

Review Article

Classification criteria for skin-sensitizing chemicals: a commentary

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A formalized, standardized and effective mechanism for the identification of substances which possess significant skin sensitization potential is a necessary first step in the process of limiting the incidence of allergic contact dermatitis. Strategies to achieve such hazard identification are unified throughout the European Union and also have been publicised by the World Health Organization. Global harmonization of these and other approaches (e.g., in the USA) is being driven by the Organization for Economic Cooperation and Development. In this paper, the benefits and limitations of these classification systems are reviewed. A common element of all the systems is that they seek to distinguish important contact allergens from chemicals which are infrequent sensitizers. The European criteria are legal requirements in the EU member states and formal classification as a skin sensitizer leads to mandatory labelling. The most notable omission from current and proposed classification criteria relates to the relative potency of a classified skin sensitizer and the exposure dose. Such information is necessary for proper risk assessment and management measures to be implemented.

Key words: contact allergy; allergic contact dermatitis; classification criteria; legislation; European Union; World Health Organization; Organization for Economic Cooperation and Development; skin sensitization. © Munksgaard, 1999.

Accepted for publication 6 October 1998

The Aim of Classification

The classification of substances and preparations (mixtures of 2 or more substances) in terms of their hazardous properties represents the essential first step in risk assessment/management, whether it is for the protection of the general public or to promote occupational health. However, in the context of health protection, valuable and meaningful consequences can only be implemented when this abstract information on intrinsic properties is put into proper perspective and so interpreted into practical action(s) of relevance to the real world. These actions necessarily involve risk assessment – it is rarely possible absolutely to exclude hazards – and risk management, which includes important elements of risk communication. In terms of skin sensitization, this means that criteria should enable the identification, in a formal and systematic

manner, of substances/preparations with significant skin sensitization potential. Additionally, the criteria must incorporate a means to judge the potency of the sensitizing hazard, if it is present. Only if this latter information is available is it possible to make a risk assessment.

European Classification Criteria

European criteria for the classification of skin sensitizers are reproduced in Appendix 1 (1); a simplified presentation is given in Table 1. They are legal requirements within all member countries of the European Union (EU). The essential aim of these criteria is to permit the identification of chemical substances with a significant ability to cause skin sensitization. So, substances which cause more than a low reaction rate in predictive guinea pig tests would be regarded as positive and

Table 1. Simplified EU classification criteria for skin sensitization

For a substance which does classify:	For a substance which does not classify*:
Guinea pig maximization test result $\geq 30\%$ positive	Animal test data may be positive but below the defined thresholds
Buehler test $\geq 15\%$ positive	Positive data is from non-standard methods
Local lymph node assay positive	Structure-activity relationships indicate a concern
Positive data from human experiments	Substantial negative human experimental data exists
Positive patch test data from at least 2 sources	Isolated episodes of allergic contact dermatitis

*Classification as a skin sensitizer may be made if sufficient evidence arises via a combination of positive effects that individually are insufficient.

would be classified and labelled R43 according to the Dangerous Substances Directive (DSD) (2). A major problem here is that the predictive tests used vary widely in sensitivity between laboratories (3–5). Consequently, it may be very difficult to judge whether a test has been well conducted; false negatives are an issue of technical aspects of test conduct more than of interspecies variability between guinea pig and man. On the other hand, examples of over-prediction by the guinea pig maximization test do exist (6, 7), which serves further to complicate use of this test for classification purposes.

For these and other reasons, human data is also used to determine whether a substance meets the European Commission (EC) criteria for classification. Guidance is given on what data is to be regarded as acceptable, but problems can still arise. What is “a substantial number of persons”? What is “appropriate patch testing”? Experience with EC classification shows that these issues have to be determined on a case by case basis, but this does permit opportunities for anomalies to occur. In addition, no guidance is given as to what type of data will not lead to classification. This may be rather important, since the aim of EC classification is not to award an R43 to every substance that has ever caused skin sensitization in man, but rather to identify the more important skin sensitizers which should be subject to suitable regulatory measures.

When a substance is classified according to these EC criteria, then not only is it labelled as a skin sensitizer, it also has a threshold limit set, for which the default value is 1%. The consequence of this limit is then seen in the Dangerous Preparations Directive (DPD), which requires that preparations (i.e., mixtures of 2 or more substances) are also given R43 and the warning label “May cause sensitisation by skin contact” if the preparation contains a skin sensitizer at, or above, the threshold level (8). Unfortunately, this approach is flawed in 2 important ways. Firstly, unless the threshold limit is set on the basis of a proper understanding of the potency of the sensitizer, the value may be too low

(not a common occurrence), or of more concern may be too high because the sensitizer is actually rather potent. Currently there is no adequately defined or systematic basis for altering the 1% default value to take into account the relative potency of the sensitizer, with the consequence that most commonly the default option is taken. The second important flaw is that the approach taken by the DPD fails to take into any account the exposure which will result from the preparation. There are many variables here, both from a formulation perspective and from the method of use of the preparation, which will impact upon the actual dose of the sensitizer, which contacts the skin. As with other aspects of toxicology, it is the dose which matters, not the product concentration.

WHO Classification Criteria

The World Health Organization (WHO) criteria for classification of skin and airway sensitizing substances in the work and general environments were drawn up by a WHO Working Group, which consisted of experts in dermatology and pulmonology as well as experimental biology and toxicology. The WHO criteria for the classification of skin sensitizers are reproduced verbatim in Appendix 2 (9).

The WHO criteria focused on the weight of evidence and was originally based on a Nordic proposal inspired by the classification of carcinogens, which only include epidemiological studies as sufficient human evidence (10). The WHO criteria regard as equivalent epidemiological studies and “well conducted” studies in consecutive skin tested patients (i.e., formalize the use of clinical data for classification). In contrast to the EC criteria, the WHO criteria include guidance on both acceptable studies and on conditions for identification of skin sensitizers by clinical evaluation combined with skin tests. Both the demands for acceptable studies and for identification of skin sensitizers take in the association between exposure and clinical dermatitis. Also, demands for the use of animal evidence

are defined with reference to the methods recommended in the Organization for Economic Cooperation and Development (OECD) guidelines (11). Potency is defined, and as well as evaluation of potency taking exposure into consideration, which represents a 1st real step forward in classification criteria.

Although representing some progress compared to the EC criteria, a major obstacle relating to the WHO criteria is the lack of formal use and implementation by the WHO member states.

OECD Harmonization Proposals

The OECD has been involved in a long and detailed process of consultation in an effort to set in place globally harmonized criteria for classification. The existing EC and WHO criteria have had a substantial impact on shaping the proposals, which are now in their final draft form. The most worrying aspect is that in the effort to attain harmonization (a major struggle in itself) no progress has been made in dealing with the problems inherent in the existing criteria. The current proposals are very similar to those of the EC (12).

Significance of Exposure and Elimination of Contact Allergens

Experimental studies

The balance between the significance of genetic and exposure factors in allergic contact dermatitis has attracted relatively little attention (13). However, studies have illustrated some limited impact of genetic factors, but most important for the induction and elicitation of allergic contact dermatitis is the potency of the individual hapten and the skin exposure dose (amount/cm²) (14–16). Hence the importance of proper classification and labelling.

In sensitized individuals, allergic contact sensitization can be demonstrated by controlled re-exposure to the hapten. The diagnostic patch test on the upper back (17) is an example of such standardized re-exposure. A number of studies have demonstrated a clear dose-response and defined no-effect exposure concentrations under such patch test conditions (18, 19). An exposure test more closely simulating normal use is the repeated open application test (ROAT) (20). With these tests, the effect of realistic exposure levels for a number of haptens has been demonstrated (21–23). In addition, these types

of study permit examination of the potential effects of allergens in combination (24). Neither a positive diagnostic patch test nor a positive ROAT test leaves the patients with a persistent or recurring patch of eczema in the test area. However, the skin area may have a greater propensity to react with allergic contact dermatitis in the future when re-exposed to the specific hapten, either by direct skin contact or by systemic hapten exposure (25).

Based on experimental evidence, it can be concluded that exposure to a hapten exceeding a certain threshold concentration in a naive individual may lead to skin sensitization, whilst in an already-sensitized individual it creates the skin disease of (allergic contact) dermatitis (eczema). Subsequent elimination of exposure to the substance normally leads to spontaneous clearance of the disease, but in certain skin areas, e.g., the hands, the eczema may be chronic. Furthermore, the skin may be left in a condition, where, in comparison with earlier non-exposed skin, it will react to lower concentrations of the hapten if re-exposed.

Clinical studies

In the clinical situation, the induction and elicitation of allergic contact dermatitis typically is a consequence of repeated exposures from consumer products, topical medicaments and occupational exposures. The relation between exposure and effect can be overt or may be difficult to establish. Particularly in patients with chronic eczema, e.g., on the hands, face or lower leg, where multiple allergies and complex exposures are common, the effect of the individual haptens and products can be difficult to establish.

A number of examples exist where there is a simple relation between exposure and elimination of haptens having the consequences of dermatitis and clearance of the dermatitis during elimination of exposure. Such clear examples exist within cosmetic products (fine fragrances, deodorants), metal contact dermatitis (nickel), medicament dermatitis and plants (poison ivy and primula) (26).

The effect of exposure/elimination can be illustrated in epidemiological studies including construction workers exposed to hexavalent chromate in wet cement. The effect of exposure to hexavalent chromate in construction workers has been illustrated in a recent German study (27). Among 205 construction workers, 31.9% were chromate sensitized compared to 7.1% among 5706 workers from other branches. The elimination (decrease) of hexavalent chromate in cement in Denmark led to a decrease in the prevalence of chromate sensitiza-

tion among construction workers from 8.9% to 1.3% (28).

The effect of exposure to fine fragrances in perfume-allergic individuals has been illustrated in another epidemiological design (29). Consecutive patients with chronic dermatitis were interviewed, prior to patch testing, with respect to their experience of adverse effects from domestic and occupational exposures. Among those with a positive patch test to the fragrance mix, 62.8% gave a history of having had dermatitis in relation to the use of fine fragrances compared to 40.8% among those with a negative patch test. The long-term prognosis in fragrance sensitized individuals has not been determined, but the clinical impression is that the elimination of fragrance exposure, typically from a deodorant or a fine fragrance, leads to disappearance of the dermatitis.

How large a proportion of those at risk that develop chronic dermatitis is not well examined. In Denmark, with a population of approximately 5 million inhabitants, approximately 700,000 have a contact allergy to 1 or more environmental chemicals (30). Approximately 25,000 Danes yearly develop eczema of sufficient severity that a dermatologist finds diagnostic patch testing to be indicated. In 30%-50%, a positive patch test is found which explains (is relevant to) the current eczema.

The effect of elimination of allergens in patients with chronic eczema and contact allergy to ubiquitous haptens is more difficult to establish. This is not surprising, as chronic eczema typically is the effect of combined exposure of multiple allergens and irritants. Notwithstanding these difficulties, the effect of elimination of formaldehyde in formaldehyde-sensitive individuals repeatedly has been established to be effective (31-33).

Practical implications of classification and labelling

Classification and labelling are the basic requirements in prevention of the skin disease allergic contact dermatitis. Classification of allergens is aimed at primary prevention, that means the induction of contact allergy, either by general regulatory means or by demanding specific personal protection or education for those handling specific substances. For example, hexavalent chromate is classified as a significant contact allergen. This has led to a regulation of the content of hexavalent chromate in wet cement in the Scandinavian countries. The consequence has been a near disappearance of chromate allergy

among Scandinavian construction workers (34). Where contact may not be adequately avoided, other tactics can be employed. So, for those who have occupational contact with epoxy resins, an obligatory education has been demanded in Denmark since the 1970s (35).

Labelling of contact allergens can also assist with secondary prevention. That is to say, as information to those already contact sensitized and as a valuable help to those dermatologists who care for patients with contact dermatitis problems. The labelling of cosmetics from 1 January 1998 has been seen as a major advantage by both patients and their doctors. Labelling of industrially used products is imperfect. Ingredients are labelled when present at a threshold value or higher concentration, according to the limit set by the DSD. Often a default value of 1% is taken. However, this then fails to take into account the widely varying potencies possessed by skin sensitizers (see above). Thus the need for revision of this legislation is obvious.

Conclusions and Recommendations

Currently, the criteria for the classification of skin sensitizers will do very little to promote public health by reducing the general burden of allergic contact dermatitis. To be of greater value, the criteria for the classification and labelling of skin sensitizers should include elements of potency and, where appropriate, exposure dose. This would permit proper risk assessment/management. Suggestions that would help to progress to this aim include:

1. Establishment of a systematic approach to quantitative estimation of relative skin sensitizing potency. In the use of human epidemiology data, clear differentiation of clinically frequent from strong sensitizers.
2. Strategies for quantitative risk assessment which integrate potency and exposure dose information must be established and widely disseminated. The risk assessment must consider the effects on a specific allergen of combined exposure to other allergens and/or irritants.
3. Communication of information on skin sensitizers must be based on the actual risk to man.

Appendix A. EC Criteria for the Classification of Skin Sensitisers

Sensitisation by skin contact

Substances and preparations shall be classified as sensitising and assigned the symbol "Xi", the indi-

cation of danger “Irritant”, and the risk phrase R43 in accordance with the criteria below:

R43 May cause sensitisation by skin contact

- if practical experience shows the substance or preparation to be capable of inducing sensitisation by skin contact in a substantial number of persons
- where there are positive results from an appropriate animal test

Comments regarding the use of R43

Human evidence

The following evidence (practical experience) is sufficient to classify a substance with R43:

- Positive data from appropriate patch testing, normally in more than one dermatological clinic, or
- Epidemiological studies showing allergic contact dermatitis caused by the substance. Situations in which a high proportion of those exposed exhibit characteristic symptoms are to be looked at with special concern, even if the number of cases is small, or
- Positive data from experimental studies in man. The following is sufficient to classify a substance with R43 when there is supportive evidence:
 - Isolated episodes of allergic contact dermatitis, or
 - Epidemiological studies where chance, bias or confounders have not been ruled out fully with reasonable confidence.

Supportive evidence may include:

- data from animal tests performed according to existing guidelines, with a result that does not meet the criteria given in the section on animal studies but is sufficiently close to the limit to be considered significant, or
- data from non-standard methods, or
- appropriate structure-activity relationships.

Animal studies

Positive results from appropriate animal tests are:

In the case of the adjuvant type test method for skin sensitization detailed in Annex V or in the case of other adjuvant-type test methods, a response of at least 30% of the animals is considered as positive. For any other test method a response of at least 15% of the animals is considered positive.

Immunological contact urticaria

Some substances which meet the criteria for R42 may in addition cause immunological contact urti-

caria. In these cases, information concerning contact urticaria should be included by the use of appropriate S-phrases, usually S24 and S36/37, and in the Safety Data Sheet.

For substances which produce signs of immunological contact urticaria which do not fulfil the criteria for R42, consideration should be given to classification with R43.

There is no recognised animal model available to identify substances which cause immunological contact urticaria. Therefore, classification will normally be used on human evidence which will be similar to that for skin sensitisation (R43).

Note that if the symbol “Xn” and the indication of danger “Harmful” are assigned, the symbol “Xi” and indication of danger “Irritant” are optional.

Appendix B. WHO Criteria for Classification of Skin Sensitizers

The identification and classification of significant skin sensitizers

Specific definitions

Skin sensitization: the induction of specialized immunological memory in an individual by exposure to an allergen.

Significant skin sensitizers are that group of substances or preparations which are (presumed) capable of causing more than isolated cases of allergic contact reactions.

Methods

Clinical methods

The most important method used to identify skin sensitizers is clinical evaluation coupled with skin tests. Key details of these skin tests are presented below. Thus substances which can cause allergic contact dermatitis are defined by satisfying conditions 1–4 and preferably number 5:

1. The substance has caused dermatitis in at least one exposed person (i.e. there has been recent relevant exposure to the substance).
2. This exposed person or persons with contact dermatitis has a clear positive patch test with the well defined substance.
3. A patch test carried out when the contact dermatitis has subsided shows a positive result.
4. The chemical substance does not cause irritant reactions when tested in an appropriate number of controls. Bioavailable quantities relevant to patch concentrations should be used.
5. Patch tests with serial dilutions of the compound have shown a dose-response relationship to a degree normally found in contact allergy.

Ideally the requirement should be that the dermatitis disappears when exposure ceases. Experience has however shown that hand eczema does not always completely clear up in spite of cessation of exposure. Predictive human sensitization tests are available to evaluate sensitizing potential of substances.

Substances which can cause allergic contact urticaria should meet the following conditions:

1. The well defined chemical substance has caused allergic contact urticaria in at least one person exposed to the substance.
2. The exposed person with allergic contact urticaria has a positive skin prick test or shows allergic contact urticaria in a provocative use test and has elevated specific serum IgE antibodies.

The substance does not cause positive responses in an appropriate number of controls.

Epidemiology

To estimate the quantitative impact of contact allergens, epidemiological studies in the general population and in defined subpopulations as well as clinical studies are indicated. As an instrument for continuous monitoring of allergic contact dermatitis, clinically based surveillance scheme has been set up.

Animal methods

Several animal tests have been described which identify reliably substances which can cause allergic contact dermatitis. Some animal tests require further validation. The most important of these tests are noted in OECD Guideline 406.

Other methods

Other supporting evidence can come from structure activity considerations or from in vitro methods. These have been reviewed recently.

Evidence to be used for classification

Sufficient evidence

Epidemiological studies and/or studies in consecutive skin tested patients conducted in accordance with well established principles which demonstrate an association between exposure and the clinical evaluation of dermatitis/contact urticaria, including positive skin tests. Data from more than one patient in more than one independent centre are required.

The substance is found to cause contact sensitization in at least two separate animal studies (at least one of which must be in the guinea pig). The studies shall be conducted as recommended in the OECD guidelines. The contact sensitizing capacity should be statistically significant in comparison with non-sensitized control animals.

Limited evidence

Isolated cases of allergic contact reactions demonstrated by properly conducted skin tests, in the presence of relevant exposure and in more than one independent centre.

The substance is found to have contact sensitizing ability in one OECD test method. The contact sensitizing capacity should be statistically significant in comparison with non-sensitized control animals.

Inadequate evidence

Individual cases of allergic contact reactions demonstrated by skin tests in which the requirements for limited evidence have not been satisfied.

The substance may have contact sensitizing ability in an animal model, but the test conditions employed are inadequate or not sufficiently documented.

Evidence that the substance is not a significant skin sensitizer

Many people have been extensively exposed to the substance for a long time, but contact allergy is extremely rare.

Evidence that substances do not cause contact sensitization in laboratory animals is not definitive. None of the animal models known so far can provide such general evidence.

Supporting evidence

Supporting evidence is not classified as sufficient, limited or inadequate etc. Supporting evidence may be structure-activity considerations or in vitro stimulation of lymphocytes. Information from a new experimental model will usually be regarded as supporting evidence until it has been more closely validated in relation to known methods.

Classification scheme

Based on the above evidence substances may be classified as follows:

Class	Human evidence	Animal evidence	Other evidence
I Significant contact allergen	Sufficient evidence present	Evidence may be present or absent	Evidence may be present or absent
	Limited evidence present	Sufficient evidence present	Evidence may be present or absent
II Probably a significant contact allergen	Sufficient evidence present	Inadequate evidence present	Evidence may be present or absent
	Limited evidence present	Limited evidence present	Evidence present
III Not classifiable	All other possible combinations, but see Class IV below		
IV Not a significant contact allergen	Many people have been extensively exposed to the substance for a long time, but contact allergy is extremely rare		

In the context of immunologic contact urticaria, normally only human evidence will be available for classification.

Potency evaluation of contact sensitizers

Strong sensitization potency is indicated by a high sensitization rate in an animal model, particularly when the test concentrations are low. It is also indicated by a high frequency of allergic contact dermatitis in man when exposure is low.

Moderate sensitization potency is indicated by a lower sensitization rate in animal models provided optimal test conditions have been applied and by a lower frequency of allergic contact dermatitis in exposed individuals.

Low sensitization potency is indicated by a low sensitization rate in animal models under optimal test conditions, and also by a low frequency of allergic contact dermatitis in spite of high exposure.

The clinical data must be assessed with caution in relation to potency evaluation of the compound because the data reflect other confounding factors such as the exposure situation, bioavailability, individual predisposition and the current state of preventive measures.

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