Chapter 8:

RESPIRATORY OR SKIN SENSITISATION [1)]

DEFINITIONS

1. A respiratory sensitiser is a substance that will induce hypersensitivity of the airways following inhalation of the substance.

2. A contact sensitiser is a substance that will induce an allergic response following skin contact.

CONSIDERATIONS

3. The purpose of the harmonised criteria for classification of respiratory and skin sensitisers is to give a common ground, which could be used internationally, for the hazard classification of sensitising properties of chemicals. The criteria should be applicable on the hazard classification of chemicals irrespective of their end use.

CLASSIFICATION CRITERIA FOR SUBSTANCES

Respiratory Sensitisers

Classification Criteria

4. Substances shall be classified as respiratory sensitisers (Category 1) in accordance with the criteria given below:

- if there is evidence in humans that the substance can induce specific respiratory hypersensitivity and/or
- where there are positive results from an appropriate animal test.

1. There has been considerable discussion about what to convey about sensitisation effects to those exposed, and at what point it should be conveyed. While the current cut-off for mixtures is 1%, it appears that the major systems all believe information should be conveyed below that level. This may be appropriate both to warn those already sensitised, as well as to warn those who may become sensitised. This issue was not clear during the initial deliberations on the criteria for mixtures containing sensitisers, and thus has not been adequately discussed nor options explored.

   Before the system becomes implemented, this issue should be revisited by the ECOSOC Subcommittee on the GHS as one of its first priorities. It should be noted that the sensitisation criteria for substances will also have to be re-opened to consider this issue and the inclusion of new information and evolving testing approaches that addresses the question of strong sensitisers versus those that are weaker. Appropriate hazard communication should be considered along with the discussions on the criteria and the availability of an appropriate test method.

Rationale

Human Evidence

5. Evidence that a substance can induce specific respiratory hypersensitivity will normally be based on human experience. In this context, hypersensitivity is normally seen as asthma, but other hypersensitivity reactions such as rhinitis/conjunctivitis and alveolitis are also considered. The condition will have the clinical character of an allergic reaction. However, immunological mechanisms do not have to be demonstrated.

6. When considering the human evidence, it is necessary for a decision on classification to take into account in addition to the evidence from the cases:

- the size of the population exposed
- the extent of exposure.

7. The evidence referred to above could be

- clinical history and data from appropriate lung function tests related to exposure to the substance, confirmed by other supportive evidence which may include:
  - -- in vivo immunological test (e.g. skin prick test)
  - -- in vitro immunological test (e.g. serological analysis)
  - -- studies that may indicate other specific hypersensitivity reactions where immunological mechanisms of action have not been proven, e.g. repeated low-level irritation, pharmacologically mediated effects
  - -- a chemical structure related to substances known to cause respiratory hypersensitivity
- data from positive bronchial challenge tests with the substance conducted according to accepted guidelines for the determination of a specific hypersensitivity reaction.

8. Clinical history should include both medical and occupational history to determine a relationship between exposure to a specific substance and development of respiratory hypersensitivity. Relevant information includes aggravating factors both in the home and workplace, the onset and progress of the disease, family history and medical history of the patient in question. The medical history should also include a note of other allergic or airway disorders from childhood, and smoking history.

9. The results of positive bronchial challenge tests are considered to provide sufficient evidence for classification on their own. It is however recognised that in practice many of the examinations listed above will already have been carried out.

Animal Studies

10. Data from appropriate animal studies which may be indicative of the potential of a substance to cause sensitisation by inhalation in humans may include:

- measurements of IgE and other specific immunological parameters, for example in mice
- specific pulmonary responses in guinea pigs.

Skin Sensitisers

Classification Criteria

11. Substances shall be classified as contact sensitisers (Category 1) in accordance with the criteria given below:

- if there is evidence in humans that the substance can induce sensitisation by skin contact in a substantial number of persons, or
- where there are positive results from an appropriate animal test.

Rationale

12. For classification of a substance evidence should include any or all of the following:

- Positive data from patch testing, normally obtained in more than one dermatology clinic.
- 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.
- Positive data from appropriate animal studies.
- Positive data from experimental studies in man.
- Well documented episodes of allergic contact dermatitis, normally obtained in more than one dermatology clinic.

13. Positive effects seen in either humans or animals will normally justify classification. Evidence from animal studies is usually much more reliable than evidence from human exposure. However, in cases where evidence is available from both sources, and there is conflict between the results, the quality and reliability of the evidence from both sources must be assessed in order to resolve the question of classification on a case-by-case basis. Normally, human data are not generated in controlled experiments with volunteers for the purpose of hazard classification but rather as part of risk assessment to confirm lack of effects seen in animal tests. Consequently, positive human data on contact sensitisation are usually derived from case-control or other, less defined studies. Evaluation of human data must therefore be carried out with caution as the frequency of cases reflect, in addition to the inherent properties of the substances, factors such as the exposure situation, bioavailability, individual predisposition and preventive measures taken. Negative human data should not normally be used to negate positive results from animal studies.

14. If none of the above mentioned conditions are met the substance need not be classified as a contact sensitiser. However, a combination of two or more indicators of contact sensitisation as listed below may alter the decision. This shall be considered on a case-by-case basis.

- Isolated episodes of allergic contact dermatitis.
- Epidemiological studies of limited power, e.g. where chance, bias or confounders have not been ruled out fully with reasonable confidence.
- Data from animal tests, performed according to existing guidelines, which do not meet the criteria given in the section on animal studies but are sufficiently close to the limit to be considered significant.
- Positive data from non-standard methods.

– Positive results from close structural analogues.

CLASSIFICATION CRITERIA FOR MIXTURES

Classification of Mixtures When Data are Available for the Complete Mixture.

15. When reliable and good quality evidence from human experience or appropriate studies in experimental animals, as described in the criteria for substances, is available for the mixture, then the mixture can be classified by weight of evidence evaluation of this data. Care should be exercised in evaluating data on mixtures, that the dose used does not render the results inconclusive.

Classification of Mixtures When Data are not Available for the Complete Mixture.

Bridging Principles

16. Where the mixture itself has not been tested to determine its sensitising properties, but there are sufficient data on the individual ingredients and similar tested mixtures to adequately characterise the hazards of the mixture, this data will be used in accordance with the following agreed bridging rules. This ensures that the classification process uses the available data to the greatest extent possible in characterising the hazards of the mixture without the necessity for additional testing in animals.

Dilution

17. If a mixture is diluted with a diluent which is not a sensitiser and which is not expected to affect the sensitisation of other ingredients, then the new mixture may be classified as equivalent to the original mixture.

Batching

18. The sensitising properties of one production batch of a complex mixture can be assumed to be substantially equivalent to that of another production batch of the same commercial product and produced by or under the control of the same manufacturer, unless there is reason to believe there is significant variation such that the sensitisation of the batch has changed. If the latter occurs, new classification is necessary.

Substantially Similar Mixtures

19. Given the following:

a). Two mixtures: (i.) A + B
(ii.) C + B
b). The concentration of ingredient B is essentially the same in both mixtures.
c). The concentration of ingredient A in mixture (i) equals that of ingredient C in mixture (ii).
d). Ingredient B is a sensitiser and Ingredients A and C are not sensitisers.
e). A and C are not expected to affect the sensitisation of B.

If mixture (i) is already classified by testing, mixture (ii) can be assigned the same hazard category.

Aerosols

20. An aerosol form of the mixture may be classified in the same hazard category as the tested non-aerosolised form of the mixture provided that the added propellant does not affect the sensitising properties of the mixture upon spraying.

Classification of Mixtures When Data are Available for All Components or Only for Some Components of the Mixture.

21. The mixture will be classified as a respiratory or skin sensitiser when at least one ingredient has been classified as a respiratory or skin sensitiser and is present at or above the appropriate cut-off value / concentration limit for the specific endpoint as mentioned in Table 1 below for solid/liquid and gas respectively.

Table 1: Cut-off values/concentration limits of ingredients of a mixture classified as either skin sensitisers or respiratory sensitisers, that would trigger classification of the mixture.

Ingredient classified as:	Cut-off/concentration limits triggering classification of a mixture as:	
	Skin sensitiser Category 1	Respiratory sensitiser Category 1
Skin sensitiser	≥1.0% w/w	≥1.0%v/v
Respiratory sensitiser	≥1.0% w/w	≥0.2% v/v

HAZARD COMMUNICATION

Allocation of Label Elements

22. General and specific considerations concerning labelling requirements are provided in Chapter 4. Annex 5 contains examples of precautionary statements and pictograms which can be used where allowed by the competent authority. Additional reference sources providing advice on the use of precautionary information is also included.

Table 2: Respiratory or Skin Sensitisation Label Elements.

	Respiratory Sensitisation Category 1	Skin Sensitisation Category 1
Symbol	New health hazard symbol	Exclamation Mark
Signal Word	Danger	Warning
Hazard Statement	May cause allergy or asthma symptoms or breathing difficulties if inhaled	May cause an allergic skin reaction

DECISION LOGIC AND GUIDANCE

Decision Logic

Classification Decision Tree For Respiratory Sensitisers - Substances

Does the **individual substance** have reliable and good quality evidence available?

Human – evidence that the substance induces specific respiratory hypersensitivity

and/or

Animal – evidence that the substance induces positive results from appropriate animal test

YES — NO

If CATEGORY 1 Label with: Health Hazard Symbol "Danger" May cause allergy or asthma symptoms or breathing difficulties if inhaled

Not enough data to classify at this time

Classification Decision Tree For Respiratory Sensitisers - Mixtures

Does the **mixture** have reliable and good quality evidence available?

Human – evidence that the substance induces specific respiratory hypersensitivity

and/or

Animal – evidence that the substance induces positive results from appropriate animal test

YES — NO

If CATEGORY 1 Label with: Health Hazard Symbol "Danger" May cause allergy or asthma symptoms or breathing difficulties if inhaled

Is there sufficient data on the individual ingredients and similar tested mixture to adequately characterize this mixture?

YES — NO

***** Does any individual ingredient in the mixture have a concentration limit of?

1.0% solid/liquid
0.2% gas

YES

If CATEGORY 1 Label with: Health Hazard Symbol "Danger" May cause allergy or asthma symptoms or breathing difficulties if inhaled

NO

Not enough data to classify at this time

Can the mixture be characterized by using the Bridging Principles per numbers 16 – 19?

Dilution or Batching or Substantially Similar Mixtures

YES

If CATEGORY 1 Label with: Health Hazard Symbol "Danger" May cause an allergy or asthma symptoms or breathing difficulties if inhaled

NO

Not enough data to classify at this time

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Before the system becomes implemented, this issue should be revisited by the ECOSOC Subcommittee on the GHS as one of its first priorities. It should be noted that the sensitisiation criteria for substances will also have to be re-opened to consider this issue and the inclusion of new information and evolving testing approaches that addresses the question of strong sensitisers versus those that are weaker. Appropriate hazard communication should be considered along with the discussions on the criteria and the availability of an appropriate test method.

Classification Decision Tree For Skin Sensitisers - Substance

Does the **individual substance** have reliable and good quality evidence available?

Human – induces skin sensitisation by contact in a substantial number of people

or

Animal – induces positive results from appropriate animal test

YES

If CATEGORY 1 Label with: Exclamation Mark "Warning" May cause allergic skin reaction

NO

Not enough data to classify at this time

Classification Decision Tree For Skin Sensitisers - Mixtures

Does the **mixture** have reliable and good quality evidence available?

Human – induces skin sensitisation by contact in a substantial number of people

or

Animal – induces positive results from appropriate animal test

YES

If CATEGORY 1 Label with: Exclamation Mark "Warning" May cause allergic skin reaction

NO

Is there sufficient data on the individual ingredients and similar tested mixture to adequately characterize this mixture?

YES

***** Does any individual ingredient in the mixture have a concentration limit of?

1.0% solid/liquid/gas

YES

NO

NO

If
CATEGORY 1
Label with:
Exclamation Mark
"Warning"
May cause allergic
skin reaction

Not enough data
to classify at this time

Can the mixture be characterized by using the Bridging Principles per numbers 16 – 19?

Dilution or Batching or Substantially Similar Mixtures

YES

NO

If
CATEGORY 1
Label with:
Exclamation Mark
"Warning"
May cause an allergic
skin reaction

Not enough data to
classify at this time

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Guidance

Explanatory Notes

23. The mechanisms by which substances induce symptoms of asthma are not yet fully known. For preventative reasons these substances are considered as respiratory sensitisers. However, if on the basis of the evidence, it can be demonstrated that these substances induce symptoms of asthma by irritation only in people with bronchial hyperreactivity, they should not be considered as respiratory sensitisers.

24. At present recognised animal models for the testing of respiratory hypersensitivity are not available. Under certain circumstances, animal testing may be used, e.g. a modification of the guinea pig maximisation test for determination of relative allergenicity of proteins. However, these tests still need further validation.

25. Some substances causing respiratory sensitisation may in addition cause immunological contact urticaria and therefore should be considered for classification as a contact sensitisers.

Immunological Contact Urticaria

26. Substances meeting the criteria for classification as respiratory sensitisers may in addition cause immunological contact urticaria. Consideration should be given to classify these substances also as contact sensitisers. Substances which cause immunological contact urticaria without meeting the criteria for respiratory sensitisers should also be considered for classification as contact sensitisers.

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

Animal Studies

28. When an adjuvant type test method for skin sensitisation is used, a response of at least 30% of the animals is considered as positive. For a non-adjuvant test method a response of at least 15% of the animals is considered positive. Test methods for skin sensitisation are described in the OECD Guideline 406 (the Guinea Pig Maximisation test and the Buehler guinea pig test). Other methods may be used provided that they are well-validated and scientific justification is given.

29. The mouse ear swelling test, MEST, and the local lymph node assay, LLNA, appear to be reliable screening tests to detect moderate to strong sensitisers. The LLNA or the MEST can be used as a first stage in the assessment of skin sensitisation potential. In case of a positive result in either assay it may not be necessary to conduct a further guinea pig test.

30. When evaluating animal data, produced by testing according to the OECD or equivalent Guidelines for skin sensitisation, the rate of sensitised animals may be considered. This rate reflects the sensitising capacity of a substance in relation to its mildly irritating dose. This dose may vary between substances. A more appropriate evaluation of the sensitising capacity of a substance could be carried out if the dose-response relationship was known for the substance. This is an area that needs further development.

31. There are substances that are extremely sensitising at low doses where others require high doses and long time of exposure for sensitisation. For the purpose of hazard classification it may be preferable to distinguish between strong and moderate sensitisers. However, at present animal or other test systems to subcategorise sensitisers have not been validated and accepted. Therefore, sub-categorisation should not yet be considered as part of the harmonised classification system. (See Background Information).

Background Information

32. Categorisation of sensitisers accounting for differences in sensitising capacity among substances would be a useful concept to develop. It may be appropriate to allocate both respiratory and dermal sensitisers to, for example, one of the following categories:

Category 1, Strong Sensitiser:

A strong sensitiser would be indicated by

- a high frequency of occurrence and/or severity of occurrence within an exposed population or
- a probability of occurrence of a high sensitisation rate in humans based on animal or other tests.

Category 2, Sensitiser:

A low to moderate sensitiser would be indicated by

- a low or moderate frequency or severity of occurrence within an exposed population or
- a probability of occurrence of a low to moderate sensitisation rate in humans based on animal or other tests.

33. Some authorities currently categorise strong sensitisers. However, at present, animal or other test systems to subcategorise sensitisers as indicated above, have not been validated and accepted. Work is going on to develop such models for the potency evaluation of contact allergens.

SUMMARY TABLE

Classification and Labelling Summaries

Respiratory Sensitiser for Individual Substances			
Class	**Criteria**	**Hazard Communication Element**	
Category 1	**If there is human evidence that the individual substance induces specific respiratory hypersensitivity** and / or **Positive results from an appropriate animal test**	*Signal Word*	**Danger**
		Symbol	**Health Hazard Symbol**
		Hazard Statement	**May cause allergic or asthmatic symptoms or breathing difficulties if inhaled**

Respiratory Sensitiser for Mixtures			
Class	Criteria	Hazard Communication Element	
Category 1	** **If any individual ingredient in the mixture has a concentration of:** **1.0% Solid/Liquid** **0.2% Gas** **or** **This mixture meets the criteria set forth in the "Bridging Principles" through one of the following:** **1. Dilution** **2. Batching** **3. Substantially Similar Mixture**	*Signal Word*	**Danger**
		Symbol	**Health Hazard Symbol**
		Hazard Statement	**May cause allergic or asthmatic symptoms or breathing difficulties if inhaled**

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Skin Sensitiser for Individual Substances			
Class	**Criteria**	**Hazard Communication Element**	
Category 1	**If there is human evidence that the individual substance induces skin sensitisation by contact in a substantial number of people** OR **Positive results from an appropriate animal test**	*Signal Word*	**Warning**
		Symbol	**Exclamation Mark**
		Hazard Statement	**May cause allergic skin reaction**

Skin Sensitiser for Mixtures			
Class	**Criteria**	**Hazard Communication Element**	
Category 1	** **If any individual ingredient in the mixture has a concentration of:** **1.0% Solid/Liquid/Gas** OR **This mixture meets the criteria set forth in the "Bridging Principles" through one of the following:** **1. Dilution** **2. Batching** **3. Substantially Similar Mixture**	*Signal Word*	**Warning**
		Symbol	**Exclamation Mark**
		Hazard Statement	**May cause allergic skin reaction**

**** There has been considerable discussion about what to convey about sensitization effects to those exposed, and at what point it should be conveyed. While the current cut-off for mixtures is 1.0%, it appears that the major systems all believe information should be conveyed below that level. This may be appropriate both to warn those already sensitized, as well as, to warn those who may become sensitized. This issue was not clear during the initial deliberations on the criteria for mixtures containing sensitisers, and thus has not been adequately discussed nor options explored.

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EXAMPLES:

Skin Sensitization

*** Modified from the AIHA WEEL Monograph for pentaerytritol triacrylate. We would need AIHA's permission otherwise it would need to be modified and put into our own format.

Pentaerythritol Triacrylate:

Identification: Chemical identification information is provided here

Chemical and Physical Properties:

Uses:

Animal Toxicology Data:

A. Acute Toxicity and Irritancy

1. Oral Toxicity
2. Eye Toxicity
   Rabbits: Corrosive
3. Skin Absorption
   Rabbits: LD50 greater than 4000 mg/kg
4. Skin Irritation
   Rabbits: severely irritating
5. Skin Sensitization: Guinea pigs: PETA produced evidence of skin sensitization (delayed contact hypersensitivity) in 16 of 20 animals in the maximization test but was negative in the Buehler assay.
6. Inhalation Toxicity

Human Use and Experience:

Due to its low volatility, PETA is not expected to produce adverse effects from inhalation under normal conditions. However aerosols or vapors produced at elevated temperatures may cause respiratory tract irritation, coughing, mucous production and shortness of breath. No data were available on the concentrations required to produce these effects. All multifunctional acrylates are irritating upon contact and are known or suspected dermal sensitizers. PETA has been reported to cause dermal sensitization reactions in workers handling UV curable inks and several of these cases have been verified by patch testing. The lowest challenge concentration that elicited a positive response was 0.01%. Unanticipated exposure to PETA may occur when the compound is present in other products that may represent “hidden” sources. For example, two individuals developed allergic skin rashes several years after working with a floor top coat containing polyurethane and polyfunctional aziridine hardeners and additives. Patch testing showed positiveresponses to PETA and trimethylolpropane triacrylate (TMPTA).

Rationale for Classification:

Animal studies, human experience and patch testing have shown that PETA is a Category 1 skin sensitizer. There is insufficient data to classify PETA as a respiratory sensitizer at this time.