemed necessary to establish causality.

2.3. Quality of an animal study

International guidelines such as the pertinent OECD guidelines for testing sensitisation in animal experiments have been developed and adopted (OECD 406: guinea pig maximisation/ Buehler test; OECD 429: murine local lymph node assay; OECD 442A: Skin Sensitisation: Local Lymph Node Assay: DA; OECD 442B: Skin Sensitisation: Local Lymph Node Assay: BrdU-ELISA). Experimental studies following these guidelines are considered as valid. However, a vast number of non-guideline (unvalidated) studies are available and should be assessed on a case-by-case basis, trying to

integrate information from possibly several such studies of possibly limited validity (Schnuch et al., 2002).

Some of the basic quality criteria, general and test method specific, that should be considered are mentioned below, focusing on some key issues where deviations from guidelines are often noted SCCP/0919/05, (Uter et al., 2013).

- General: The test report must include information on vehicle and concentrations, number of animals per dose group, results, etc. according to the guideline (OECD 406, 429, 442A, 442B). It is mandatory to perform pilot studies for setting concentrations and vehicles, and to use vehicle-exposed control animals. Rationales for using a test method or vehicle other than those recommended must be given.
- LLNA specific: The dose interval shall be sufficiently broad to enable the calculation of a possible EC3 value. EC3 values shall be given as %; it has been suggested that also molar EC3 values ($\mu\text{g}/\text{cm}^2$) shall be given (Lidén et al., 2016). The lowest EC3 value should be used if there is more than one study fulfilling the OECD guideline requirements. It is not acceptable to present EC3 values as mean values. Differences in the EC3 values can be obtained for the same substance, depending on which vehicle is used.
- GPMT specific: The concentration for induction should be well-tolerated systemically and be the highest to cause mild-to-moderate skin irritation, and the concentration for challenge should be the highest non-irritant dose.

2.4. Quality of alternative methods to *in vivo* tests

At the time of writing, three OECD guidelines on alternative methods to *in vivo* tests for sensitisation potential have been adopted. These include (i) OECD 442C [Direct Peptide Reactivity Assay (DPRA)], (ii) OECD 442D [ARE-Nrf2 Luciferase Test Method, e.g., KeratinoSens™] and, (iii) OECD 442E 2012 [human Cell Line Activation Test (h-CLAT)]. These tests are intended to replace *in vivo* experiments to determine whether or not a substance is a sensitiser, and these methods should to be regarded as valid(ated) – albeit purely qualitative – evidence similar to animal experiments. It should be noted, however, that the LLNA OECD 429 contributes quantitative information on sensitisation potency and thus important information for subcategorization of skin sensitisers, required by CLP and GHS, which cannot yet be provided by the alternative methods mentioned. Presently, a guidance (REACH Guidance R7a) on how to combine results with several *in vitro/in chemico* tests to achieve optimum predictive accuracy is under revision. However, when carried out according to OECD guidelines, these methods are fully validated to detect if a substance should be regarded as a skin sensitiser.

2.5. Quality of 'other' evidence

Supporting evidence besides human, animal, *in vitro* and *in chemico* experiments, includes structure activity relationships (SARs). SAR analysis has at present no formal regulatory validation for skin sensitisation, nevertheless it may provide useful indicative information on sensitising potential when no or limited clinical or animal data are available. SAR studies must consider a possible formation of haptens (allergens) from compounds able to act as prehapten by, e.g. autooxidation outside the body as well as metabolic activation in the skin of compounds able to act as pro-haptens (Karlberg et al., 2013, 2008; Lepoittevin, 2006).

3. Aggregating evidence for a final conclusion

Ideally, information from single studies should be extracted into a structured, e.g., tabular format, along the lines of the proposal of the Cochrane Collaboration (<http://handbook.cochrane.org/> last accessed 23 September 2016), with added special information referring to the above mentioned criteria and a conclusion regarding the strength of evidence provided by each study.

The criteria listed below are followed as a flow chart (Fig. 1) to arrive at a conclusion. This implies that once classification into one category is achieved, subsequent categories need not be considered.

3.1. Established contact allergen in humans

Allergens falling in this category are capable of causing “more than isolated cases of allergic contact reactions” and thus would qualify as “significant contact allergen” according to the WHO classification (Flyvholm et al., 1996). It must be stressed that this definition refers to risk only in qualitative terms (Basketter et al., 1999). ‘Qualitative’ thus means that some hazard and sufficient exposure have combined and indicate that risk exists after human exposure. In principle, the same number of sensitised cases could be due to a very confined exposure to a potent allergen, or to broad exposure to a weak allergen.

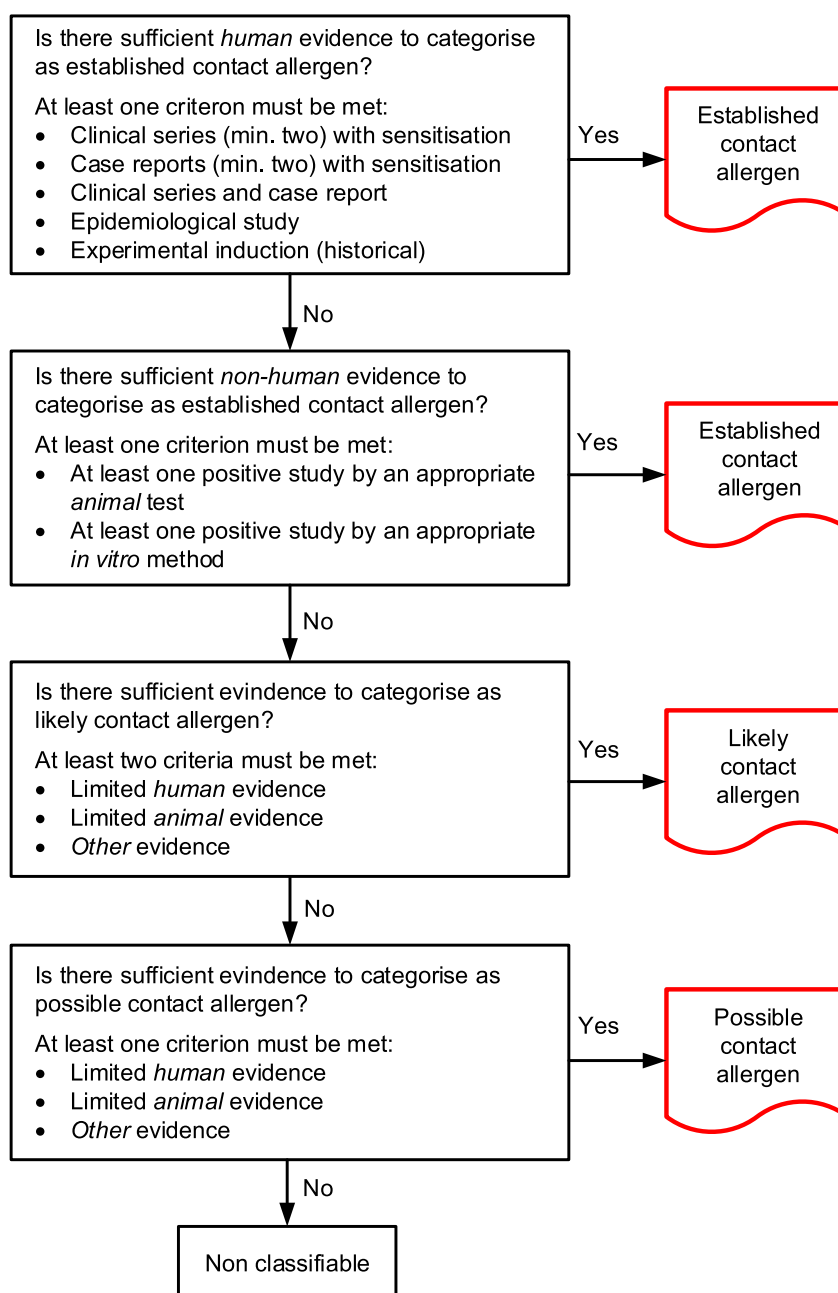


Fig. 1. Decision logic for categorisation of substances as established, likely, and possible contact allergens. Largely as applied in the SCCS opinion on fragrance substances (SCCS, 2012). The criteria are further explained in Section 3.

Moreover, the definition of an ‘established’ contact allergen per se does not utilise information on negative test results, i.e., does not consider relative frequency – that is, a certain number of cases in a clinical series may have been observed in a (few) hundred, or several thousand patients, or, in the extreme, just two or more case series (see below). Notwithstanding these limitations, a contact allergen eliciting many positive patch test reactions will appear a more significant threat for the health of the exposed population than an allergen causing just “more than isolated cases”.

Thus, although based on quantity to some extent, the “established contact allergen” is primarily a qualitative concept. Additional information on the frequency of skin sensitisation – which will also very much depend on the extent of patch testing the respective substance – and, if possible, exposure, is needed for decisions on targeting research and prevention, as appropriate.

To qualify as an *established contact allergen*, we consider that at least one of the following criteria must be met:

- At least two clinical series fulfilling the quality criteria from two different centres with cases of sensitisation, or at least three separate clinical series from different centres if a study, or studies, do not meet all quality criteria. (→ *sufficient human evidence present*)
or
- Case reports from at least two independent centres describing more than two patients altogether in whom clinically relevant skin sensitisation had unequivocally been proven (→ *sufficient human evidence present*)
or
- At least one clinical series fulfilling the quality criteria, together with at least one case report of clinically relevant skin sensitisation (→ *sufficient human evidence present*);
or
- Epidemiological study among an occupationally exposed group, another selected group, or a general population sample with cases of sensitisation (→ *sufficient human evidence present*)
or
- Experimentally induced sensitisation (e.g. unequivocally positive human maximisation tests/repeated insult patch test) (→ *sufficient human evidence present*). Such tests are considered unethical to perform (SCCP, 2000) and only of historical relevance. New studies for this regulation are not permitted; however, existing historical evidence may be used (ECHA, 2015).

3.2. Established contact allergen according to non-human evidence

To qualify as an *established contact allergen*, at least one of the following criteria must be met:

- At least one positive result in an animal study carried out according to accepted guidelines, or in another appropriate animal test, evaluated on a case-by-case basis, providing unequivocal evidence of a sensitisation potential (→ *sufficient animal evidence present*)
or
- At least one positive study by an appropriate *in vitro* method (→ *sufficient in vitro evidence present*)

3.3. Likely contact allergen, if human, animal and other evidence is considered

To qualify as a *likely contact allergen*, if classification as “established ...” is not applicable, at least two of the following criteria

must be met:

- Individual cases of allergic patch test reactions not fulfilling the requirements for sufficient evidence (→ *limited human evidence present*)
or
- A positive result in at least one non-guideline animal study, which should be evaluated on a case-by-case basis (→ *limited animal evidence present*)
or
- Other evidence, e.g. results from non-guideline alternative tests or from structure-activity considerations based on sufficiently valid results for closely related compounds (→ *other evidence present*).

3.4. Possible contact allergen, if human, animal and other evidence is considered

To qualify as a *possible contact allergen*, if classification as “established ...” or as “likely ...” contact allergen is not applicable, at least one of the following criteria must be met:

- Individual cases of allergic patch test reactions not fulfilling the requirements for sufficient evidence (→ *limited human evidence present*)
or
- A positive result in at least one non-guideline animal study, which should be evaluated on a case-by-case basis (→ *limited animal evidence present*)

3.5. “Non-classifiable”

If a substance cannot be classified into the categories mentioned above, it is generally termed “non-classifiable”. This may be owing to lack of studies, or insufficient quality of studies, and cannot be interpreted as providing evidence for the substance being a “non-sensitizer”.

4. Discussion

The classification of substances regarding hazard and risk of inducing contact allergy and eliciting allergic contact dermatitis, respectively, is an important issue for scientists and regulatory institutions dealing with consumer or work-related safety and health world-wide. Thus, a number of suggestions and formal regulations, respectively, have been published. These are summarised in Fig. 2, including the approach used in the SCCS opinion SCCS/1459/11, which is based mainly on the WHO working group approach and the criteria used in the initial version of CLP. All use the same basic elements, with the same definitions of positive human and animal results.

In the SCCS opinion, we tried to support the practical application of the grading and decision process by supplying a set of definitions and algorithms for classification and categorisation of substances (Fig. 1). The consideration of the quality, particularly of the human studies (Schnuch et al., 2002; Uter et al., 2016), contributing to the eventual classification is stressed. Quantitative requirements (number of studies) were also used for assigning substances into different categories (established, likely, and possible contact allergen). The number of published cases (more or less than 100) were also used for categorisation into substances of special concern.

The CLP regulation EC 1272/2008 is based on hazard

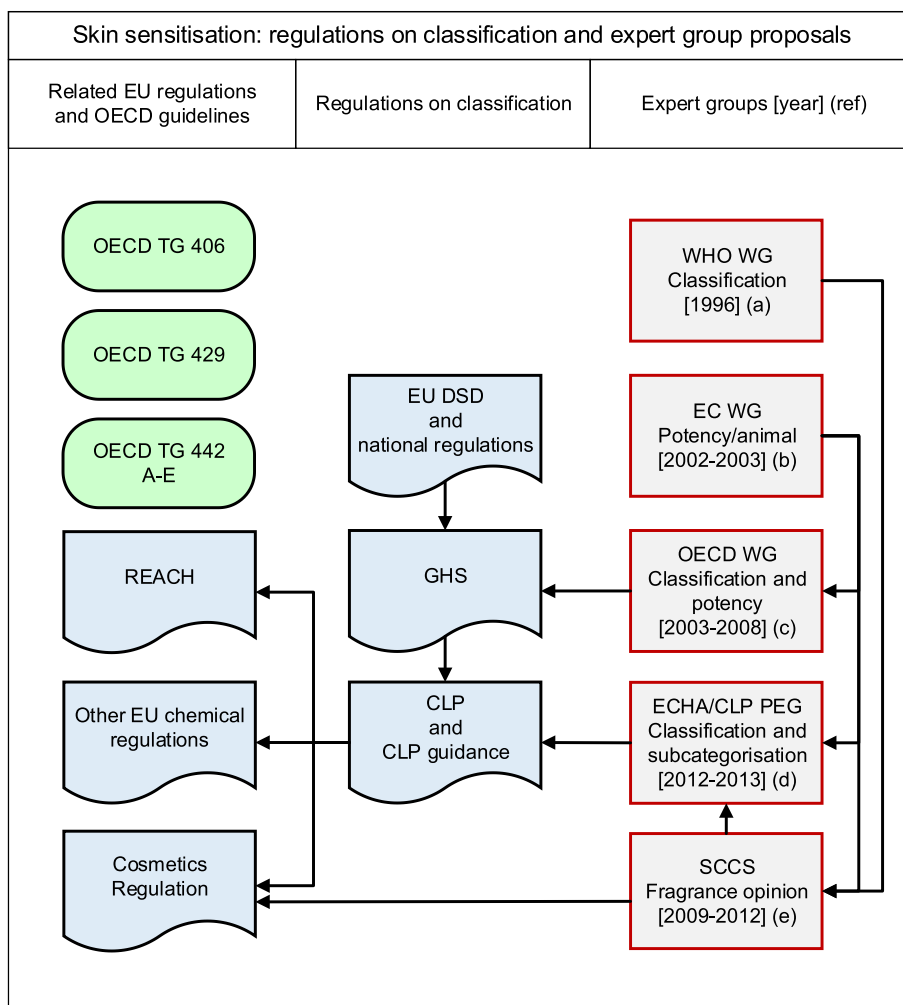


Fig. 2. Overview on regulations, guidelines, and expert groups on skin sensitisation and classification. Arrows indicate influence. References: (a) Flyvholm et al., 1996; (b) Basketter et al., 2005; (c) ECHA, 2015; (d) GHS rev. 6, 2015 (amendments on skin sensitizers were introduced in GHS rev. 2, 2007 and rev. 3, 2009); (e) SCCS, 2012.

identification and potency and CLP is using the same type of human and animal data as the SCCS opinion. It has been amended several times since initial publication and is currently the binding standard for classification of skin sensitizers and shall be applied within REACH and other EU legislations on chemicals. CLP also defines qualitative and quantitative criteria for human and animal studies for classification. Minimum numbers of human studies or of sensitised individuals are not specified, but is explained as “normally obtained in more than one dermatology clinic” and “sensitisation ... in a substantial number of persons”. CLP now includes a distinction between classified skin sensitizers according to their sensitisation potency; strong (subcategory 1A) and other (subcategory 1B). To this end, the CLP guidance on application of the criteria for classification describes how estimation of potency shall be done, based on human experience and animal data; it also describes the labelling requirements for 1A versus 1B. When human and animal data show conflicting results, a weight of evidence approach should be used; however, negative human data should not normally negate positive animal results (ECHA, 2015).

While CLP and associated guidance documents do offer a valid starting point for classification of skin sensitizers, a number of further improvements is suggested, based on our experience and driven by the availability of alternative methods for assessing skin sensitisation hazard, namely, the validated OECD guidelines (OECD

442C, 442D, 442E):

- Positive results of alternative methods carried out according to accepted guidelines, providing unequivocal evidence of a sensitising potential of the substance, would lead to the conclusion that sufficient alternative evidence is present. Therefore, they are fully equivalent to guideline animal studies for hazard identification.
- Potency information is crucial for CLP subclassification to 1A vs. 1B. Often, however, human and animal evidence will be lacking, like regularly in case of new substances. In this case, subcategory 1A after hazard identification by alternative methods is suggested. If 1B is strived for, animal tests need to be performed to estimate potency.
- Quality standards and conventions under 2.3 should be applied to animal data, which should be explained in guidance documents.
- Clinical (human) dose-response data, from repeated open or patch test testing in sensitised patients, show that the elicitation threshold generally is very low. The current limits for label information (EUH208) are thus not sufficiently low to protect sensitised individuals. The most reasonable and pragmatic approach, until all ingredients need to be identified, would be that all classified skin sensitizers (H317) shall be identified by

name on the label, regardless of concentration. This is already required for all cosmetic ingredients except for fragrance substances (Cosmetics Regulation), for preservatives in detergents (Detergents Regulation), for chromium (VI) (EUH203), and for isocyanates (EUH204)

- If human data are lacking, animal-derived potency information is a prerequisite not only for adequate classification as 1A vs. 1B (see above), but also for an initially establishing above-mentioned thresholds. This stresses the necessity of obtaining quantitative animal data once alternative methods have identified sensitisation hazard.

5. Conclusion

In conclusion, SCCS opinion SCCS/1459/11, which is based mainly on the WHO working group approach and the criteria used in the initial version of CLP all use the same basic elements, with the same definitions of positive human and animal results. Also the total number of published cases of contact allergy to a substance is criterion in the subcategorization in both sets of criteria. However, CLP has more open definitions, and, moreover, qualitative and quantitative criteria. CLP requires potency assessment which is the basis for downstream consequences. The fragrance opinion model is categorising according to strength of evidence based on the number of studies.

The context of use for these two sets of criteria is different:

- The fragrance opinion criteria are developed for application to cosmetic products covered by the current Cosmetics Regulation which is based on risk assessment, where full ingredient labelling is a requirement for all ingredients except fragrances. Most cosmetics are used intendedly on skin or hair and are supposed to be safe for the consumer.
- The CLP regulation is based on identification of hazard and potency of chemicals. The intention is to ensure that the hazards are communicated to workers and consumers through classification and labelling. One of the main targets for the CLP are products used occupationally. In such scenarios providing information about hazards and how to protect oneself from exposures shall be provided on labels, and further information to users, except consumers, shall be given in safety data sheets is the basic philosophy. This explains the differences in use of data between the two systems. A more potent allergen will trigger warnings and labelling at lower concentrations than in case of a less potent allergen in the CLP.
- However, as even very low concentrations of contact allergens may elicit an allergic reaction it is suggested that all classified allergens, in cosmetics, consumer or occupational products, would be labelled as ingredients irrespective of the concentration in these products.

We would expect that the evaluation process of skin sensitising potential cannot be implemented on a purely administrative level, but needs joint specific expertise in the field of clinical and experimental contact allergy and specific chemistry, i.e., an independent expert panel, with all conflicts of interests duly and publicly declared, such as the SCCS (https://ec.europa.eu/health/scientific_committees/consumer_safety_en, last accessed 11 March 2017) and its *ad hoc* working groups, or, in the realm of occupational exposure, the German MAK commission (www.dfg.de/mak, last accessed 11 March 2017). As resources are limited, the set of substances to be evaluated must be carefully selected, e.g., based on (i) clinical alerts, (ii) experimental data, (iii) structural

alerts and (iv) exposure information.

Conflict of interests

All authors of the present submission, except Prof. J.-P. Lepoittevin, were part of the SCCS working group on 'fragrance allergens in cosmetic products' (see http://ec.europa.eu/health/sites/health/files/scientific_committees/consumer_safety/docs/sccs_o_102.pdf).

The SCCS has members who are independent. As well as working under the remit of transparency and excellence, there is an annual declaration of interests (actual or perceived) published on the EU website. The authors (except Prof. J.-P. Lepoittevin) have been involved with SCCS deliberations but this is within the theme of independence stated above.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.fct.2017.03.031>.

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