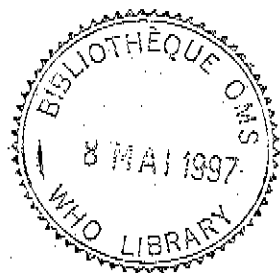




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*CRITERIA FOR
CLASSIFICATION OF
SKIN- AND AIRWAY-
SENSITIZING
SUBSTANCES IN THE
WORK AND GENERAL
ENVIRONMENTS*

Report on a WHO Working Group
Copenhagen, Denmark
17-20 January 1996

1996

EUR/HFA target 25

Target 25 - Health of People at Work

By the year 2000, the health of workers in all Member States should be improved by making work environments more healthy, reducing work-related disease and injury, and promoting the wellbeing of people at work

Summary

The gradually growing incidence of skin and airway sensitizations and hypersensitivity in Europe requires the intensification of preventive measures. The WHO Regional Office for Europe organized a meeting to review and propose criteria to classify the substances with a sensitizing potential. Experts in clinical dermatology and pulmonology, as well as experimental medical biology and toxicology, accordingly met in Copenhagen to discuss criteria proposed by the Nordic Committee on Building Regulations and other documents. The participants reached consensus on criteria to identify and classify significant skin sensitizers and substances causing specific airway hypersensitivity. In addition, the participants made recommendations on the practical use of classification in primary, secondary and tertiary prevention, and on the setting of national preventive strategies.

Keywords

HYPERSENSITIVITY
RESPIRATORY TRACT DISEASES
DERMATITIS, CONTACT
HAZARDOUS SUBSTANCES - classification
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Foreword

One of the important missions of the World Health Organization (WHO) is to support the capacity of the Member States in health policy making and to provide them with technical information necessary to implement effectively the established policy. In order to include a large range of views while preparing technical documents, international consultations are held with the participation from scientific and regulatory experts in relevant disciplines from different countries. Certainly their skilful work determines the scientific quality and practical usability of resultant documents. The activities of WHO are frequently sponsored by international and national organizations interested in diminishing health inequities and in the dissemination of recently available information on alleviation of infections or diseases.

The present Working Group on criteria for classification of skin and airway sensitizing substances in the work and general environments held in Copenhagen, Denmark, 17-20 January 1996 was organized by the WHO Office for Europe in collaboration with the National Institute of Occupational Health, Copenhagen, Denmark. The meeting was co-sponsored by the Nordic Council of Ministers (Nordic Committee of Building Regulations and Nordic Group on Working Environment Research) and the Swedish Building Research Council.

It is expected that the proposed criteria, when endorsed by national authorities, will strengthen the measures for the prevention of allergies and other hypersensitivities in the WHO European Member States and extend the harmonization of legal requirements amongst countries. It is also expected that the report will serve scientists in directing further research.

1. Introduction

Exposure to exogenous substances and preparations may result in allergy or other hypersensitivities, leading to conditions such as contact dermatitis and asthma. There are indications that these problems are of growing importance and that preventive measures should be intensified. Consequently there is a need for national authorities, health professionals and risk managers to have information on the substances with a potential for sensitization.

The WHO Regional Office for Europe in assisting national authorities in promoting human health is developing classification criteria for sensitizing substances and the International Programme on Chemical Safety (UNEP/ILO/WHO) is preparing a monograph on the scientific principles and methods for assessing allergic hypersensitivity associated with exposure to chemicals. The European Union has developed a system for classification and labelling of sensitizers based on human and animal data as well as other evidence.

Important work has been done by the Nordic Committee on Building Regulations (NKB) of the Nordic Council of Ministers, which has proposed a system for classification of sensitizing chemicals inspired by the classification of carcinogens adopted by the International Agency for Research on Cancer (IARC). This classification of carcinogens, based on weight of evidence, is as follows:

group 1	carcinogenic to humans
group 2A	probably carcinogenic to humans
group 2B	possibly carcinogenic to humans
group 3	not classifiable
group 4	probably not carcinogenic to humans

In order that national regulations and practices on the classification of substances which can cause allergy or other hypersensitivities in the skin and the airways can be comparable and provide equal levels of health protection between countries, substances suspected to be sensitizers should be classified in an uniform manner. There are great differences in the potency of sensitizing substances and also between the occurrence and quantities of the substances used. Qualitative classification should therefore be complemented by information, where available, on potency, size of exposed population, intensity of exposure and dose-response relationship.

The purpose of the present work was to review and agree the criteria for the assessment of the ability of substances to cause skin allergy or airway hypersensitivity. It is anticipated that the agreed criteria for recognition and evaluation of allergic potential of substances should permit identification and classification of sensitizers.

2. Terminology

2.1 General definitions

Atopy

A genetic predisposition to development of specific IgE antibodies against common allergens.

Hypersensitivity

Abnormally increased response to a stimulus.

Inducer

An inducer leads to the de novo generation of an altered state of reactivity to a specific substance. Alternative words are "initiator" or "cause". Induction should be distinguished from responses provoked ("elicited", "triggered") by subsequent exposures to the inducing cause or other factors.

Potency

Expression of a biological activity of a substance based on a standard or reference parameter e.g. ED₅₀.

Sensitization

Induction of specialized immunological memory in an individual by exposure to an allergen.

Specific hypersensitivity

The induction of an altered state of specific reactivity in an individual by exposure to inducing substances and preparations.

2.2 Risk assessment***Hazard***

The potential of a chemical to cause adverse health effects.

Risk

The probability of adverse health effect(s) under defined conditions of exposure.

Risk assessment

A scientific process defining the adverse health effects resulting from the exposure of individuals or populations to hazardous chemicals.

Risk assessment comprises:

- Hazard identification
- Dose-response assessment
- Exposure assessment
- Risk characterisation (estimation).

Hazard identification

The determination of whether or not a chemical is causally linked to adverse health effects. It may be based on clinical or epidemiological data, animal bioassay, *in vitro* testing, or structure-activity relationships (SAR).

Dose-response assessment

The assessment of the relationship between dose and the incidence of adverse effect(s) in an exposed population.

This is designated to establish the relationship between dose and the type, severity and incidence of adverse effects. Such information may be available from data from human studies but, more usually, is obtained from experimental animal studies. In the case of animal

studies the data must be extrapolated to humans. Extrapolation must take account of inter- and intraspecies variability and this is achieved by the use of uncertainty factors or mathematical models. For "threshold" chemicals a no observed adverse effect level (NOAEL) should be obtained, otherwise a lowest observed adverse effect level (LOAEL) has to be used.

In the case of sensitizers there is inter-individual variability in induction and in provocation of a response in sensitized subjects, with considerable variation in threshold. There is also inter-species variability involved when extrapolating from animal models. It should also be noted that studies using a range of doses/concentrations are seldom available.

Exposure assessment

Measurement or estimation of the intensity, frequency and duration of exposure.

Risk characterization (estimation)

Estimating from the dose-response and exposure assessments the incidence of adverse health effect(s) under different conditions of exposure.

Safety assessment

Determination of an exposure that will not result in adverse effects in a population exposed for a lifetime.

2.3 Risk management

An applied judgmental and technical process that uses risk assessment to make decisions on actions to protect human health.

3. Review of normative approaches

Classification of chemicals is addressed by legislation in a number of countries throughout the world, including varying criteria for classification of sensitizing substances.

Within the OECD countries, the European Union has developed criteria for classification of skin and respiratory sensitizers on the basis of the properties of the chemicals:

Respiratory sensitizers are classified on the basis of:

- evidence that the substance can induce specific respiratory hypersensitivity
- or positive results from an appropriate animal test or tests
- specific provisions exist for isocyanates

Skin sensitizers are classified on the basis of:

- practical experience showing the substance or preparation to be capable of inducing sensitization by skin contact in a substantial number of persons
- or positive results from an appropriate animal test.

Other countries are adopting similar criteria to the EU Member States, including Norway, Australia and Switzerland. Criteria in Canada are very close to the EU criteria, focusing however on evidence from the work place. In the US several agencies address sensitizing properties in a similar way, including a description of the clinical presentation. In the Russian Federation the allergenicity of a substance is indicated on the list of occupational exposure

limit values. The proposal from the Nordic Committee on Building Regulations (NKB) of the Nordic Council of Ministers is unique in introducing an element of strength of evidence in the classification of allergens thus permitting the combination of this proposal with regulatory requirements.

At the UN Conference in Rio in 1992, the commitment of participants to work towards a global harmonization of classification systems was given. The WHO Regional Office for Europe, in comprehension of this agreement, wishes to develop a system for classification of allergens that is compatible with existing regulation trends. The clarification on the type and interpretation of data to be used for classification is given for both airway hypersensitivity and skin sensitization.

4. Individual risk factors

4.1 Risk groups for allergic contact sensitization

Allergic contact sensitivity to environmental chemicals is never inborn but always a consequence of earlier exposure. Most knowledge on the frequency of contact allergy stems from consecutive patch tested eczema patients or group studies with specific occupational exposure. Very few studies have evaluated the frequency of contact allergy in unselected populations (Nielsen and Menné, 1992).

Breeding experiments in animals combined with experimental sensitization have shown a genetic predisposition to develop allergic contact sensitization (Parker et al., 1975). Further studies indicate that this predisposition is directed against specific chemicals. Human family studies with experimental allergens have illustrated a marked genetic propensity to contact sensitization. The outcome of human twin studies is not uniform. A large study including nickel sensitive female twins found a significant genetic predisposition to develop nickel sensitization (Menné and Holm, 1983). A number of studies have evaluated genetic markers in allergic contact dermatitis patients. Different human lymphocyte antigen (HLA) types have been evaluated without establishing significant associations. In the clinical situation the influence of heredity for allergic contact dermatitis is not observed (Menné and Holm, 1986). It seems that exposure factors overshadow the genetic effect in everyday life.

Concomitant skin damage, skin disease, drugs and UV irradiation, etc., influence induction and also elicitation of contact allergy. Individuals with ongoing hand eczema or leg eczema have a higher frequency of contact allergy to environmental chemicals. The dose necessary to elicit contact allergy is significantly lower in damaged skin compared to normal skin.

4.2 Risk groups for airway hypersensitivity

There are great individual variations in susceptibility and predisposition to airway hypersensitivity; the predisposing factors are only partially understood.

Atopy, defined as an increased tendency to develop IgE antibody to common allergens, is an inherited characteristic. Atopy increases the risk of sensitization by proteins; an increased tendency to develop IgE antibody to some low molecular weight chemicals such as tetrachlorophthalic anhydride and complex platinum salts has also been demonstrated. However, for the induction of hypersensitivity by the majority of low molecular weight chemical compounds including di-isocyanates, atopy seems to be of little or no relevance (Nielsen et al., 1995). Also atopic dermatitis in childhood is a risk factor for developing asthma in adolescence (Weiss et al., 1985; Martinez et al., 1988).

Smoking is a risk factor (Calverley et al., 1995) for the development of specific IgE antibody against some occupational agents, e.g. tetrachlorophthalic anhydride, complex platinum salts, piperazine. It is, however, unclear whether smoking increases the risk of developing rhinitis or asthma (Taylor and Pickering, 1994). Smoking also potentiates sensitization in laboratory animals. Maternal smoking more than doubles the risk for the child of becoming atopic in genetically predisposed individuals and increases the risk of developing asthma in adolescence.

There is an inverse relationship between asthma and the number of siblings in a family, as well as with socio-economic status. This has been construed as evidence indicating that perinatal infections influence the production of IgE antibody (Strachan, 1989; Mutius et al., 1994).

Bronchial hyperresponsiveness is a feature of asthma; it is more common among atopics than non-atopics. Individuals with hyperresponsive bronchi and asthma are sensitive to the elicitation of asthma by all types of irritants, whereas there is little evidence indicating they have increased risk of induction of specific airways hypersensitivity.

5. Criteria for classification of sensitizers

5.1 General

For the purpose of this document we define "inducing" substances and preparations as substances and preparations which, if they are inhaled or if they penetrate into the skin, are capable of inducing specific hypersensitivity such that on further exposure to the substance or preparation characteristic adverse effects are produced. Specific hypersensitivity may be allergic sensitization or of uncertain mechanism.

Sensitization is the induction of specific immunological memory in an individual exposed to an allergen. The adverse effects may be expressed in different organs. This discussion is concerned with contact allergy in the skin and specific reactions in the airways. Classification of substances and preparations of importance for contact allergies in the skin and specific reactions in the airways respectively follows the same main principle which is appropriate challenge testing supplemented by other tests. It is important to understand that an airway sensitizer is not necessarily also a skin sensitizer and vice versa.

There are differences in the approach to the identification of skin and airway allergens. Airway responses can be potentially life threatening though both airways and skin responses lead to morbidity. Patch tests are more widely available in dermatology than are specific provocation tests in pulmonary medicine. The methodology of animal tests is more advanced for contact allergy than airway hypersensitivity. The implications of these differences are:

1. The concept of "significance" is valuable for contact allergy. Significant skin sensitizers are the group of substances or preparations which are or are presumed capable of causing more than isolated cases of allergic contact reactions.
2. In contact allergy, the results of certain standardized animal tests are accepted to be predictive of hazards to human health.

5.2 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.

5.2.1 Methods

5.2.1.1 *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 the 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, in particular, does not always completely clear up in spite of cessation of exposure. Predictive human sensitization tests are available to evaluate sensitizing potential of substances (Patrick and Maibach, 1995).

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

5.2.1.2 *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. (Nielsen and Menne, 1992). As an instrument for continuous monitoring of allergic contact dermatitis, clinically based surveillance scheme has been set up (Schnuch and Lemacher, 1992).

5.2.1.3 *Animal methods*

Several animals tests have been described which identify reliably substances which can cause allergic contact dermatitis (Andersen and Maibach, 1985, OECD, 1992). Some animal tests

require further validation (Montelius et al., 1994). The most important of these tests are noted in OECD Guideline 406 (OECD, 1992).

5.2.1.4 Other methods

Other supporting evidence can come from structure activity considerations or from in vitro methods. These have been reviewed recently (Andersen and Maibach, 1985; Basketter et al., 1995).

5.2.2 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.

5.2.3 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	Inadequate evidence present	Sufficient 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.

5.2.4 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 (Andersen et al., 1996). 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.

5.3. The identification and classification of substances causing specific airway hypersensitivity

5.3.1 Methods

There are several tests used in man for assessing airway hypersensitivity.

5.3.1.1 Clinical methods

a) Bronchial provocation testing

There are international and other guidelines such as "Guidelines for bronchoprovocation on the investigation of occupational asthma". Report of the Subcommittee on Bronchoprovocation for Occupational Asthma (Cartier et al., 1989). Testing can be of the airways alone, or of the whole person where responses in the eyes, nose and respiratory tract can be monitored. In general, tests should be carried out in centres with specialized knowledge. Well defined agents should be used before attributing a response to a particular chemical. Testing should be preceded by measurement of non-specific bronchial responsiveness. Suitable control exposures should be made with monitoring of lung function for the next 24 hours. The exposure during challenge testing should be relevant to the exposure in the workplace or other environment. High irritant exposure should be avoided. Where possible the levels of exposure should be measured. Lung function should be monitored for 24 hours after exposure.

A positive bronchial response is a sustained fall in FEV₁ (or perhaps peak expiratory flow) of 20% from baseline or at least 15% compared with the control exposure. It may occur within minutes of exposure, or may be delayed for several hours. Positive reactions may last for several days. Before the reaction can be shown to be due to specific sensitivity rather than a non-specific irritant effect, either:

1. A similar exposure to control persons with a higher degree of non-specific bronchial responsiveness should not elicit any bronchial response, or
2. Similar exposures in the workplace (using personal monitoring) can be shown to cause no respiratory reaction in workers with increased non-specific bronchial responsiveness; for instance by frequent measurement of lung function on days with and without work exposure to the test agent.

b) Serial measurement of lung function over many days with and without exposure

There are well defined methods for carrying out and analyzing serial measurements of lung function on days with and without exposure to a possible inducing agent. A positive response can demonstrate occupational asthma, but cannot determine the precise cause. Testing is required 4-8 times daily over several weeks (Burge, 1982; Moscato et al., 1995; Gannon et al., 1996)

c) Tests for non-specific bronchial responsiveness

Tests are generally carried out with increasing doses of histamine or methacholine. There are several well documented protocols suitable for use (Cockcroft et al., 1977; Sterk et al., 1993).

d) Skin tests

Prick tests should be carried out with well characterized chemicals or conjugates shown not to produce positive reactions in appropriate control persons at the doses used. Positive (histamine) and negative (diluent or vehicle) tests should be made. For new agents a dose response should be shown. A positive test is a weal significantly greater than the negative control. A positive test demonstrates sensitization but not necessarily disease. They are an important part of clinical investigation and surveillance for specified agents, e.g. complex platinum salts (Venables et al., 1985). There is a need for appropriate conjugates to be developed for many low molecular weight airway sensitizers. Intracutaneous tests are also available. They can be potentially dangerous, can lead to sensitization and respiratory and generalized reactions, frequently give non-specific reactions and are not recommended outside research institutions.

e) Tests on blood

Tests for specific IgE can be used in place of skin prick tests or to supplement them. A positive test has similar significance to skin prick tests. Tests on blood using other immunoglobulins or cells need further evaluation before they can be used for classification purposes.

5.3.1.2 Epidemiology

The main uses of epidemiology are determining the frequency of disease, demonstrating exposure-response relationships, and identifying risk factors for sensitization. There is a problem with case definition. Most studies report work-related symptoms (and immunological tests where available), rather than occupational asthma. Standard questionnaires are available, but lack specificity, particularly in the older smoking population, and in general are unable to diagnose occupational asthma or alveolitis.

5.3.1.3 Other organs**Nose**

Nasal responses can be measured following chamber exposure or nasal provocation. Care is needed to exclude non-specific reactions. Tests should be performed in centres with particular experience of nasal challenge. There are currently no international guidelines for nasal provocation tests. Nasal responses alone are not sufficient for the classification of a substance as an inducer of airway hypersensitivity.

Alveoli

Alveolar responses can follow bronchial provocation testing. They are more difficult to monitor. Significant reactions usually result in a fall in FEV1 or FVC and an increase in breathlessness and sometimes body temperature. The demonstration of an alveolar response following challenge testing is not needed before classifying a chemical as a cause of allergic alveolitis. Specificity can be determined from specific IgG measurements (Hendrick et al., 1980).

Eyes

Reactions in the eyes may occur following chamber exposure. They can be monitored by tear film break-up time or with symptom diaries. Eye responses alone are not sufficient for the classification of inducers of airway hypersensitivity.

5.3.1.4 Animal models

Animal models have been successfully used to detect human airway sensitizers by using classical immune endpoints. Investigators have used variations of these models to show that several chemical substances can induce immune responses. Although these models have not been through rigorous validation or standardization procedures, the data from the models point to the robustness of these approaches (Sarlo and Karol, 1994). Substances that induce specific hypersensitivity via non-classic immune mechanisms may be harder to assess although a few animal models have relied on pulmonary responses as an endpoint. The usefulness of these models as predictive tests is unknown at this time. However, positive data should be considered when evaluating substances for classification.

A guinea pig model developed by Karol (Karol, 1983) has been used to examine the immunology and pulmonary responses to toluene di-isocyanate (TDI). This model has been adapted to evaluate responses to other chemicals and is the most widely used model. Other investigators have developed guinea pig injection models to examine immune and respiratory responses. A mouse IgE test has been proposed as a fast, inexpensive test that can be used to identify whether or not a chemical has the potential to cause respiratory allergy (Dearman et al., 1992).

5.3.2 Evidence to be used for classification

Sufficient evidence:

In principle, sufficient human evidence that a substance is the inducer of specific airway hypersensitivity can be obtained only by specific provocation testing.

Sufficient evidence for classification originates in human experience. Sufficient human evidence is available when it can be shown in more than one patient in more than one independent centre that there is a characteristic airway response after exposure to the substance and this can be provoked by a non-irritant exposure to the substance.

Currently animal data alone or in combination with structure activity relationships cannot be used as sufficient evidence.

Limited evidence:

Limited evidence for classification originates in limited human data and/or animal data and/or other supporting information. Limited evidence includes:

- (a) One positive provocation test carried out to the standard for sufficient human evidence;
- (b) Any positive provocation test not carried out to the standards for sufficient human evidence;
- (c) Case reports including variation in lung function or airway responsiveness consistent with occupational asthma;
- (d) Case reports including demonstration of specific IgE antibody in a skin test or a serological test;
- (e) Epidemiological evidence of an increased frequency of a marker of occupational asthma in relation to exposure to the substance;

- (f) Evidence of airway and/or immune sensitization from appropriate animal test;
- (g) Structure-activity analyses predictive of airway hypersensitivity;
- (h) Reasoning by analogy with a substance already classified in group I; for example, di-isocyanates and acid anhydrides.

Inadequate evidence:

There are no interpretable data available to classify the substance.

Evidence that the substance does not induce specific airway hypersensitivity:

Data exist which suggest that the substance does not cause specific hypersensitivity.

5.3.3 Classification scheme

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

Class	Human evidence	Animal evidence	Other evidence
I Inducer of specific airway hypersensitivity	Sufficient evidence present	Evidence may be present or absent	Evidence may be present or absent
II Probable inducer of specific airway hypersensitivity	Limited evidence present	Evidence may be present or absent	Evidence may be present or absent
	Evidence absent	Evidence present	Evidence may be present or absent
	Evidence absent	Evidence absent	Evidence present
III Not classifiable	There are no interpretable data available to classify the chemical substance		
IV Not an inducer of specific airway hypersensitivity	Data exist which suggest that the chemical substance does not cause specific hypersensitivity		

5.3.4 Assessment of potency for substances that induce airway hypersensitivity

Potency is difficult to define. Using human data, rough estimates of risk potential can be made using well defined exposed cohorts. The following is a grouping of airway sensitizers in man, derived from working populations whose exposure has occurred during unexceptional circumstances (e.g. without large spills etc.)

Very strong risk potential

A material which can cause airway hypersensitivity in a substantial percentage of the exposed population, e.g. in the range of 30% as with complex platinum salts (e.g. see Calverley et al., 1995).

Strong risk potential

A material which more than occasionally can cause airway hypersensitivity in an exposed population; e.g. in the range of 5% as in the case of di-isocyanates.

Weak risk potential

A material which occasionally causes sensitization in an exposed population; e.g. in the case of nickel salts in electroplating.

Although the potency of allergen preparations is traditionally assessed by modifications of IgE tests in human sera with reference to international standard preparations, there is no single reference for comparing potency of different allergens. There is also a lack of data of the potency of different conjugates.

Animal models have not been validated for predicting respiratory sensitizing potency in humans. An approach to estimation of the potency of a chemical by examination of animal data has been proposed (Sarlo and Clark, 1992; Sarlo and Karol, 1994). The approach is dependent on the identification of an appropriate "benchmark" chemical that is used in the animal test.

6. Practical use and impact of the classification for prevention

Prevention of allergy/hypersensitivity caused by chemicals is the primary objective. The classification system provides a scientific basis for compiling accepted lists of substances causing allergy/hypersensitivity in order to facilitate risk management and assist in priority setting. However additional information is also required on potency (intrinsic sensitizing capacity) and the nature and extent of exposure. Thus risk assessment is needed to implement full preventive measures.

For substances in Class I or II, action is indicated to protect human health. The level of action is dependent upon the degree of risk which is estimated from potency, exposure and distribution. For substances in Class III, it is strongly recommended that further information be provided to permit a proper classification. The risk of use of substances in Class IV is minimal.

There are different levels of preventive measures which can be divided into:

1. primary prevention focused on avoiding induction of specific hypersensitivity and sensitization;

2. secondary prevention focused on avoiding provocation of specific reactions;
3. tertiary prevention focusing on avoiding chronic damage in sensitized and diseased individuals.
- 4.

Primary prevention may be achieved by control of exposure. That includes substitution, reduction of exposure, and prohibition of substances. In addition, provision of hazard information (labelling, information data sheets) to potentially exposed groups is essential for prevention of sensitization. Furthermore, it is important to give directions for use, including advice about protective measures. Protective measures may include exhaust ventilation, encapsulation of sources, or personal protection.

Secondary prevention includes health surveillance systems to discover early signs of sensitization/induction, or early signs of disease (using simple and cost efficient methodology, such as questionnaires and peak flow measurements). In the case of observations of such early signs, appropriate additional measures should be taken.

Tertiary prevention includes providing health care and prevention of aggravation of disease. Furthermore, proven aetiology may give a foundation for the economic compensation from the employer, insurance company, or government. This may represent economic incentives for primary prevention.

The information received under the secondary and tertiary levels of prevention will yield information on deficiencies in the primary level. This gives a basis for improvements in primary preventive measures. If sensitization occurs risk management should be revised.

7. Recommendations

General recommendations

1. The proposed criteria for classification should be adopted by member governments;
2. Skin and airway sensitizers/inducers should be listed and classified; institution responsible for classification of sensitizers should be identified;
3. The sensitizers should be prioritized for preventive action, based on size of exposed population, nature and extent of exposure, sensitizing potency and any other criteria relevant to risk assessment;
4. An appropriate risk management strategy should be developed;
5. Member governments should share their experience by publication of lists and other documents and by communication to those with responsibility for occupational health and to the public about exposure to sensitizers;
6. Information on product ingredients should be given also for sensitizing substances present at concentrations lower than 1%.

Recommendations for research and development

1. Increased understanding of mechanisms of sensitization in humans and animals;

2. Increased understanding of the factors modifying the relationship between exposure to a sensitizer and the resultant risk of sensitization and elicitation; these may be irritants, adjuvants, or other factors;
3. Development of animal models of airway hypersensitivity and bearing in mind the desirability of limiting research on animals, developing in vitro models;
4. Development of non-biological tests and evaluation procedures, e.g. structure-activity evaluations;
5. Development of alternatives to specific bronchial provocation testing;
6. Development and standardization of test methods, test materials and reporting of results;
7. Development of methods to evaluate exposure;
8. To facilitate future classification work, standards/protocols for all kinds of clinical and epidemiological investigations of potential sensitizers should be developed;
9. Further development of clinical, occupational and environmental surveillance systems;
10. Development of a methodology for systematic potency evaluation of sensitizing substances.

8. Important selected references

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Annex 1

List of working papers and background documents

Working Papers

- ICP/OCH/152 RB (6) Introduction to classification systems for chemical substances and the Nordic experiences with a proposed classification system
for chemical allergens
Drs Mari-Ann Flyvholm and Jan V. Bakke
- ICP/OCH/152 RB (7a) Epidemiological evidence for increase in skin allergy
Professor Jan E. Wahlberg
- ICP/OCH/152 RB (7b) Epidemiological evidence for increase in airway allergy
Dr Jan V. Bakke and Professor Henrik Nordman
- ICP/OCH/152 RB (8a) Methods for epidemiological surveillance of prevalence and incidence of skin allergy
Dr A. Schnuch
- ICP/OCH/152 RB (8b) Methods for epidemiological surveillance of prevalence and incidence of airway allergy
Dr P. Sherwood Burge
- ICP/OCH/152 RB (9a) Methods for animal studies on detection and assessment of chemical skin allergens
Professor Klaus E. Andersen
- ICP/OCH/152 RB (9b) Methods for animal studies on detection and assessment of chemical airway allergens
Dr Kathy Sarlo
- ICP/OCH/152 RB (10a) Guidelines for use of hospital and clinical data on allergy in classification criteria for chemical skin allergens
Professor Torkil Menné and Bodil B. Knudsen M.D.
- ICP/OCH/152 RB (10b) Guidelines for use of hospital and clinical data on allergy in classification criteria for chemical airway allergens
Dr P. Sherwood Burge
- ICP/OCH/152 RB (11) Proposed criteria for classification of allergens present in the working environment based on assessment of human and animal data
Drs Mari-Ann Flyvholm and Jan V. Bakke

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