Globally harmonised classification for Health and Environmental Hazards

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Abstract

The classification criteria developed by the Organisation for Economic Co-operation and Development (OECD) for Health and Environmental Effects are based on the analysis of the existing classification criteria of dangerous chemicals used by transport and supply/use systems around the world. The main existing systems are the international system for Transport of Dangerous Goods, and the systems of the USA, Canada and the EU.

The OECD countries and the Co-ordinating Group for the Harmonisation of Chemical Classification Systems of the Inter-organisation Programme for the Sound Management of Chemicals (IOMC HCCS CG) have endorsed the harmonised criteria be included in the Globally Harmonised System (GHS) for the following end points:

- Hazardous to the Aquatic Environment
- Acute Toxicity
- Skin Irritation/Corrosion
- Eye Irritation/Corrosion
- Sensitisation
- Germ Cell Mutagenicity
- Carcinogenicity
- Reproduction Toxicity
- Specific Target Organ Systemic Toxicity

Criteria will be incorporated with other harmonised elements into an International Recommendation for Globally Harmonised Classification and Labelling System which will be adopted by the Economic and Social Council of the United Nations. The adoption is planned to take place in 2003.

Introduction

United Nations' (UN) Conference on Environment and Development (UNCED) in 1992 identified the harmonisation of classification and labelling of chemicals as one of six action program areas in Chapter 19 of Agenda 21. The mandate for the harmonisation of classification and labelling was defined by UNCED objective: "a globally harmonised hazard classification and compatible labelling system (GHS) including material safety data sheets and easily understandable symbols, should be available, if feasible, by the year 2000".

The co-ordination of the harmonization work was addressed to a Co-ordinating Group of Harmonisation of Chemical Classification Systems of the Interorganisation Programme for Sound Management of Chemicals[1] (IOMC CG HCCS) which was established as a consequence of the resolution of the Intergovernmental Forum on Chemical Safety (IFCS) established in Stockholm in 1994. IFCS III in October 2000 endorsed the achievements of Harmonisation of Hazard Classification and Communication and specified further time schedules and goals for the future remaining work. GHS should be available for the final adoption by UN Economic and Social Council in 2003.

International organisations that are engaged in the harmonization work are OECD, International Labour Organisation (ILO) and UN Committee of Experts of Transport of Dangerous Goods (UNCETDG). The responsibility of the OECD is to develop classification criteria for health and environmental effects.

Organisation of OECD work on harmonization of classification criteria

OECD Expert Groups (earlier called Working Group) have worked out proposals on harmonized criteria on health and environmental effects, which are endorsed by the Task Force (earlier called Advisory Group) for adoption by the OECD Joint Meeting. After adoption by the Joint Meeting the so called Integrated Document /1/ is transferred to the IOMC CG HCCS which will merge results of harmonization exercises into one package.

For each end-point (specific hazard) the following steps are undertaken:

Step 1:
An analysis of existing classification systems, including the scientific basis for the system and its criteria, rationale and explanation of the use. A step 1 document is established on the basis of information provided by countries or systems (like transport), responding to inquiries of the OECD Secretariat.

Step 2:
A proposal for a harmonised classification system and criteria for each end point (class) is developed using as a basis the elements of existing systems.

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[1] IOMC organisations: UNEP, ILO, WHO, FAO, UNITAR, OECD

Step 3:
Step 2 document is revised on the basis of discussions taking place between experts. Either a consensus is achieved or the specific non-consensus items are identified as alternatives. Task Force endorses proposals, and if necessary, develops further compromises.

Step 4:
Final proposal is submitted to the OECD Joint Meeting for approval and subsequently to the IOMC CG-HCCS for global implementation.

Scope of the Harmonized Classification System

The harmonized classification system should cover in principle all substances and mixtures. However, application of elements of the system may vary by type of product or stage of the life cycle. The IOMC CG HCCS has produced a general principle covering the concern, how the harmonized classification system could meet the needs of various end-users of different sectors:

"harmonization means establishing a common and coherent basis for chemical hazard classification and communication, from which the appropriate elements relevant to means of transport, consumer, worker and environment protection can be selected."

Some hazards (end-points) have been sub-divided into sub-classes to be able to accommodate the needs of existing systems. The harmonised system would allow existing systems to pick up those elements that they need. If the elements are chosen they should be used in accordance with the GHS. As an example it can be mentioned that system for transport of dangerous goods will not use the end-points covering long-term health hazards. Transport would also take up only most hazardous classes of acute toxicity and leave the milder classes outside the transport system. The transport and the other systems would, however, use the cut-off's for classification of acute toxicity as specified by the GHS, in a harmonised way.

The developed criteria should be applicable to both substances and mixtures on the basis of data available on hazards. However, some limitations may be necessary, when criteria are applied to mixtures. Those limitations are specified in the context of classification criteria for mixtures.

The classification will be based on hazards, i.e. on intrinsic properties of chemicals.

Hazard identification and classification criteria

Before classification criteria can be applied, the hazards of a chemical must be identified.

Test data may be used as basic information for identification of the hazard. Test data will be compared with the classification criteria, and conclusions on classification can be made..

Sometimes the classification may take place on the basis of pass or fail test result whereas in other cases interpretation is needed on dose-response curves and observations during testing, or observation may take place, when the test is finished. Test results should always be reproducible and they should provide valid data for a given end-point.

The GHS criteria for determining health and environmental hazards should be test method neutral, allowing different approaches as long as they are scientifically sound and validated and produce mutually acceptable data.

Reliable epidemiological data and other reliable information on humans (statistics on occupational diseases, data from accident data bases, reliable case-studies etc.) should be taken account for classification purposes. Testing on humans solely for hazard identification purposes is generally not acceptable.

For some hazard end-points classification results directly when the data satisfy the criteria. For other end-points the classification may take place on the total weight of evidence approach taking account all available information both on humans and animal experiments as well as on *in vitro* studies and other sources. Weight of evidence based classification is often demanding, and expert judgement may be needed to be able to carry out the task.

The new classification criteria are meant to be applied by the industry itself for "self-classification" as far as possible.

The GHS classification criteria may be different from the existing ones. This may create problems in interpretation of existing test data in comparison with classification criteria. Sometimes it may be difficult to determine the quality of the old studies. Expert judgement may be needed in these cases. Test data already generated for the classification of chemicals under the existing systems should be accepted when classifying under the new GHS criteria. Duplicative testing and unnecessary use of test animals should be avoided.

End points covered

As a result of OECD step 1 analysis it has turned out that the major existing classification systems are:

- International system for transport of dangerous goods
- Canadian requirements on classification
- US requirements on classification
- EU legislation on classification.

The most common end-points covered by the existing systems were chosen for development of harmonised criteria. The criteria have been finalised for:

Health effects:
- acute toxicity

- skin irritation/corrosion
- eye irritation/corrosion
- sensitisation
- germ cell mutation
- reproductive toxicity
- carcinogenicity
- specific target organ systemic toxicity (TOST)

Environmental effects:
- hazardous to the aquatic environment.

The work has been started on some other end-points, some end-points are not yet covered:
- Narcotic effects (work started in November 2000)
- Aspiration Hazard (work started in November 2000)
- Respiratory irritation (work started in November 2000)
- Water activated toxicity/corrosion (work started in November 2000)
- Local dermal effects after repeated exposure
- Immunotoxicity
- Hazardous to the terrestial environment.

Acute toxicity

Acute toxicity of chemicals is considered on the basis of acute lethal toxicity tests measured as LD_{50}- or LC_{50}-values in rats or rabbits. If LD_{50}- or LC_{50}-data are available on animal experiments, they can directly be compared with the criteria. If data are available on other type of acute toxicity studies or other type of data are available, the results should be adjusted to respond to the LD_{50}- or LC_{50}-values.

Chemicals (substances or mixtures) can be allocated to one of the five classes based on acute toxicity by the oral, dermal or inhalation route according to the criteria expressed as LD_{50} (oral, dermal)- or LC_{50} (inhalation) cut-off-values. The cut-off's are specified in table 1.

Table 1 Acute toxicity hazard classes and (approximate) LD50/LC50 values defining the respective classes

	Class 1	Class 2	Class 3	Class 4	Class 5
Oral (mg/kg)	5	50	300	2000	Up to 5000 See special criteria
Dermal (mg/kg)	50	200	1000	2000	
Gases (ppm)	100	500	2500	5000	
Vapours (mg/l)	0,5	2,0	10	20	
Dust and mists (mg/l)	0,05	0,5	1,0	5	

Skin irritation/corrosion

Corrosive substances cause necrosis of tissues. Chemicals which may cause reversible effects, like inflammation, erythema/eschar or oedema, are considered to be irritant.

Criteria on skin corrosion/irritation are based on elements of existing systems and are using as a basis the knowledge available on the existing testing methods and their sensitivity. Table 2 provides the classification criteria.

Table 2 Skin irritation/corrosion

Class 1			Class 2	Class 3
Destruction of dermal tissue: visible necrosis in at least one animal			Reversible adverse effects in dermal tissue Mean Draize score in 2 of 3 animals: 2,3 ≤ erythema/ eschar/edema < 4,0, or persistent inflammation	Reversible adverse effects in dermal tissue Mean Draize score in 2 of 3 animals: 1,5 ≤ erthema/eschar/ edema < 2,3
Subclass 1 A Exposure < 3 minutes Observation < 1 hour	Subclass 1 B Exposure < 1 hour Observation < 14 days	Subclass 1 C Exposure < 4 hours Observation < 14 days		

General consideration should take place before testing is undertaken. The new *in vitro* tests will provide a good solution to the existing testing problem. Existing human experience and existing data on animal studies should be focused on first. Also information on structurally related compounds may help to make classification decisions. pH-extremes, like pH ≤ 2 and ≥ 11,5 may indicate dermal effects, especially when buffering capacity is known. Generally such chemicals are expected to produce significant effects on skin. A tiered weight of evidence approach is specified by the OECD criteria.

Eye irritation/corrosion

Classification criteria are provided for eye irritation/corrosion in Table 3.

Table 3 Eye irritation/corrosion

Class 1	Class 2	
• Irreversible damage to cornea, iris, conjunctive 21 days after exposure in at least one animal • Mean Draize score in 2 of 3 animals: corneal opacity ≥ 3, iritis > 1,5	• Reversible adverse effects on cornea, iris, conjunctiva • Mean Draize score in 2 of 3 animals: Corneal opacity ≥ 1, iritis ≥ 1, redness ≥ 2, chemosis ≥ 2	
	Subclass 2A Reversible in 21 days	Subclass 2B Reversible in 7 days

Before any testing is undertaken all existing information on the chemical should be reviewed. This approach includes same considerations as in the case of corrosion/irritation on the skin and a tiered approach should be applied when considering the usefulness of existing data for classification purposes.

Respiratory or skin sensitisation

A respiratory sensitiser is a substance that will induce hypersensitivity of the airways following inhalation of the substance. A contact sensitiser is a substance that will induce an allergic response following skin contact. Only one class is defined. Table 4 provides the classification criteria for sensitisation.

Table 4 Sensitisation

Respiratory sensitisation	Class 1 • Evidence in humans of specific respiratory hypersensitivity, or • Positive results from animal test
Dermal sensitisation	Class 1 • Evidence in humans of sensitisation by skin contact, or • Positive results from animal tests

Evidence on specific respiratory hypersensitivity will normally be based on human experience. The symptoms of hypersensitivity are normally asthma, rhinitis/conjunctivitis or alveolitis. A character of an allergic reaction is typical, but immunological mechanisms do not have to be demonstrated. When considering the human evidence it is necessary to take account also

- Size of the exposed population
- Extent of exposure.

As evidence on the effect, results of clinical studies are considered. The cause-effect relationship should be demonstrated by a clinical history. Animal studies may provide additional information on measurements of immunological responses.

Skin sensitisers can be identified on the basis of human evidence using positive results e.g. of patch testing, epidemiological studies or evidence based on appropriate case studies. Results of animal studies can be used as a basis for classification.

Normally positive results seen either in animal tests or on the basis of human evidence is sufficient for classification. If the information is conflicting, a weight of evidence based consideration should take place. If there is some indication on the basis of available information on possible sensitising effects, this information should be considered on a case by case basis. Detailed guidance is provided by the OECD criteria.

Mutations in germ cells

Chemicals of concern for their possible mutagenic effects are those which may cause mutations in the germ cells of humans and these mutations can be transmitted to the progeny. Evidence on mutagenic effects is normally based on animal tests, but information on *in vitro* tests and *in vivo* tests in mammalian somatic cells is also considered. A mutation is defined as a permanent change in the amount or structure of the genetic material in a cell.

The classification system comprises two different classes of germ cell mutagens to accommodate the weight of evidence available. Class 1 covers substances which are *known to produce mutations* in human germ cells. Class 1 is divided into two subclasses depending on where the evidence comes from. The effect is assessed on the basis of positive epidemiological studies on humans (subclass 1A) or on the basis of positive results *in vivo* heritable germ cell tests in mammals, human germ cell tests, or i*n vivo* somatic mutagenicity tests, combined with some evidence of germ cell mutagenicity (subclass 1B).

Class 2 covers substances which *may induce heritable mutations* in human germ cells. The classification may be based on positive evidence from tests in mammals and somatic cell tests, or i*n vivo* somatic genotoxicity supported by *in vitro* mutagenicity.

Classification for heritable effects in human germ cells is made on the basis of well conducted, sufficiently validated tests, preferably as described in OECD Test Guidelines. Evaluation of the test results should be done using expert judgement and all the available evidence should be weighed for classification.

Carcinogens

Carcinogens are chemical substances which induce cancer or increase its incidence. Substances which have induced benign and malignant tumours in well performed experimental studies on animals are considered also to be presumed or suspected human carcinogens unless there is strong evidence that the mechanism of tumour formation is not relevant for humans.

Class 1 covers substances which are *known or presumed carcinogens*. The classification is based either on human evidence (subclass 1A) or demonstrated animal carcinogenicity (subclass 1B). Class 2 covers *suspected carcinogens*, where limited evidence is available on humans or animals.

Weight of evidence consideration should take place when classification is considered.

Reproductive toxicity

Reproductive toxicity includes adverse effects on sexual function and fertility in adult males and females, as well as developmental toxicity in the offspring. For classification purposes, the known induction of genetically-based inheritable effects in the offspring is addressed elsewhere, since in the present classification system it is considered more appropriate to address such effects under the separate end-point of germ-cell mutagenicity.

Class 1 covers *known or presumed human reproductive or developmental* toxicants. The classification is based either on human evidence (class 1A) or animal studies (class 1B). Class 2 covers *suspected human reproductive or developmental* toxicants, where limited evidence is available on the effect on humans or animals. Additional class is linked to hazards caused by breastfeeding in case mother is exposed to chemicals which may affect the breast milk.

A weight of evidence approach is used for classification.

Target organ systemic toxicity, single exposure and repeated exposure

Substances may be classified as causing target organ systemic toxicity (TOST) effects if they produce specific, non lethal target organ/systemic toxicity arising from single or repeated exposure. All significant health effects that can impair function, both reversible and irreversible, immediate and/or delayed are included.

Classification depends upon the availability of reliable evidence that a single or repeated exposure to the substance has produced a consistent and identifiable toxic effect in humans, or, in experimental animals, toxicologically significant changes which have affected the function or morphology of a tissue/organ, or has produced serious changes to the biochemistry or haematology of the organism and these changes are relevant for human health. It is recognised that human data will be the primary source of evidence for this end point.

Classification takes place by using weight of evidence approach. Expert judgement is needed for evaluation. Criteria are provided in table 5.

Table 5 Target organ systemic toxicity, single exposure and repeated exposure

Class 1	Class 2
Significant toxicity in humans • Reliable, good quality human case studies or epidemiological studies Presumed significant toxicity in humans • Animal studies with significant and/or severe toxic effects relevant to humans at generally low exposure (guidance)	Presumed to be harmful to human health • Animal studies with significant toxic effects relevant to humans at generally moderate exposure (guidance) • Human evidence in exceptional cases

Explanatory notes are provided for application of the OECD criteria.

Hazardous for the aquatic environment

The basis of the identification of the hazard is the aquatic toxicity of the substance, which may be modified by further information on the degradation and bioaccumulation behaviour. The system is intended for substances, not for mixtures. Table 6 specifies the criteria.

Table 6 Hazardous for the aquatic environment

Acute Class 1 Acute toxicity ≤ 1,00 mg/l	Acute Class 2 Acute toxicity > 1,00 but ≤ 10,0 mg/l	Acute Class 3 Acute toxicity > 10,0 but ≤ 100 mg/l	
Chronic Class 1 Acute toxicity ≤ 1,00 mg/l and lack of rapid degradability and log K_{ow} ≥ 4 unless BCF < 500	Chronic Class 2 Acute toxicity > 1,00 but ≤ 10,0 mg/l and lack of rapid degradability and log K_{ow} ≥ 4 unless BCF < 500 and unless chronic toxicity > 1 mg/l	Chronic class 3 Acute toxicity > 10,0 but ≤ 100,0 mg/l and lack of rapid degradability and log K_{ow} ≥ 4 unless BCF < 500 and unless chronic toxicity > 1 mg/l	Chronic class 4 Acute toxicity > 100,0 mg/l and lack of rapid degradability and log K_{ow} ≥ 4 unless BCF < 500 and unless chronic toxicity > 1 mg/l

Conclusions

Classification criteria developed by the OECD on health and environmental effects include many familiar elements. At the same time they are somewhat different from all existing classification criteria.

Implementation of the new criteria can be started when all elements of GHS are available and adopted by the UN Economic and Social Council. The final adoption as an international non-binding instrument will take still some years and is expected to take place in 2003.

OECD will continue its activity as an expert body developing new classification criteria and updating the existing ones under the new GHS Committee structure of UN Economic and Social Council.

The GHS will provide a common framework for classification and labelling of chemicals. GHS will help to ensure that coherent information is provided on chemicals worldwide.

References

1. http://www.oecd.org/ehs/Class/HCL6.htm, Organisation of Economical Co-operation and Development (OECD), Harmonized Integrated Hazard Classification System for Human Health and Environmental Effects of Chemical Substances, as endorsed by the 28th Joint Meeting of the Chemicals Committee and the Working Party on Chemicals in November 1998