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Detailed Review Document on Classification Systems for Sensitising Substances in  
OECD Member Countries

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Series on Testing and Assessment

**No. 13**

**Detailed Review Document on  
Classification Systems for Sensitizing Substances  
in OECD Member Countries**

**Environment Directorate**

**ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT**

**Paris 1999**

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The work of the OECD related to chemical safety is carried out in the **Environmental Health and Safety Programme**. As part of its work on chemical testing, the OECD has issued several Council Decisions and Recommendations (the former legally binding on Member countries), as well as numerous Guidance Documents and technical reports. The best known of these publications, the **OECD Test Guidelines**, is a collection of methods used to assess the hazards of chemicals and of chemical preparations such as pesticides and pharmaceuticals. These methods cover tests for physical and chemical properties, effects on human health and wildlife, and accumulation and degradation in the environment. The OECD Test Guidelines are recognised worldwide as the standard reference tool for chemical testing.

More information about the Environmental Health and Safety Programme and its publications (including the Test Guidelines) is available on the OECD's World Wide Web site (see page 6).

The Environmental Health and Safety Programme co-operates closely with other international organisations. This document was produced within the framework of the Inter-Organization Programme for the Sound Management of Chemicals (IOMC).

**The Inter-Organization Programme for the Sound Management of Chemicals (IOMC) was established in 1995 by UNEP, ILO, FAO, WHO, UNIDO and the OECD (the Participating Organizations), following recommendations made by the 1992 UN Conference on Environment and Development to strengthen co-operation and increase international co-ordination in the field of chemical safety. UNITAR joined the IOMC in 1997 to become the seventh Participating Organization. The purpose of the IOMC is to promote co-ordination of the policies and activities pursued by the Participating Organizations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.**

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## **FOREWORD**

The Detailed Review Document on classification systems for sensitizing substances in OECD Member countries has been prepared by Sweden and Germany as part of the work being carried out in the OECD's Programme on Harmonization of Classification and Labelling Systems.

This publication was produced within the framework of the Inter-Organization Programme for the Sound Management of Chemicals (IOMC).





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## **EXECUTIVE SUMMARY**

A review of classification systems and regulations concerning sensitizing substances is presented in this document. The document is based on responses by 13 Member countries to a questionnaire study conducted within the OECD. All the countries responding reported that they have legislation concerning sensitizing substances, with criteria for classification. Eleven countries also maintain lists of substances classified as sensitizers. In all cases the regulations require labelling of sensitizing chemical products.

In the criteria presented in this review there is a similar approach to assessing sensitizing properties, that is, qualitative aspects concerning sensitization and/or quantitative aspects concerning the number of individuals affected by sensitization. The differences found may, in some cases, lead to different conclusions as regards the sensitizing properties of a substance. Examples of differences in the criteria are: the required number of individuals affected by sensitization; inclusion or exclusion of such allergy-like reactions where immunological mechanisms have not been demonstrated; inclusion or exclusion of atopics; and inclusion of immunological contact urticaria. As regards respiratory hypersensitivity, the lack of recognized models for testing may reduce the possibilities to predict this property for a substance.

## **INTRODUCTION**

The OECD, in close co-operation with the IOMC (Inter-Organization Programme for the Sound Management of Chemicals) Co-ordinating Group for the Harmonization of Chemical Classification Systems, has acted as the focal point for the harmonization of the classification and labelling of chemicals based on their intrinsic ability to cause health effects.

At the first meeting of the OECD's Advisory Group on Harmonization of Classification and Labelling in February 1995, it was decided that Sweden and Germany would be responsible for writing the Detailed Review Document (DRD), as the first step leading towards consensus on a harmonized classification system concerning criteria and classification systems for sensitizing substances in OECD countries. For this purpose a questionnaire was sent to the members of the Advisory Group, who were requested to arrange for its completion. Responses were received from 17 national authorities in 13 OECD countries (see Tables 1, 3 and 4).

This review is based on the questionnaire responses as well as any enclosed attachments.

## OVERVIEW OF LEGISLATION CONCERNING SENSITIZING SUBSTANCES

An overview of legislation concerning sensitizing substances in OECD countries is provided in **Table 1**.

**Australia** has legislation for workplace hazardous substances, outlined in National Model Regulations on the Control of Workplace Hazardous Substances [NOHSC:1005(1994)]. The criteria for assessment of substances and preparations are adopted from European Union Directives 67/548/EEC and 88/379/EEC, as well as the guidance given for applying the criteria. There is no separate list of sensitizing substances, but they are included in the List of Designated Hazardous Substances. It is based mainly on the list of substances in Annex 1 of Directive 67/548/EEC. The proposed EU criteria (see below) will probably be adopted in future.

From **Canada** responses were received from the Product Safety Bureau, WHMIS Division, of Health Canada, and the Pest Regulatory Agency of Health Canada. Hazardous chemicals in the workplace are regulated by the Controlled Products Regulations (CPR) and consumer chemical products are regulated by the Consumer Chemicals and Containers Regulations (CCCR), both issued under the Hazardous Products Act. Legislation concerning sensitizers is given under the CPR. There is no list of sensitizers. The CCCR is currently under revision, but sensitizing hazard is not treated specifically in the proposal. The Pest Control Products Act has no specified regulation for sensitizers, but it requires identification of significant hazard, which may include sensitization.

The Environmental Health Bureau, Ministry of Health and Welfare, in **Japan** reported that there is no legislation concerning sensitizing substances. According to the National Institute of Industrial Health, Ministry of Labour, Japan has no classification system or list regarding sensitizers. However, there are regulations concerning specific agents, for example beryllium and TDI, in the "Industrial Safety and Health Law". The Agricultural Production Bureau, Ministry of Agriculture, Forestry and Fisheries, reported that there is legislation, criteria and guidelines for sensitizers used in agricultural pesticides: "The Guidance to Evaluate Agricultural Pesticides concerning the Safe Use and their Application". However, limited information about this legislation was enclosed.

**Norway** is going to implement the revised criteria proposed by the European Union (see below). At present it has legislation with national criteria for sensitizers, the "Regulations concerning Labelling, Sale etc. of Chemical Substances and Preparations that May Involve a Hazard to Health". Guidance is given on how to apply the criteria, especially for respiratory hypersensitivity. There is also a list of sensitizers called the "List of Sensitizing Substances". Norway has a Scientific Group for Identification of Sensitizing Substances attached to the two responsible authorities. It prepares criteria documents for substances suspected of being sensitizing, with a conclusion for each substance indicating that it meets, or does not meet, the criteria or that there is not enough documentation to assess the sensitizing properties. A list of the substances the Group has reviewed is available. It contains about 75 substances.

**Switzerland** has a “Federal Law on Trade in Toxic Substances”. According to this law, toxic substances should be classified in accordance with their overall hazard by the authorities into one of five toxicity categories before they can be marketed. The basis for classification is acute oral toxicity (LD50), but other toxicity data should also be taken into consideration. After classification and approval by the authority, the substance is included in the List of Toxic Substances. Thus this list contains all toxic substances which are approved for trade. Sensitizing properties are indicated in the list. According to the response to the questionnaire, criteria and guidelines are the same as in the EU. However, full harmonization with the EU provisions on classification and labelling is planned. The Federal Law on Trade in Toxic Substances is already under revision.

From the **United States**, responses were received from three regulatory authorities: the Environmental Protection Agency (EPA), Office of Pesticide Programs; the Occupational Safety and Health Administration (OSHA), Department of Labor; and the Consumer Product Safety Commission (CPSC). Each has legislation concerning sensitizing substances. Their regulations are the “Federal Insecticide, Fungicide and Rodenticide Act”, section 1G (EPA, Office of Pesticide Programs); the “Occupational Safety and Health Act” and 29 CFR Parts 1910, 1915, 1917, 1918, 1926, 1928 (OSHA); and the “Federal Hazardous Substances Act”, section 2K and 16 CFR 1500-3(c)(5) (CPSC). CPSC has a list of “strong sensitizers”. They include five substances or groups of substances which meet the definition of “strong sensitizer”. According to the questionnaire response, the EPA Office of Pesticide Programs and OSHA do not produce lists of sensitizers.

The Member States of the **European Union** have common legislation for sensitizing substances, found in Directive 67/548/EEC. It has criteria for classification of substances as sensitizing by inhalation and by skin contact, and also some guidance on how to interpret test results in relation to the criteria. About 230 substances are classified as sensitizing based on the Directive. They are included, among all substances with other classifications, in the list of substances in Annex 1 of the Directive. In Directive 88/379/EEC, rules are given for assessing the sensitizing properties of preparations.

A revision of the criteria in Directive 67/548/EEC is going on and a proposal has been established. The present criteria have been elaborated, and more guidance on how to apply them is given in the proposal.

**Table 1. Overview of legislation concerning sensitizing substances**

Question	AUSTRALIA	BELGIUM	CANADA Product Safety Bureau, WHMIS	CANADA Pest Management Regulatory Agency	DENMARK	FRANCE	IRELAND	JAPAN Environmental Health Bureau	JAPAN Agricultural Production Bureau
Allergen legislation	yes	yes (EU)	yes	yes	yes (EU)	yes (EU)	yes (EU)	no	yes
Classification criteria	yes (EU)	yes	yes	yes	yes	yes	yes	no	yes
Guidelines	yes	no	yes	no	no	yes	no	no	yes
List of allergens	yes	yes	no	NA	yes	yes	yes	no	no

Question	NETHERLANDS	NORWAY	SWEDEN	SWITZERLAND	UK	USA EPA Office of Pesticide Programs	USA OSHA Department of Labor	USA CPSC
Allergen legislation	yes (EU)	yes	yes (EU)	yes	yes (EU)	yes	yes	yes
Classification criteria	yes	yes	yes	yes	yes	yes	yes	yes
Guidelines	yes	yes	yes	yes	yes	yes	NA	yes
List of allergens	yes	yes	yes	yes	yes	no	NA	yes

NA = no answer in the questionnaire

## CRITERIA FOR CLASSIFICATION

In the following, a description is given of the criteria which different authorities apply when assessing the sensitizing properties of chemicals. **It has only been possible to cover the authorities who enclosed their regulations as attachments to the questionnaire.**

### Canada

In the Controlled Products Regulations skin sensitization is defined as

*an immunologically-mediated cutaneous reaction in a person who is not atopic or in an animal that is not atopic on exposure to a substance to which the person or animal has been exposed.*

Respiratory tract sensitization is defined as

*the development in a person who is not atopic of severe asthma-like symptoms on exposure to a substance to which the person has been exposed.*

A pure substance or tested mixture is a skin sensitizer if

*in an animal assay carried out in accordance with OECD Test Guideline No. 406 for skin sensitization it produces a response in 30% or more of the test animals, when using one of the techniques incorporating the use of an adjuvant; or it produces a response in 15% or more of the test animals, when using one of the techniques not incorporating the use of an adjuvant; or*

*evidence shows that it causes skin sensitization in persons following exposure in a workplace.*

A pure substance or tested mixture is a respiratory tract sensitizer if

*there is evidence that shows that it causes respiratory tract sensitization in persons following exposure to it in the workplace.*

An untested mixture is skin sensitizing if

*one of its components is a skin sensitizer and is present at a concentration of 1% or more. The corresponding concentration limit for respiratory tract sensitizers is 0.1%.*

For the assessment of chemicals, appropriate OECD Guidelines for Testing of Chemicals should be used or any other test or method, carried out in accordance with generally accepted standards of good scientific practice.

As mentioned previously, there are no special regulations for sensitizers in the Pest Control Products Act, but as identification of significant hazard is required, sensitization may be included. Assessment of dermal sensitization should be based on recognized test protocols such as those of the OECD and US EPA, or on other evidence. Test requirements on mixed products

will be waived; the assessment of sensitizing properties should be based on the constituents known to be sensitizing.

## Norway

Norway has national criteria and guidelines for sensitization, but is going to implement the EU criteria when they are revised. The current national criteria are described in the following:

Substances that can induce allergy by contact with skin, characterized by redness, swelling, blisters or itching, are called contact allergens if the following criteria are complied with:

*practical experience (clinical tests, clinical experience or epidemiology) shows that the substance has the ability to induce allergic reactions by contact with skin in a not inconsiderable percentage of exposed persons; and/or*

*the substance causes a positive reaction when testing for allergy in relevant animal experiments.*

A positive reaction is when at least 30% of the test animals in an adjuvant test or at least 15% in a non-adjuvant test show an allergic reaction. Tests should be carried out in accordance with the methods described in the OECD Guidelines for Testing of Chemicals.

Substances which may induce allergy or other form of hypersensitivity in the respiratory system or in the eyes are called sensitizing substances if the following criteria are complied with:

*the substance can induce an allergic reaction in the eyes or in the upper or lower parts of the respiratory system by a specific immune reaction; and/or*

*the substance can, at low (non-toxic) doses, induce a hypersensitive reaction in the eyes or in the upper or lower parts of the respiratory system without it being possible to demonstrate a certain immunological mechanism of reaction.*

The basis for classification comprises:

*practical experience (clinical tests, clinical experience or epidemiology) shows that the substance can induce allergy or other form of hypersensitivity in the eyes or the respiratory system in a not inconsiderable number of exposed persons.*

When there are special conditions, the authorities may base the classification on other factors. This applies also to contact allergens.

The guidelines for application of the criteria are relatively extensive for respiratory hypersensitivity. The type of data which an evaluation could be based on is described, detailed definitions of relevant concepts are given, and limits are set up to exclude conditions which are regarded as peripheral health effects in this matter.

Classification of preparations should always be based on the content of sensitizers in the preparations, even if a test on a preparation has given negative results. 1% of a sensitizer in a preparation is usually the limit for classification of the preparation.

Certain substances in the List of Substances have lower individual concentration limits.

## United States

The EPA, Office of Pesticide Programs reported criteria for dermal sensitization. Skin sensitization or allergic contact dermatitis is defined as

*an immunologically-mediated cutaneous reaction to a substance. In the human, the responses may be characterized by pruritus, erythema, edema, papules, vesicles bullae or a combination of these. In other species the reactions may differ and only erythema and edema may be seen.*

Any of seven indicated test methods is considered acceptable. The results are judged as positive or negative. As a possible future change, it is mentioned that test requirements on products may be waived more frequently; instead, the evaluation will be based on components known to be sensitizers.

OSHA reported the following definition of a sensitizer:

*a chemical that causes a substantial proportion of exposed people or animals to develop an allergic reaction in normal tissue after repeated exposure to the chemical.*

Where available, human data such as epidemiological studies and case reports shall be considered in the evaluation. For animal studies no test method is specified. The evaluation could be based on one good study which is designed and conducted according to established scientific principles and which reports statistically significant conclusions.

For assessing mixtures, empirical data should be used. If not, available mixtures containing 1% or more of a sensitizer should be regarded as sensitizing. If the concentration is lower than 1%, the mixture should be regarded as sensitizing if the sensitizer is expected to be released and to exceed certain exposure limit values.

CPSC defines a strong sensitizer as follows:

*a substance which will cause on normal living tissue through an allergic or photodynamic process a hypersensitivity which becomes evident on re-application of the same substance. Before designating any substance as a strong sensitizer (the authority) upon consideration of the frequency of occurrence and severity of the reaction, shall find that the substance has a significant potential for causing hypersensitivity.*

Supplementary explanations are given of terms in the definition:

A *sensitizer* is a substance that will induce an immunologically-mediated (allergic) response, including allergic photosensitivity. This allergic reaction will become evident on re-exposure to the same substance. Occasionally a sensitizer will induce and elicit an allergic response on first exposure by virtue of active sensitization.

In determining that a substance is a *strong sensitizer* the following factors, if available, should be considered: quantitative or qualitative risk assessment, frequency of occurrence and range of severity of reactions in healthy or susceptible populations, the results of experimental assays in humans or animals with human data taking precedence over animal data, other data on potency or bioavailability, data on reactions to a cross-reacting substance, the threshold of human



sensitivity, epidemiological studies, case histories, occupational studies and other appropriate *in vivo* and *in vitro* studies.

The minimal *severity of reaction* for a substance being a “strong sensitizer” is a clinically important allergic reaction.

*Significant potential for causing hypersensitivity* is a relative determination which must be made separately for each substance. It may be based upon chemical or functional properties of the substance, documented medical evidence of allergic reactions obtained from epidemiological surveys or individual case reports, controlled *in vivo* or *in vitro* experimental assays, or susceptibility profiles in normal or allergic subjects.

The reaction of allergic hypersensitivity occurs in *normal living tissue* which includes the skin and other organ systems such as the respiratory or gastrointestinal tract, either singularly or in combination, following sensitization by contact, ingestion or inhalation.

Substances which have sensitizing properties without meeting the criteria of strong sensitizers are not defined as hazardous.

## **European Union**

### Present criteria

The European Union is in the process of adopting new criteria, but as the “old” ones are still in force they are also presented here.

For sensitization by skin contact they read as follows:

*if practical experience shows the substances or preparations to be capable of inducing a sensitization reaction in a substantial number of persons by skin contact, or on the basis of a positive response in experimental animals.*

Results from animal tests should be interpreted as follows. When at least 30% of the animals give positive response in an adjuvant test method this should be taken as positive. For any other test method 15% should be taken as positive. Recommended test methods are given in the directive, but comparable methods may be used.

The criteria for sensitization by inhalation read as follows:

*if practicable evidence is available which shows the substances and preparations to be capable of inducing a sensitization reaction in humans by inhalation, at a greater frequency than would be expected from the response of the general population.*

Isocyanates are treated specifically. Unless there is evidence that the substance does not cause sensitization they should always be classified as sensitizers.

A preparation, where one or more of its components is a sensitizer, should be classified as sensitizing if the concentration is 1% or more of the sensitizer unless an individual concentration limit for the sensitizer is stated in Annex 1 (the List of Substances) of the Directive. However,

as a general rule, if a test on the preparation is available these results should be used in the first place for classification.

These rules are not included in the revision of the criteria, but will remain in force until further notice.

#### Revised criteria

The proposed new criteria have been adopted by the European Commission working group and the final decision to enable them to come into force is expected soon. The proposed criteria and guidelines are a development of the present system. More extensive information has been added to make clear what the requirements are to meet the criteria.

The criteria for skin sensitization read as follows:

*if practical experience shows the substance or preparation to be capable of inducing sensitization by skin contact in a substantial number of persons, or*

*where there are positive results from an appropriate animal test.*

In the comments that follow, it is explained what is meant by “practical experience”, that is, what kind of human evidence is sufficient to meet the criteria. If there is human evidence which is weaker than in the previous case, but it is supplemented by supportive evidence, a substance can still be classified as a sensitizer. Examples are given of what kind of data supportive evidence may include. The meaning of “positive results from an appropriate animal test” is the same as in the current criteria.

The criteria for sensitization by inhalation read as follows:

*if there is evidence that the substance or preparation can induce specific respiratory hypersensitivity*

*where there are positive results from appropriate animal tests.*

Isocyanates are treated specifically as in the present criteria. They should always be classified unless there is evidence that they do not cause respiratory hypersensitivity. In the first case the evidence should normally be based on human experience. Together with this evidence it is necessary to consider the size of the population exposed and the extent of exposure. Beside asthma, reactions such as rhinitis and alveolitis should be considered. An important clarification of the criteria has been introduced, that is, immunological mechanisms do not have to be demonstrated. But the clinical character must be that of an allergic reaction. The evidence could be a clinical history with appropriate lung function tests, confirmed by other supportive evidence, or positive bronchial challenge tests.

Appropriate animal tests may be IgE measurements, for example in mice, and studies of specific pulmonary responses in guinea pigs.

It has been considered necessary to introduce criteria for substances which can cause immunological contact urticaria. There are no recognized animal models available to evaluate this effect, so classification will normally be based on human evidence, with criteria similar to

those for skin sensitization. If a substance is classified as a sensitizer by inhalation, and in addition causes immunological contact urticaria, a safety advice phrase should be applied to inform about the skin hazard. For other substances causing immunological contact urticaria, classification as a skin sensitizer should be considered.

## ICCA

In the following, parts of a discussion paper (ref. 1) from the International Council of Chemical Associations (ICCA) are presented. This was originally prepared for presentation at the IPCS Co-ordinating Group Meeting in November 1994 concerning globally harmonized classification systems for hazardous products.

The existing regulatory classification systems for sensitizing workplace chemicals in Canada, the United States and the European Union were reviewed. Areas of agreement and differences were identified, and an approach for harmonization was proposed.

For skin sensitization the following was proposed:

adopt OECD Test Guideline No. 406 with criteria of a positive response in at least 30% of test animals when using adjuvant and 15% of test animals when not using adjuvant

develop a criterion or test protocol together with a qualitative definition of skin sensitization in humans (consistency with respiratory sensitization in describing occurrence).

For respiratory sensitization the following was proposed:

develop a qualitative definition or criterion for respiratory sensitization in humans (consistency with skin sensitization in describing occurrence).

## REGULATORY CONSEQUENCES AND SPECIFIC CONTROL MECHANISMS

In **Table 2** the regulatory consequences of classification of sensitizers are shown, according to the responses in the questionnaire. As can be seen, classification always leads to labelling of chemical products. Some countries report that they have special restrictions on sale/handling. As an example, France mentioned the EU Directive concerning restrictions on the marketing and use of certain objects containing nickel. Denmark, Japan, Norway, Sweden and Switzerland responded that sensitizers should be reported to a substance/product register. In many cases the classification of substances as sensitizers leads to consequences for other legislation, usually legislation for the workplace environment. This concerns, for example, Australia, Denmark, Norway and Sweden.

In **Table 3** the requirements of Canada, the United States (OSHA) and the European Union for labelling products containing sensitizers are shown. In all three cases the assessment of sensitizing properties of mixtures should be based on tests on the mixture itself. If such test results are not available, the evaluation should be based on the presence and concentration of sensitizers in the mixture. Concentration limits applied are shown in the table. In all cases but one, 1% is the limit for labelling. The

exception is the Canadian rule for products containing respiratory sensitizers, where 0.1% is applied as the limit for labelling. In the EU regulations many substances which are classified as sensitizers and are found in Annex 1 of the Directive, the List of Substances, have individual concentration limits which should be applied instead of the general limit of 1%.

According to the Norwegian regulations, classification should always be based on the sensitizing properties of the constituents. Testing of mixtures is not permitted as a basis for classification, even when the results are negative. In the questionnaire, US EPA responded that in future it may waive test requirements on mixtures more frequently and base the labelling on constituents known to be sensitizing. The Pest Management Regulatory Agency of Health Canada commented that it has a similar view.

In **Table 4** specific control mechanisms for the observance of regulations for sensitizers are shown, according to the questionnaire responses. As can be seen, most countries have a national or a regional inspectorate and some kind of control/reporting system.

**Table 2. Regulatory consequences of the classification of sensitizers**

<b>Regulatory consequences</b>	AUSTRALIA	BELGIUM	CANADA Product Safety Bureau, WHMIS	CANADA Pest Management Regulatory Agency	DENMARK	FRANCE	IRELAND	JAPAN Environmental Health Bureau	JAPAN Agricultural Production Bureau
Labelling	yes	yes	yes	yes	yes	yes	yes	NA	yes
Special restrictions on sale/handling etc.	no	yes	yes	no	no	yes	no	NA	yes
Declaration to a (product/substance) register	NA	NA	no	no	yes	no	no	NA	yes
Consequences for other rules/legislation	yes	yes	yes	no	yes	no	no	NA	no

<b>Regulatory consequences</b>	NETHERLANDS	NORWAY	SWEDEN	SWITZERLAND	UK	USA EPA Office of Pesticide Programs	USA OSHA Department of Labor	USA CPSC
Labelling	yes	yes	yes	yes	yes	yes	yes	yes
Special restrictions on sale/handling etc.	yes	no	no	no	yes	no	NA	yes
Declaration to a (product/substance) register	no	yes	yes	yes	no	no	NA	NA
Consequences for other rules/legislation	NA	yes	yes	no	no	no	NA	NA

NA = no answer in the questionnaire

**Table 3. Labelling requirements for sensitizers in mixtures/preparations**

	Concentration limit for skin sensitizers	Concentration limit for respiratory sensitizers
CANADA <sup>1</sup>	≥ 1%	≥ 0.1%
EU <sup>2</sup>	≥ 1%	≥ 1%
US (OSHA) <sup>3</sup>	≥ 1%	≥ 1%

## Notes:

1

- In the first place, available test results should be applied for classification and labelling.
- If not available, the concentration limits shown should be applied.

2

- In the first place, available test results should be applied for classification and labelling.
- If not available, the concentration limits shown should be applied. In case a lower individual concentration limit is stated for a substance in Annex 1 of Directive, this limit should be applied.

3

- In the first place, available test results should be applied for appropriate hazard warnings.
- If not available, the concentration limits shown should be applied. If a substance is present in a lower concentration than shown here, and can be expected to be released and to exceed established OSHA permissible exposure limits or the ACGIH Threshold Limit Values, this should also lead to appropriate hazard warnings.

**Table 4. Specific control mechanisms for observance of regulations for sensitizers**

<b>Specific control mechanisms</b>	AUSTRALIA	BELGIUM	CANADA Product Safety Bureau, WHMIS	CANADA Pest Management Regulatory Agency	DENMARK	FRANCE	IRELAND	JAPAN Environmental Health Bureau	JAPAN Agricultural Production Bureau
National/regional inspectorates	yes	yes	yes	no	yes	yes	yes	NA	yes
Control/reporting systems	yes	yes	yes	yes	yes	yes	no	NA	yes
Other mechanisms	NA	NA	yes	no	no	NA	no	NA	NA

<b>Specific control mechanisms</b>	NETHERLANDS	NORWAY	SWEDEN	SWITZERLAND	UK	US EPA Office of Pesticide Programs	US OSHA Department of Labor	US CPSC
National/regional inspectorates	yes	yes	yes	yes	yes	NA	yes	yes
Control/reporting systems	NA	yes	yes	yes	no	NA	NA	yes
Other mechanisms	NA	no	no	NA	no	yes	NA	NA

NA = no answer in the questionnaire

## OVERALL COMPARISON OF EXISTING SYSTEMS

In the following, national regulatory systems for sensitizers and the system of the European Union are compared, with comments on structure, similarities and differences. In two regulatory systems (those of CPSC and OSHA in the United States) the criteria are the same for sensitization by skin contact and by inhalation. The other systems have separate criteria.

The regulatory systems described in this document use a similar approach to identify and classify sensitizers, that is, a qualitative description of sensitizing substances and the quantitative requirements, concerning the number of affected individuals, to meet the criteria. Some systems have only one of these two aspects, while others have both. Below, the similarities and differences are reviewed under different headings.

### Definition of sensitization

In the US EPA and Canadian definition of skin sensitization it should be an *immunologically-mediated cutaneous reaction* in a person or an animal. EPA also describes (as does Norway) the symptoms by which the reaction could be characterized. OSHA uses an *allergic reaction in normal tissue*. CPSC uses an *immunologically-mediated (allergic) response, including allergic photosensitivity in normal living tissue*.

Photosensitivity is only mentioned in the criteria of CPSC.

Regarding respiratory sensitization, the Canadian regulations say there should be *severe asthma-like symptoms* in a person. OSHA and CPSC have the same definition as for skin sensitization. Norway has extensive guidelines with qualitative aspects of allergy and other forms of hypersensitivity. In the revised EU criteria it is stated that *besides asthma, reactions such as rhinitis and alveolitis should be considered*. It is also stated that *immunological mechanisms do not have to be demonstrated*, but the clinical character must be that of an allergic reaction.

Only in the criteria of Norway and the EU (revised) is it clearly stated that allergy-like reactions, where no immunological mechanisms have been demonstrated, should be included in the criteria. Apparently these reactions are also covered by the Canadian criteria. Many substances cause such reactions. By including them in the classification system, more individuals could be protected from illness.

As regards respiratory sensitization, the scope of the effect may differ in the regulations. The revised EU criteria state that asthma reactions and other *reactions such as rhinitis and alveolitis* should be considered. OSHA and CPSC include reactions in *normal (living) tissue*, which apparently include effects other than asthma. Norway includes the eyes in the criteria.

In the Canadian rules atopics are excluded by the criteria, both for skin sensitization and respiratory sensitization. In the revised EU criteria for respiratory sensitization, the “clinical history” could be one basis for assessment. Possibly this could be interpreted as meaning that atopy should be considered. In the criteria of OSHA and CPSC, the expression “normal tissue” could also be interpreted as meaning that sensitization of atopics is not included. By excluding atopics, the data for the evaluation



of a substance might be reduced and its classification might consequently be influenced. Whether atopy should be excluded may be discussed from both scientific and ethical viewpoints.

### **Immunological contact urticaria**

In the revised EU criteria, immunological contact urticaria is specifically mentioned. As this could be a serious effect for the individual, including substances with such properties in the classification system is of great concern. There is no recognized animal model for testing, so the evaluation will normally be based on human evidence, similar to that for skin sensitization.

### **Quantitative aspects**

Most of the regulations have some requirements concerning the number of individuals affected in order to meet the criteria. For human data on skin sensitization the EU criteria (present and proposed) say that *a substantial number of persons* should be sensitized, although in the comments to the proposal it is mentioned that, when there are few cases but a high proportion are sensitized, this should give special concern. OSHA and Norway use somewhat similar expressions, *a substantial proportion of exposed people* and *a not inconsiderable percentage of exposed persons*, respectively. CPSC says that *frequency of occurrence* should be considered, which could be interpreted as the number of cases in a certain population. The different ways of expressing quantity may reflect the related difficulties, as well as different ethical viewpoints. A problem in studying contact allergy to a substance in a population is determining the extent of exposure. This may be known, for example, in occupational studies in a workplace, but in a general population it is usually not known. Hence, conclusions are difficult to draw on the ratio of the number of cases in a population to the total number of exposed individuals. If such ratios were known, it would be possible theoretically to single out the strongest allergens. When a certain number of individuals were sensitized, but the extent of exposure was not known, the strongest and most widespread allergens could then be singled out.

For testing skin sensitization in animals the EU criteria (present and proposed) and those of Canada and Norway state the limits for a positive response in a test, that is, at least 30% of the animals should be sensitized in an adjuvant test and 15% in a non-adjuvant test. OSHA says a substantial proportion of exposed animals having developed an allergic reaction, or statistically significant conclusions from one good study, will satisfy the criteria.

For respiratory sensitization the following ways to express quantity in humans are found: *a greater frequency than would be expected from the response of the general population* (EU, present), *the size of the exposed population and the extent of exposure should be taken into account* (EU, revised), *a substantial proportion of exposed people* (OSHA), *frequency of occurrence* (CPSC), and *a not inconsiderable number of exposed persons* (Norway). The quotation above from the present EU criteria is somewhat obscure.

### **Evidence required**

In some regulations the kind and amount of evidence the evaluation should be based on are described. The revised EU criteria give a general and structured description of what kind of data are required for skin sensitization and respiratory sensitization, regarding both human data and animal data. Concerning human data on dermal sensitization, the evidence is graded according to strength. For dermal sensitization in animals, the methods as described in the regulations, or comparable methods, should be used. Canada recommends OECD Test Guidelines or any other method carried out in accordance with established scientific principles. US EPA recommends one of seven indicated test methods for dermal

sensitization. OSHA says available human data, like epidemiological studies and case reports, should be considered. No animal test is specified, but one good study performed with established scientific principles is accepted. CPSC gives general recommendations on the type of studies but not on the number of studies. The Norwegian criteria state that the OECD Test Guideline for dermal sensitization in animals should be used. For humans there are general recommendations. For respiratory sensitization in humans there are more detailed guidelines on the kind of data required to meet the criteria.

In all regulations, evaluation of skin sensitizing properties could be based on human data *or* animal data. Regarding respiratory sensitization, there is no validated and recognized animal model yet. Thus most existing data are based on human experience. This is a problem, especially for the evaluation of new substances on the market and for pesticides undergoing pre-market evaluation. However, the revised EU criteria may be interpreted as saying that IgE measurements (e.g. in mice) and specific pulmonary responses in guinea pigs are sufficient to meet the criteria.

### **Potency ranking**

In the CPSC regulations a “strong sensitizer” is defined; on the basis of frequency of occurrence of hypersensitivity and the severity of reactions, the substance shall have a significant potential for causing hypersensitivity. Sensitizers which are not found to be strong sensitizers are not defined as hazardous substances.

In other regulatory systems, no grading of sensitizers according to potency is performed.

However, the Danish authority suggested introducing the concept of potency evaluation. For this purpose an animal model for potency evaluation of contact allergens has been developed (ref. 2, 3). In the model, which is a development of the Guinea Pig Maximization Test (GPMT), a multiple-dose design is applied. However, the model needs further validation before it could be included in test guidelines.

### **Assessment of sensitizing properties of mixtures**

According to the regulations of Canada, OSHA and the European Union, the assessment of the sensitizing properties of mixtures should, in the first place, be based upon available results from animal tests on the mixtures. This rule could be questioned, as there are test methods which are designed for the testing of pure substances and, consequently, the sensitivity is too low to detect sensitizers in low concentrations in mixed products. An assessment of the sensitizing properties of a mixture according to the properties of the individual constituents would in many cases give a more accurate result. This view is adopted in the Norwegian regulatory system and is also, in practice, applied by other authorities.

The general concentration limit of 1% for classification of mixed products found in most regulatory systems is too high for many substances, as sensitization of exposed individuals can occur at concentrations below this limit. In the allergen lists of Norway and the EU, this general limit has been evaded by the assignment of individual concentration limits for many substances. However, reconsideration of the general concentration limit has been suggested.

In order to protect already sensitized individuals from exposure, Denmark and Switzerland have emphasized the need to label products as sensitizers irrespective of their concentrations. The 1 per cent limit for classification and labelling is not adequate to protect these individuals, in whom a reaction may be provoked by concentrations far below this limit.

## REFERENCES

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2. Andersen K E, Völund A, Potency Evaluation of Contact Allergens dose-response studies using the Guinea Pig Maximization Test. Nordiske Seminar og Arbejdsrapporter 1993:570. Nordic Council of Ministers, Copenhagen (1993).
3. Andersen K E, Völund A, Frankild S, The Guinea Pig Maximization Test with a Multiple Dose Design. Acta Derm Venereol (Stockh) 75, 463-69 (1995).

### Appendix: Responsible Authorities and Contact Persons

COUNTRY	RESPONSIBLE AUTHORITY	CONTACT PERSON
AUSTRALIA	National Occupational Health and Safety Commission	Ms Janie C Heywood A/g Manager Chemical Regulatory Instruments Chemical Assessment Division Worksafe Australia GPO Box 58 Sydney NSW 2001 Tel +61-2-5659461 Fax +61-2-5659465
BELGIUM	Maîtrise des Risques Min. Santé Publique Cité Administrative de l'Etat 1010 Brussels	Mr A Pauwels Maîtrise des Risques Tel +322 210 64 12 Fax +322 210 48 80  Dr T Lakhanisky Toxicologie Institut d'Hygiène et d'Epidémiologie Tel +322 642 5104 Fax +322 642 5001
CANADA	WHMIS Division Product Safety Bureau Health Canada  Pest Management Regulatory Agency Health Canada	Kim Headrick Place du Portage, Phase 1 50 Victoria Street 17th Floor, Zone 2 Postal Locator: 7017A2 Hull, Quebec K1A 0C9 Tel +1 819-994-4669 Fax +1 819-953-3857  Dr Donald L Grant Pest Management Regulatory Agency Health Canada Room 1000, Main Statistics Building Tunney's Pasture Postal Locator 0301B Ottawa, Ontario K1A 0L2 Tel +1 (613) 957-1679 Fax +1 (613) 941-2632

DENMARK	Danish Environmental Protection Agency, Ministry of Environment	Lea Stine Tobiassen Ministry of Environment and Energy Danish EPA Strandgade 29 DK-1401 Copenhagen K Tel +45 32 66 01 00 Fax +45 32 66 02 61
FRANCE	Ministries of Labour, Economy, Industry, Agriculture, Environment and Health	Mme J Cheron Institut National de Recherche et de Sécurité 30 rue Oliver Noyer 75680 Paris Cedex 14
GERMANY	Federal Institute for Health Protection of Consumers and Veterinary Medicine	Mr Klaus Wettig Federal Institute for Health Protection of Consumers and Veterinary Medicine Thielallee 88-92 D-14195 Berlin Tel +49-30-8412-3866 Fax +49-30-8412-3851  Dr Eva Schlede Federal Institute for Health Protection of Consumers and Veterinary Medicine Thielallee 88-92 D-14195 Berlin Tel +49-30-8412-3296 Fax +49-30-8412-3851
IRELAND	Health and Safety Authority	Dr Iona Pratt Health and Safety Authority 10 Hogan Place Dublin 2 Tel +353 1-6620400 Fax +353 1-6620417
JAPAN	Environmental Health Bureau Ministry of Health and Welfare  Ministry of Agriculture, Forestry and Fisheries (MAFF)	Mr Shigeki Tsuda Office of Environmental Chemical Safety Environmental Health Bureau Ministry of Health and Welfare  Mr Katsuhiko Matsura Plant Protection Division MAFF 1-2-1 Kasumigaseki Chiyoda-ku Tokyo 100 Tel +81-3-3501-3964 Fax +81-3-3591-6640

NETHERLANDS	The Ministry of Health, Welfare and Sport	Dr H Roelfzema Ministry of Health, Welfare and Sport Directorate VVP S.W.Churchillaan 366 2280 MK Rijswijk Tel +31-70-3406965
NORWAY	Norwegian Pollution Control Authority (SFT) and Directorate of Labour Inspection	SFT: Linda Reiersen / Solvår Hardeng PO Box 8100 Dep 0032 Oslo 1 Tel +47-22573400 Fax +47-22676706  Directorate of Labour Inspection: Marianne Rudfoss PO Box 8103 Dep 0032 Oslo Tel +47-22957000 Fax +47-22466214
SWEDEN	National Chemicals Inspectorate	Nils Gunnar Lindquist Hazard and Risk Assessment Division National Chemicals Inspectorate Box 1384 S-171 27 Solna Tel +468-7306724 Fax +468-7357698
SWITZERLAND	Division of Toxic Substances Swiss Federal Office of Public Health	Dr Heinz Reust Swiss Federal Office of Public Health Division of Toxic Substances Bollwerk 27 / P.O. Box CH- 3001 Berne Tel +41-31-3229625 Fax +41-31-3112918
UNITED KINGDOM	Health and Safety Executive	Mr A Strawson Health and Safety Executive Rose Court 2 Southwark Bridge London SE1 9HS Tel +44 171 717 6252 Fax +44 171 717 6190

UNITED STATES	Environmental Protection Agency (EPA) Office of Pesticide Programs	Mary Waller Office of Pesticides US EPA Phone +1 703-308-8811
	Occupational Safety and Health Administration (OSHA) Department of Labor	Jennifer Silk OSHA Phone +1 202-219-7075
	US Consumer Product Safety Commission	KC Gupta Directorate for Epidemiology & Health Sciences CPSC Bethesda, MD 20207