Organisation de Coopération et de Développement Economiques
Organisation for Economic Co-operation and Development

OLIS : 15-Dec-2000
Dist. : 18-Dec-2000

Or. Eng.

ENVIRONMENT DIRECTORATE
JOINT MEETING OF THE CHEMICALS COMMITTEE AND
THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY

OECD SERIES ON TESTING AND ASSESSMENT
Number 25

DETAILED REVIEW DOCUMENT ON HAZARD CLASSIFICATION SYSTEMS FOR SPECIFIC TARGET ORGAN SYSTEMIC TOXICITY FOLLOWING SINGLE OR REPEATED EXPOSURE IN OECD MEMBER COUNTRIES

98711

ENV/JM/MONO(2000)11 Unclassified

Or. Eng.

OECD Environmental Health and Safety Publications

Series on Testing and Assessment

No. 25

DETAILED REVIEW DOCUMENT ON HAZARD CLASSIFICATION SYSTEMS FOR SPECIFIC SYSTEMIC TARGET ORGAN TOXICITY FOLLOWING SINGLE OR REPEATED EXPOSURE IN OECD MEMBER COUNTRIES

Environment Directorate

ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT

Paris

November 2000

Also Published in the Series on Testing and Assessment:

No. 1, *Guidance Document for the Development of OECD Guidelines for Testing of Chemicals (1993; reformatted 1995)*

No. 2, *Detailed Review Paper on Biodegradability Testing (1995)*

No. 3, *Guidance Document for Aquatic Effects Assessment (1995)*

No. 4, *Report of the OECD Workshop on Environmental Hazard/Risk Assessment (1995)*

No. 5, *Report of the SETAC/OECD Workshop on Avian Toxicity Testing* (1996)

No. 6, *Report of the Final Ring-test of the Daphnia magna Reproduction Test* (1997)

No. 7, G*uidance Document on Direct Phototransformation of Chemicals in Water* (1997)

No. 8, *Report of the OECD Workshop on Sharing Information about New Industrial Chemicals Assessment (1997)*

No. 9, *Guidance Document for the Conduct of Studies of Occupational Exposure to Pesticides During Agricultural Application (1997)*

No. 10, *Report of the OECD Workshop on Statistical Analysis of Aquatic Toxicity Data* (1998)

No. 11, *Detailed Review Paper on Aquatic Testing Methods for Pesticides and industrial Chemicals* (1998)

No. 12, *Detailed Review Document on Classification Systems for Germ Cell Mutagenicity in OECD Member Countries (1998)*

No. 13, *Detailed Review Document on Classification Systems for Sensitising Substances in OECD Member Countries* 1998)

No. 14, *Detailed Review Document on Classification Systems for Eye Irritation/Corrosion in OECD Member Countries* (1998)

No. 15, *Detailed Review Document on Classification Systems for Reproductive Toxicity in OECD Member Countries* (1998)

No. 16, *Detailed Review Document on Classification Systems for Skin Irritation/Corrosion in OECD Member Countries(1998)*

No. 17, *Environmental Exposure Assessment Strategies for Existing Industrial Chemicals in OECD Member Countries (1999)*

No. 18, *Report of the OECD Workshop on Improving the Use of Monitoring Data in the Exposure Assessment of Industrial Chemicals (2000)*

No. 19, *Draft Guidance Document on the Recognition, Assessment and Use of Clinical Signs as Humane Endpoints for Experimental Animals used in Safety Evaluation (November 1999)*

No. 20, *Revised Draft Guidance Document for Neurotoxicity Testing (in preparation)*

No. 21, *Detailed Review Paper : Appraisal Of Test Methods For Sex Hormone Disrupting Chemicals (2000)*

No. 22, *Guidance Document for the Performance of Out-door Monolith Lysimeter Studies* (2000)

No. 23, *Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures (2000)*

No. 24, *Draft Guidance Document on Acute Oral Toxicity Testing* (2000)

About the OECD

The Organisation for Economic Co-operation and Development (OECD) is an intergovernmental organisation in which representatives of 29 industrialised countries in North America, Europe and the Pacific, as well as the European Commission, meet to co-ordinate and harmonise policies, discuss issues of mutual concern, and work together to respond to international problems. Most of the OECD's work is carried out by more than 200 specialised Committees and subsidiary groups composed of Member country delegates. Observers from several countries with special status at the OECD, and from interested international organisations, attend many of the OECD's Workshops and other meetings. Committees and subsidiary groups are served by the OECD Secretariat, located in Paris, France, which is organised into Directorates and Divisions.

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 chemical preparations. 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 world-wide 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 8).

The Environmental Health and Safety Programme co-operates closely with other international organisations. This document was produced within the framework of the Inter-Organisation 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 Organisations), 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 Organisation. The purpose of the IOMC is to promote co-ordination of the policies and activities pursued by the Participating Organisations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

OECD Environment Directorate,
Environmental Health and Safety Division

2 rue André-Pascal
75775 Paris Cedex 16
France

Fax: (33-1) 45 24 16 75

E-mail: ehscont@oecd.org

FOREWORD

The Detailed Review Document on Classification Systems for Specific Target Organ/ Systemic Toxicity in OECD Member Countries has been prepared by a Drafting Group involving Belgium(lead country), Canada, Netherlands, Norway, UK, USA, TUAC and BIAC as part of the work being carried out by the OECD's Programme on Harmonization of Classification and Labelling Systems.

This document has been produced within the framework of the Inter-Organisation Programme for the Sound Management of chemicals (IOMC).

TABLE OF CONTENTS

INTRODUCTION

1. In the context of the OECD Programme on Harmonisation of Classification and Labelling of Chemicals, Belgium agreed at the first meeting of the Advisory Group to gather information from the OECD member's countries via a questionnaire and to prepare a report on existing systems and/or criteria for systemic toxicity following single or repeated exposure (target organ oriented systemic toxicity).

2. At the sixth Meeting of the Advisory Group (OECD, Paris 22nd-24th April 1998), further clarification was requested in the Step 1 document to explain the rationale behind current national criteria and approaches. At a subsequent teleconference on May 28, 1998 involving Belgium, Canada, Netherlands, Norway, US, TUAC and BIAC, it was decided that Step 1 document should be expanded to describe systems for target organ oriented systemic toxicity following both single and repeated exposure.

3. The latest version of the Step 1 document including comments from US, Canada and Norway was revised in an ad hoc meeting at the OECD (Paris, 4th February 1999) in presence of Belgian, Canadian, Dutch, Swedish, UK, US, BIAC and Japanese representatives.

SCOPE AND DEFINITIONS

Scope

4. Target organ oriented systemic toxicity following single or repeated exposure usually covers a wide range of endpoints. In the present global harmonisation system (GHS) of classification, effects such as acute toxicity, skin and eye irritation, skin and respiratory system sensitisation, carcinogenicity, mutagenicity and reprotoxicity are addressed separately, and so are not included in the present proposal. All other toxicologically relevant endpoints, including neurotoxicity and immunotoxicity, are included in the scope of systemic toxicity following single or repeated exposure.

5. The terms "target organ oriented systemic toxicity" is usually considered to address any or all organ and tissue components of the body systems of mammals. Route of exposure can be by oral administration, by inhalation or by dermal application. Effects at the site of application are excluded.

6. Target organ toxicity induced either by single or repeated exposure is considered in this scope and covers [both transient and] irreversible effects.

Definitions

7. Definitions used in the existing systems, which have been considered, differ from each other as follows:

CANADA:

8. *Adverse effect to health*: A pure substance is classified as having a chronic toxic effect if it elicits a response of sufficient severity to threaten life or cause serious permanent impairment in a statistically significant proportion of the test population.

9. The *Controlled Products Regulations* (CPR) provides a definition for *chronic toxic effect*: adverse effect to the health of a person or test animal that develops, over time, following a single exposure

to a toxic substance or from prolonged or repeated exposure to a toxic substance under conditions that do not produce that effect from a single exposure. *Statistically significant* is defined as shown by statistical procedures to have a high probability of being due to something other than chance.

10. *Acute lethality* means death of animals immediately or within 14 days after a single administration of or exposure to a toxic substance.

EU and NORWAY:

11. In the EU system, classification is concerned with both acute and long-term effects of substances whether resulting from a single or repeated or prolonged exposure. These substances are classified as (the guidance criteria are described in the Annex VI of the directive 67/548/EC):

* *Very toxic* when very low quantities (dose limits specified) cause death or acute or chronic damage to health. They are assigned the symbol T^+ with the indication of danger “very toxic” and an appropriate risk phrase;
* *Toxic* when low quantities (dose limits specified) cause death or acute or chronic damage to health. They are assigned the symbol T with the indication of danger “toxic” and an appropriate risk phrase;
* *Harmful* when reasonable quantities (dose limits specified) cause death or acute or chronic damage to health.
  They are assigned the symbol Xn with the indication of danger “harmful” and an appropriate risk phrase.

12. Any of these classifications applies to substances when inhaled, swallowed or absorbed via the skin. Specific R-phrases are used to indicate the severity of effect and also the route of exposure.

13. *Serious damage to health:* serious damage to health refers to death, toxicologically significant clear functional disturbance or morphological changes caused by single or repeated or prolonged exposure by an appropriate route. Particularly important are the irreversible changes.

KOREA:

14. *Chronic adverse effects:* death or serious damage significant functional impairment, coent clinical changes, and impairment of blood and homopoetic system, and other irreversible changes in target organs.

US:

15. *CPSC,* which covers consumer protection under the Federal Hazardous Substances Act, defines a chronic health effect as a substantial persistent injury or illness that develops over time from a single, prolonged or repeated exposure to a substance. The persistent effects may be reversible or irreversible. *Substantial personal injury or illness* means any injury or illness of a significant nature. It need not be severe or serious. What is excluded by the word "substantial" is a wholly insignificant or negligible injury or illness.

16. Under the Occupational Safety and Health Act (OSHA), chronic or target organ effects are defined as follows, "Chronic effects generally occur as a result of long-term exposure and are of long duration." Chemicals which produce such target organ effects include (but are not limited to) hepatotoxins, nephrotoxins, neurotoxins, agents which act on the blood or hematopoetic system, agents

which damage the lungs, etc. It should be noted that any chemical is to be identified as hazardous for which there is statistically significant evidence on target organ effects based on at least one study conducted in accordance with established scientific principles.

17. Under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), pesticides can be labelled as target organ toxicants, which might lead to long term effects. Although general criteria have not been set forth for this purpose, guidelines for hazard assessment are available for certain endpoints, such as neurotoxicity. In addition, the hazard of certain chemicals, which can cause long-term effects after a single exposure (such as methanol), can be identified.

DESCRIPTION AND RATIONALE OF THE CLASSIFICATION SYSTEMS IN PLACE

THE CANADIAN SYSTEM:

18. The Canadian workplace system is based on the intrinsic hazards of chemicals. Classification is based on the evaluation and scientific judgement of test results conducted according to the specified OECD Test Guidelines or other tests or methods which have been carried out in accordance with generally accepted standards of good scientific practices. A single positive study performed according to good scientific principles and with statistically significant positive results may justify classification. The Canadian system is developed for labelling and MSDS purposes as a condition for sale or importation of the substance to workplaces in Canada.

19. For the purpose of establishing whether a product is subject to the workplace regulations, the supplier uses the specific classification criteria for that endpoint, or evaluation and scientific judgement based on test results on the product or a product with similar properties. In addition, to establish that a product is or is not classified as having a chronic toxic effect, the supplier may use information of which the supplier is aware or ought reasonably to be aware in place of the classification criteria or test results on the product or similar product. If the product (or substance) meets the criteria, it is then classified as a controlled product under workplace regulations. The supplier is then required to label and provide a MSDS as a condition of sale or importation of the product (or substance) to workplaces in Canada.

20. In the development of the workplace criteria, industry, labour and provincial & federal governments examined both the EU system and the proposed US system for hazard communication. The stakeholders decided that they needed criteria, which focussed on adverse health effects that were of sufficient severity to threaten life or cause serious permanent impairment of body organs and the cardiovascular or nervous systems, in a statistically significant proportion of the population. Stakeholders wanted the criteria to be quantitative to focus on those chemicals more likely to pose a hazard to workers.

THE EU SYSTEM INCLUDING NORWAY:

21. In the EU system (Annex VI of directive 67/548/EC), classification of dangerous substances is concerned with both acute and long-term effects.

22. In EU directive 67/548/EC, in order to create a complete and consistent system of classification for single and/or repeated-dose organ toxicity - in analogy to the acute toxicity - a qualitative and quantitative differentiation of the hazard is established with cut-offs (see table 1 & 2).

23. The appropriate risk phrase not only takes into account the route of exposure but the instance of exposure as well:

R39 (Danger of serious irreversible effects) is used for very toxic and toxic substances when there is strong evidence that irreversible damage is likely to be caused by a single exposure by an appropriate route. The severity of effect, i.e. Very toxic or Toxic, and also the route(s) of exposure are indicated by combining R39 with equivalent acute toxicity R-phrases, e.g. R39/28 means 'Very toxic by the oral route', R39/23/24 means 'Toxic by inhalation and dermal contact'.

R40 (Possible risk of irreversible effects) is used for harmful substances, when there is strong evidence that irreversible damage is likely to be caused by a single exposure by an appropriate route. The route(s) of exposure are indicated by combining R40 with equivalent acute toxicity R-phrases, e.g. R40/20/22 means 'Harmful by inhalation or ingestion'.

R48 (Danger of serious damage to health by prolonged exposure) is used for toxic or harmful substances, in case of serious damage (clear functional disturbance or morphological changes which have toxicological significance), and including death, likely to be caused by repeated or prolonged exposure by an appropriate route.

TABLE 1: EU cut-off values for single exposure.

CATEGORY	LD_{50} oral mg/kg bw	LD_{50} dermal mg/kg bw	LC_{50} inhalation mg/l/4h
Very toxic T^+	≤ 25	≤ 50	≤ 0.25
Risk phrase	R39/28	R39/27	R39/26
Toxic T	25-200	50-400	0.25-1.00
Risk phrase	R39/25	R39/24	R39/23
Harmful Xn	200-2000	400-2000	1-5
Risk phrase	R40/22	R40/21	R40/20

TABLE 2: EU cut-off values for repeated or prolonged exposures.

CATEGORY	LD_{50} oral mg/kg bw/day	LD_{50} dermal mg/kg bw/day	LC_{50} inhalation mg/l, 6h/day
Toxic T	≤ 5	≤ 10	≤ 0.025
Risk phrase	R48/25	R48/24	R48/23
Harmful Xn	≤ 50	≤ 100	≤ 0.25
Risk phrase	R48/22	R48/21	R48/20

24. The evidence of health effect is most usually obtained from animal experiments. If adequate evidence is available to demonstrate in practice that the toxic effect of a substance on man is, or is likely to be, different from that suggested by the experimental results obtained in animal tests, then such a substance should be classified according to the toxic effects in man. When considering data derived from practical experience, special attention should be given to exposure levels.

25. The above guide values apply directly where severe lesions have been observed in a subchronic (90 days) toxicity test. When interpreting the results of a sub-acute (28 days) toxicity test, these figures should be increased approximately three fold. If a chronic (2 years) toxicity test is available, it should be evaluated on a case-by-case basis. If results of studies of more than one duration are available, then those from the study of the longest duration should normally be used.

26. Repeated dose toxicity expressed by R48 refers to systemic effects showing a time-dependent increase in severity: smaller doses compared to the respective acute LD50 values would cause impairment by repeated application resulting in a cumulative activity. This procedure is deemed justified since important differences in the aim/purposes, doses/concentrations and mechanism of action as well as in consequences (measures/regulations) exist when acute and chronic toxicities are concerned. Yet the doses have to be small compared to effective acute doses, since the findings in acute toxicity studies are frequently non-specific. Otherwise, detoxification processes (metabolism/ elimination) cannot intervene due to overloading: specific target organ effects caused by small doses would be overlooked if the latter were not sufficiently below the acute cut-offs.

27. Human repeated/long-term exposure levels are expected to be generally far below those relevant for acute toxicity.
Furthermore, consequences (control measures/regulations) differ for substances, which are classified for acute toxicity or repeated exposure toxicity.

28. In order to extend these qualitative arguments into a quantitative framework, cut-off criteria were developed. The starting point is the cut-off value for acute oral toxicity i.e. 2000 mg/kg bw. A strict application of the equivalence to total doses applied would simply result in dividing 2000 by the number of applications (90 days yields a cut-off limit of 22). Yet taking into account adaptive processes approximately a factor of 40 was chosen: thus a cut-off of 2000/40 = 50 mg/kg/day for 90 days study was established. For 4-weeks studies, the equivalent cut-off was derived by multiplying by a factor of 3, i.e. 150 mg/kg/d.

29. A similar rationale was applied for the dermal and inhalatory routes. These criteria were established in 1982/83 (83/467/EEC). In 1991, the inhalatory cut-offs were revised and changed from 0.5 mg/l 6 h into 0.25 mg/l 6 h (91/325/EEC); additional comments were developed as guidance.

30. In addition to the above EU classification, additional risk phrases (without attribution of symbol or indication of danger) can be assigned to substances for specific effects which result from a single or repeated exposure such as:

- R 66: Repeated exposure may cause skin dryness or cracking;
- R 67: Vapours may cause drowsiness and dizziness.

31. Australia, Korea and some of the East-European countries follow the EU system.

THE US SYSTEM:

32. CPSC's system calls for a weight of evidence approach to determine the potential of a substance to cause harm to humans. All available information from human and animal studies is identified and evaluated in identifying the hazard of consumer products. An assessment is then conducted to determine the likelihood of substantial harm to humans under expected conditions of exposure or reasonably

foreseeable misuses of the product, in order to classify and prepare an appropriate warning label. There is only one class of target organ toxicity under this system.

33. This system provides the consumer with evaluated information on a label so that he can use the product effectively to avoid the health hazard. The consumer is not trained to evaluate the likelihood of injury/illness from exposure to potentially hazardous substances (i.e. dose needed to produce the effect, exposure etc.) and should be informed when a substance has a reasonable probability of harm under the conditions of use. The consumer must also be provided with information on how to minimise the potential for harm. Provision of unevaluated information on a label would lead the consumer to either ignore the caution or refuse the use of the substance.

34. OSHA bases its hazard communication system on the premise that workers have a right-to-know the hazards and identities of the chemicals to which they are potentially exposed to at work. Given that premise, coverage is very broad in terms of chemicals for which information is to be communicated. OSHA differentiates the information that is required on labels versus MSDSs. Labels are required to include well-substantiated hazards, while MSDSs are to include all information relevant to the chemical, including results of a single statistically significant study. The point is to let people know as soon as there is evidence of a potential adverse health effect so proper steps can be taken to reduce exposures, and thus reduce the likelihood of the effect being manifested in exposed workers.

35. The rationale proceeds from the fact that workers are often exposed 40 hours a week or more to a large variety of chemicals, which have the potential to cause a number of chronic effects. There is significant evidence that workers are experiencing such chronic effects, from liver damage caused by solvent exposure to lung damage caused by inhalation of crystalline silica. Therefore, any evidence of chronic toxicity in any target organ is be required to be conveyed to workers; such evidence could include studies in either humans or animals.

TESTING REQUIREMENTS

CANADA:

36. There is no requirement for the testing of materials in order to classify them for any of the WHMIS classes. The classification is based on existing data. Although CPR 52 and 59 specify that classification of a substance as producing chronic effect is based on test results from subchronic studies (90 day), CPR 33 specifies that if there are no tests carried out in accordance with the applicable OECD Test Guideline, the supplier may use a test or method described in the US Food and Drug Administration guidelines or the US Environmental Protection Agency guidelines published in the Federal Register or "any other test or method that is carried out in accordance with generally accepted standards of good scientific practice at the time the test is carried out" can be used. In addition, professional judgement can be used to establish that a substance is a controlled product. The Controlled Products Regulations allow consideration of any information that the supplier is aware, or ought reasonably to be aware.

EU AND NORWAY:

37. The evaluation of doses and concentrations for target organ oriented systemic toxicity is usually made from subchronic studies, usually 90 days. The results can serve as a guide when interpreting the effects seen in a sub-acute toxicity study (28 days) or from a two years chronic toxicity study.

38. If the only evidence available is practical human experience and demonstrates a clear toxic effect in man, then such substances can be classified on this evidence by expert judgement.

US:

39. For consumer products, a weight of evidence approach is used, employing all available data, in vitro, animal (persistent effects observed in single exposure acute studies, multi-exposure sub-chronic and chronic studies ranging in duration from 3 months to two years or more), human (accidental to epidemiological). Industry is not required to submit data to CPSC for this purpose, but is responsible for determining the potential of a substance to cause substantial harm to humans.

40. OSHA requires labels to include well-substantiated hazards, while MSDSs are to include all information relevant to the hazard identification of industrial chemicals. Industry is not required to submit studies to OSHA, however, all available data are used to determine hazardous properties of chemicals.

41. The data required for registration of all pesticides includes subchronic toxicity studies. In addition, chronic studies must be submitted for all agricultural pesticides with food uses. For non-agricultural pesticides, chronic toxicity data must be submitted if lower tier studies indicate concern.

TABLE 3: Comparison of the cut-offs limits in the different classification schemes.

SYSTEM	CLASSIFICATION	CONCENTRATIONS		
	LABELLING	oral (mg/kg bw/day)	dermal (mg/kg bw/day)	inhalation
Canada	Class D/div2/subdiv A	≤10	≤ 20	25 ppm vol gas or vap ≤ 10 mg/m^3 dust, mist or fume
	Class D/div2/subdiv B	≥10 but ≤100	≥20 but ≤200	25 but ≤ 250 ppm vol gas or vap ≥ 10 but ≤ 100 mg/m^3 dust, mist or fume
EU + Norway	Toxic	≤ 5	≤ 10	≤ 0.025 mg/l, 6h/day
	Harmful	≤50	100	≤ 0.25 mg/l, 6h/day
Korea	Harmful	NOAEL≤50	NOAEL ≤ 100	NOAEL ≤ 0.5 mg/l, 6h/day
Norway*	Toxic	TC ≤ 10	TD ≤ 20	TD ≤ 0.2 mg/l, 6h/day
	Harmful	10<TD ≤50	20<TD ≤ 100	0.2 <TC ≤ 1.0 mg/l, 6h/day
Norway OAR	Specific warning phrases	Specific method for calculating the corrected occupational air requirement (OAR)		
US	Toxic for specific organ systems	No cut off values; OSHA uses hazard-based system while CPSC determines likelihood of injury to humans.		

ANNEX 1. Comparison of the classification schemes.

	Are chronic effects caused by single exposure included	Are reversible effects included	Is the classification system predominantly exposure or effect-oriented	Are cut-off values used, (number of cut-off values, see Table 1)	Key expressions used in (regulation which establishes) the criteria
Canada	Yes	No	Effects	Yes	A response of sufficient severity to threaten life or cause serious permanent impairment of body organs and the cardiovascular or nervous systems in a statistically significant proportion of a person or test animal that develops over time following a single exposure to a toxic substance or from prolonged or repeated exposure to a toxic substance under conditions that do not produce an effect from a single exposure
EU + Norway	Yes	Yes but irreversible changes are particularly important .	Exposure	Yes	For repeated dose toxicity: Serious damage to health, i.e. death, toxicologically significant clear functional disturbance or morphological changes
Japan				No	'Chronic Toxicity' is not defined in the Industrial Safety and Health Law and Related Legislation.
Korea	Yes	Yes		Yes	Chronic Adverse effects: death or serious damage, significant functional impairment, consistent clinical changes, and impairment of blood or homopoietic systems, and other irreversible changes in target organs.
USA	Yes	Yes	Effects	No	The US consumer product and workplace systems do not use numerical cut-offs. These systems are based upon evaluation of the weight of evidence using all available information relating to hazard. The workplace system (OSHA) is based on determination of the intrinsic hazards of industrial chemicals. Target organ effects are required to be indicated on the label and MSDS. In the case of consumer protection, likelihood of harm is also evaluated before warnings are included on the label.

ANNEX 2. Inventory of replies from the Member States to the questionnaire.

COUNTRY	*NATIONAL LEGISLATION*	*CRITERIA / GUIDELINES*	*APPLICATION OF CRITERIA*	*CONTROL IN PLACE*
Australia	NOSHC:1008 (1994)	Annexe VI :Dir. 67/548/EC	R48/AnnVI/dir 67/548/EC	
Belgium	Arrêté Royal du 24 mai 1982	Annexe VI :Dir. 67/548/EC	R48/AnnVI/dir 67/548/EC	Min. Social Affairs, Public Health & Environment
Canada	Controlled Products Regulation (CPR) under the authority of Hazardous Products Act (HPA)	Definition for "chronic toxic effect" and for "statistically significant"	Professional judgement + CPR sections 33(2),52, 58, 59 & 63	Health Canada and federal, provincial & territorial occupational safety & health agencies.
Czech Republic	(in application 01/01/1999)	Annexe VI :Dir. 67/548/EC	R48/AnnVI/dir 67/548/EC	
Denmark	Consolidated Act (Min. Environment n° 583/July 9, 1993) Statutory order (Min. Environment n° 829/Oct.15, 1993)	Annexe VI :Dir. 67/548/EC	R48/AnnVI/dir. 67/548/EC	Chemical Inspection Danish EPA
France	Arrêté du 20 avril 1994	Annexe VI :Dir. 67/548/EC	R48/AnnVI/dir. 67/548/EC	Responsible ministries (Consumers, workers etc.)
Germany	Chemikaliengesetz v. 25 Juli 1994	Annexe VI :Dir. 67/548/EC	R48/AnnVI/dir. 67/548/EC	BgVV
Japan	None	None	Professional judgement	-
Korea	Toxic Chemicals Control Act , Occupational Safety and Health Act	Annexe VI :Dir. 67/548/EC	R48/AnnVI/dir 67/548/EC	Ministry of Environment , Ministry of Labour
The Netherlands	Transposed dir. 67/548/EC	Annexe VI :Dir. 67/548/EC	R48/AnnVI/dir. 67/548/EC	Min. Health, Welfare & Sports
Norway	Regulation relating to the classification, labelling, etc. of dangerous chemicals 21 August 1997	Occupational Air Requirement (OAR) (specifically for solvents) Annexe VI :Dir. 67/548/EC	Available data+SAR+expert judgement R48/AnnVI/dir. 67/548/E	Norwegian Pollution Control Authority Directorate of Labour Inspection Norv. Petroleum Directorate
Sweden	Transposed dir. 67/548/EC	Annexe VI :Dir. 67/548/EC	R48/AnnVI/dir. 67/548/EC	National Chemical Inspectorate
Switzerland	Swiss Federal Law on Trade in Toxic Substances	None	Expert judgement/case-by-case	-
USA	Federal Hazardous Substances Act Occupational Safety and Health Act	16 CFR 1500.135C	Available data+expert judgement	Consumer Product Safety Commission.