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COMMITTEE OF EXPERTS ON THE TRANSPORT OF DANGEROUS GOODS AND ON THE GLOBALLY HARMONIZED SYSTEM OF CLASSIFICATION AND LABELLING OF CHEMICALS
Sub-Committee of Experts on the Globally Harmonized System of Classification and Labelling of Chemicals
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GLOBAL HARMONIZATION OF SYSTEMS OF CLASSIFICATION AND LABELLING OF CHEMICALS

Possible areas of future work

Transmitted by the experts from the Canada, Finland and the United States of America

Introduction

The purpose of this document is twofold:

1. To identify possible areas of future work that were identified by the technical focal points, specifically the OECD and the ILO, during the development of the Globally Harmonized System for the Classification and Labelling of Chemicals; and

2. To provide a list of possible issues to be considered for the workplan of the Sub-Committee for the next biennium. The Sub-Committee will need to finalize its workplan for 2003-2004 at its meeting in December 2002 for submission to the Committee of Experts on the Transport of Dangerous Goods and on the Globally Harmonized System for the Classification and Labelling of Chemicals. It is not expected that time will permit the Sub-Committee to work on all of the listed issues. Therefore, the Sub-Committee will need to set priorities for future work.

A. CLASSIFICATION: HEALTH HAZARD CATEGORIES

1. Acute toxicity

1.1 New test methods for acute toxicity

Objective: To revise the classification criteria for acute toxicity to take account of the experimentally obtained acute toxicity range estimates to point estimates for the respective routes of exposure.

2 Respiratory and dermal sensitization

2.1 Cut-Off/Concentration limits for sensitizers

Objective: To revise the cut-off/concentration limits for sensitizers.

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%, 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 sensitizers, and thus has not been adequately discussed nor options explored.

2.2 Strong vs. weak sensitizers

Objective: To examine the available information concerning strong vs. weak sensitizers and, if appropriate, propose revisions to the classification criteria for respiratory and/or dermal sensitization.

The IOMC Coordinating Group for the Harmonization of Classification and Labelling noted that the sensitization criteria for substances should be re-opened to consider the inclusion of new information and evolving testing approaches that addresses the question of strong sensitizers 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.

Note: The following text was provided as "Background Information" in the OECD *Harmonized Integrated Classification System for Human Health and Environmental Hazards of Chemical Substances and Mixtures.*

1. Categorisation of sensitizers 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 sensitizers to, for example, one of the following categories:

   Category 1, Strong Sensitizer:

   A strong sensitizer 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 sensitization rate in humans based on animal or other tests.

Category 2, Sensitizer:

A low to moderate sensitizer 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 sensitization rate in humans based on animal or other tests.

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

3. Carcinogenicity

3.1 Estimating Potency for Labelling Limits

Objective: To examine methods for potency estimation**.**

The relative hazard potential of a chemical is a function of its intrinsic potency. There is great variability in potency among chemicals and it may be important to account for these potency differences. The work that remains to be done is to examine methods for potency estimation. Carcinogenic potential, as used here, does not preclude risk assessment.

Note: The following text was provided as "Background Information" in the OECD *Harmonized Integrated Classification System for Human Health and Environmental Hazards of Chemical Substances and Mixtures.*

Considerations of Potency for Labelling Limits

(1) The considerations as laid out below were excerpted from the Report of the Meeting of the Working Group on Harmonisation of Classification and Labelling of Carcinogens, Washington, DC, 17-18 October 1995.

Purpose

(2) The purpose of establishing a potency scheme to be used for labelling of substances, preparations (mixtures) and contaminants is to provide for practical minimum levels of carcinogens in substances for which labelling would be required. It will result in labelling highly potent materials more strictly and less potent materials less strictly. A further purpose is to eliminate unnecessary labelling. In addition, use of a potency scheme may encourage risk reduction through purification of chemical substances or reformulating preparations.

Background

(3) A large number of chemicals have been classified as carcinogenic and placed into various categories for labelling or other regulatory purpose. Chemicals that have been identified as carcinogenic may also occur as components of preparations (mixtures), impurities or additives. Gold and co-authors (Environ Health Perspect 79: 259, 1989) calculated doses from animal testing which result in tumours in half the dosed animals (TD50 values span a

range of more than eight orders of magnitude). Most classification systems do not take into account the wide range of potencies of these chemicals.

(4) Carcinogens are in some countries divided into three potency groups: high, medium and low. Potency is in these instances determined using dose-response data in the observed dosing range for laboratory animals. Additional indicators of potency such as tumour site and species specificity, or species differences in toxicokinetics may also be used. Such potency groups are used to set upper limits for the classification of substances as carcinogens and for the purpose of initiating labelling. They have also been used for the classification and determination of labelling provisions for preparations (mixtures) of carcinogenic chemicals.

(5) Some countries have implemented a scheme where 0.1% is used as a default limit value for labelling of substances and preparations (mixtures) as carcinogens with sufficient data for carcinogenicity. In these countries chemicals with medium carcinogenic potency are labelled if they occur in chemical substances at or above this level. Many carcinogenic compounds fall into the medium range. Carcinogens with high potency might be classified and labelled at lower levels and carcinogens with low potency could be classified and labelled only when they occur at higher levels. Some countries use 1% as a default limit value for low potency carcinogens and for carcinogens with more limited data.

(6) Some regulatory authorities do not have the obligation to perform potency determinations. If a chemical carcinogen is a candidate for a potency rating outside of the default range, such chemicals should be referred to an international group for its determination.

Observations

(7) The Working Group agreed that it would be useful to explore further the concept of using potency to make labelling decisions. Initial thoughts of the Working Group are presented here.

(8) Potency ranking of carcinogens should not be determined or refined more precisely than by ten-fold factors in light of differences in species response, tumour types and the limits of standardisation of test protocols. In light of these points, a scheme for classification and labelling purposes which separates carcinogens into potency groupings serves the practical purposes listed above.

(9) The use of potency for establishing limits does not preclude the ability of authorities to perform quantitative risk assessments of exposures to carcinogenic substances for regulatory purposes.

(10) Potency determinations should be based on well performed studies which are peer reviewed, performed according to good laboratory practices, or are deemed acceptable by regulatory authorities.

3.2 Factors to be taken into consideration when assessing carcinogenic hazards

Objective: To develop guidance on the factors noted in Chapter 3.6, paragraph 9.

The proceedings of a WHO/IPCS working group on harmonized risk assessment for carcinogenicity points to a number of scientific questions arising for classification of chemicals e.g. mouse liver tumours, peroxisome proliferation, receptor-mediated reactions, chemicals which are carcinogenic only at toxic

doses and which do not demonstrate mutagenicity. Accordingly, there is a need to articulate the principles necessary to resolve these scientific issues, which have led to diverging classifications in the past. Once these issues are resolved, there would be a firm foundation for classification of a number of chemical carcinogens. (Excerpt from Chapter 3.6, paragraph 16.)

4. Reproductive toxicity

4.1 Classification of mixtures containing substances having effects on or via lactation

Objective: To develop classification criteria for mixtures containing substances having effects on or via lactation.

Harmonized criteria for the classification of mixtures containing substances which have effects on lactation have to date not been developed. The data base for this hazard category is extremely limited, and experience will have to be gained in using the category in the harmonized system before the issue of classification of mixtures containing components which can contaminate breast milk can be addressed.

4.2 Potency and cut-off doses:

Objective: To amend the classification criteria for toxic to reproduction to consider cut-off dose levels related to the relative potency of a chemical.

The following text was provided as "Background Information" in the OECD *Harmonized Integrated Classification System for Human Health and Environmental Hazards of Chemical Substances and Mixtures*.

> In the present scheme, the relative potency of a chemical to produce a toxic effect on reproduction is not included in the criteria for reaching a conclusion regarding classification. Nevertheless, during the development of this scheme it was suggested that cut-off dose levels should be included, in order to provide some means of assessing and categorizing the potency of chemicals for the ability to produce an adverse effect on reproduction. This concept has not been readily accepted by all member countries because of concerns that any specified cut-off level may be exceeded by human exposure levels in certain situations, e.g. inhalation of volatile solvents, the level may be inadequate in cases where humans are more sensitive than the animal model, and because of disagreements about whether or not potency is a component of hazard. There has been interest in this concept to further consider it as a future development of the classification scheme.

4.3 Limit dose:

Objective: To examine whether a specified dose should be included as a limit dose in the classification criteria for toxic to reproduction.

The following text was provided as "Background Information" in the OECD Harmonized Integrated Classification System for Human Health and Environmental Hazards of Chemical Substances and Mixtures.

(1) There is general agreement about the concept of a limit dose, above which the production of an adverse effect may be considered to be outside the criteria which lead to classification. However, there was no agreement within the OECD Task Force regarding the inclusion within the criteria of a specified dose as a limit dose. Some Test Guidelines

specify a limit dose, other Test Guidelines qualify the limit dose with a statement that higher doses may be necessary if anticipated human exposure is sufficiently high that an adequate margin of exposure would not be achieved. Also, due to species differences in toxicokinetics, establishing a specific limit dose may not be adequate for situations where humans are more sensitive than the animal model.

(2) In principle, adverse effects on reproduction seen only at very high dose levels in animal studies (for example doses that induce prostration, severe inappetence, excessive mortality) would not normally lead to classification, unless other information is available, e.g. toxicokinetics information indicating that humans may be more susceptible than animals, to suggest that classification is appropriate. Please also refer to the section on Maternal Toxicity for further guidance in this area.

(3) However, specification of the actual 'limit dose' will depend upon the test method that has been employed to provide the test results, e.g. in the OECD Test Guideline for repeated dose toxicity studies by the oral route, an upper dose of 1000 mg/kg unless expected human response indicates the need for a higher dose level, has been recommended as a limit dose.

(4) Further discussions are needed on the inclusion within the criteria of a specified dose as a limit dose.

4.4 Terminology

Objective: To clarify the following terms used in Chapter 3.7, paragraphs 5 and 6: reproductive toxicity, developmental toxicity, reproductive ability and capacity, class and category

5. Examples of classification

Objective: To develop examples which illustrate the classification criteria.
The Sub-Committee on the GHS may wish to consider the development of further examples which illustrate the GHS classification criteria.

B HAZARD CLASSIFICATION: ENVIRONMENTAL HAZARD CATEGORIES

1. Chronic toxicity

Objective: To further develop the classification scheme to accommodate chronic toxicity to aquatic organisms for assigning a chronic hazard category.

While the current system will continue to rely on the use of acute toxicity data in combination with a lack of rapid degradation and/or a potential to bioaccumulate as the basis for classification for assigning a chronic hazard category, it is recognised that actual chronic toxicity data would form a better basis for classification where these data are available. It is thus the intention that the scheme should be further developed to accommodate such data (*cf.* Para 17, chapter 3.10 GHS document).

Background

The third meeting of the *Ad hoc* Working Group on Harmonisation of Classification Systems for Substances Hazardous for the Aquatic Environment confirmed that chronic toxicity should

be an integral component of the classification criteria and that a Chronic toxicity Sub-Group should meet and analyse this issue and make recommendations to the *Ad hoc* Working Group. Several discussion documents were produced and the subgroup did discuss e.g.:

- How to Integrate Chronic Toxicity into the Existing Schemes
- Cut-off Levels for Chronic toxicity
- Preference of Chronic Toxicity Data over Acute Toxicity Data
- Tests for Defining Chronic Toxicity
- Revised Classification Scheme

C HAZARD COMMUNICATION

1. Harmonization of standard precautionary statements:

Objective: To harmonize precautionary statements into fully standardized label elements.

The GHS label elements include precautionary statements. Whilst precautionary information was considered for standardization, there was insufficient time to develop detailed proposals. Examples of precautionary statements and pictograms are found in Annex 4 of the GHS Document.

2. Guidance on the preparation of a safety data sheet:

Objective: To develop guidance on the preparation of the safety data sheet under the Globally Harmonized System for the Harmonization of Classification and Labelling of Chemicals.

The Sub-Committee on the GHS may wish to consider the development of guidance on how to prepare a SDS.

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