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No. 12

Detailed Review Document on Classification Systems for Germ Cell Mutagenicity in OECD Member Countries

Environment Directorate

ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT

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

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

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

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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 harmonize 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 of chemical preparations such as pesticides and pharmaceuticals. These methods cover tests for physical and chemical properties, effects on human health and wildlife, and accumulation and degradation in the environment. The OECD Test Guidelines are recognised worldwide as the standard reference tool for chemical testing.

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

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

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

FOREWORD

The Detailed Review Document on classification systems for germ cell mutagenicity in OECD Member countries was prepared in 1996 as part of the work being carried out in the OECD's Programme on Harmonization of Classification and Labelling Systems. The lead countries on this project were Germany, the Netherlands, the United Kingdom and the United States.

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

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EXECUTIVE SUMMARY

This Detailed Review Document (DRD) presents an overview of classification systems/guidelines used in OECD Member countries relating to the mutagenicity of chemicals, based on responses to a questionnaire. Several OECD Member countries have implemented legislation, including classification systems and lists of mutagens; these countries include Canada, Japan and EU Member States. The United States has implemented mutagenicity risk assessment guidelines for determination of potential human germ cell mutagens. Several countries, including the Czech Republic, Norway and Switzerland, intend to apply the EU legislation in the near future. New Zealand is moving towards harmonization with Australia, with respect to establishing guidelines for mutagenicity assessment.

The existing classification systems make use of similar approaches to describe the various degrees of evidence for (germ cell) mutagenicity. These include:

a) human and/or animal evidence *in vivo* for germ cell mutagenicity, and/or

b) animal evidence for somatic cell mutagenicity, and/or

c) intrinsic (*in vitro*) mutagenic properties.

Classification of substances and preparations as mutagens usually leads to labelling and to restrictions on sale and/or use.

GENERAL INTRODUCTION

In close co-operation with the IOMC (Inter-Organization Programme for the Sound Management of Chemicals) Co-ordinating Group for the Harmonization of Chemical Classification Systems, the OECD has acted as the focal point for the harmonization of the classification and labelling of chemicals based on their intrinsic ability to cause health effects. At the first meeting of the OECD's Advisory Group on Harmonization of Classification and Labelling in February 1995, it was agreed that Germany, the Netherlands, the United Kingdom and the United States would act as lead countries to undertake work on the endpoint "germ cell mutagenicity". For this toxicological endpoint, a Detailed Review Document would be prepared in the form of a (Step 1) report in which various classification systems would be described and similarities and differences between the existing systems be identified.

The report would also take into account other relevant aspects, such as recent or planned changes in the criteria used as the basis for classification, and should serve as a basis for a subsequent (Step 2) report aimed at reaching harmonization between the existing systems.

The lead countries established an *ad hoc* Working Group composed of experts from Germany, the Netherlands, the UK and the US. Its composition is shown in **Table 1**.

A questionnaire (summarized in **Table 2**) was sent to heads of national delegations to the OECD, and to the Commission of the European Communities (DG XI). Some difficulties were encountered in obtaining responses to the questionnaire from several OECD countries, as shown in **Table 3**. This report represents a comprehensive review of the information received up to 20 April 1996.

SCOPE AND DEFINITIONS

In the present context, commonly used or applied definitions of the terms “mutation”, “mutagenic”, “mutagen” and “genotoxic” are used. The term “mutation” will apply both to heritable genetic changes at the phenotypic level, and to the underlying DNA modifications when known (including, for example, specific base-pair changes and chromosomal translocations). The term “mutagenic” and “mutagen” will be used for agents giving rise to an increased occurrence of mutations in populations of cells and/or organisms. The more general terms “genotoxic” and “genotoxicity” apply to agents or processes which alter the structure, information content or segregation of DNA, or which (temporarily) alter its replication.

It is understood that the toxicological endpoint of “mutagenicity” can be interpreted in several ways. For the purpose of the present harmonization of classification systems, the primary endpoint under consideration will be “germ cell mutagenicity”, since it is meant to avoid or reduce the exposure of humans to chemical substances that may cause heritable damage, i.e. genetic changes to the progeny via the germ line.

With regard to the individual test systems and organisms used in determining mutagenic and/or genotoxic effects, many have been described so far and recommended for use in the routine evaluation of the genotoxic properties of chemicals. Consensus agreements on the constituents of test strategies (and test batteries) are beginning to emerge. An overview of existing test systems for the detection of specific (classes of) chemical mutagens and for the assessment of specific endpoints related to *in vitro*, somatic or germ cell mutagenesis has been published recently (ref 1) and is referred to in the present context.

OVERVIEW OF MUTAGEN LEGISLATION IN OECD COUNTRIES

Individual responses to the questionnaire are summarized in **Tables 4, 5 and 6**. It appears that most countries that responded have introduced legislation concerning (germ cell) mutagenicity, briefly described as follows:

In the EU countries (Directive 67/548/EEC) legislation covers the general public and occupational populations as well as consumers, while the Japanese Industrial Safety and Health Law addresses only the workplace. The Canadian Hazardous Products Act covers both the general public and occupational populations, but mutagenicity criteria are included only for the latter (the Controlled Products Regulations).

In general, these pieces of legislation are accompanied by specific criteria for classification, and advisory groups and documentation are usually available. The classification of mutagenic substances in Canada, Japan and the EU is based on specific published criteria (see Table 5). These criteria define *hazard*, while *risk*, which combines hazard with exposure, is not taken into account in the classification.

The Czech Republic, Norway and Switzerland are in the process of changing their respective positions on classification criteria in order to harmonize with the EU legislation. New Zealand has, at present, no formal classification system of mutagenic substances for consumers and the general population. The new occupational safety and health (OSH) guidelines recognize mutagenicity as a

property of cytotoxic drugs and some other chemicals, but somatic and germ cell effects are not distinguished.

New Zealand is in the process of adopting a new bill which will replace legislation covering toxic substances, pesticides, dangerous goods and explosives. It is likely that, in the future, formal guidelines for assessing substances for mutagenic effects will be drawn up. In addition to the legislative changes, New Zealand is moving towards harmonization with Australia for assessment in many areas (i.e. pesticides, therapeutics, food additives).

At this point it must be noted that groups of chemicals and products with specific functions and uses, e.g. pharmaceuticals, pesticides and food additives, are also subject to classification when possible but usually have their own regulations. A review of the existing regulations for the above-mentioned compounds in different countries can be found in Carere et al. (ref 1).

In the EU, Annex I of Directive 67/548/EEC provides a list of all substances which have an agreed classification. A similar list is available in Japan. There is currently no list of recognized non-mutagens, but the lists available in Japan also contain substances for which only negative mutagenicity test results have been obtained. None of the countries reported any specific transport regulation covering mutagens.

REGULATORY SCHEMES AND CRITERIA FOR CLASSIFICATION

The various national regulatory schemes/guidelines and criteria for classification of mutagens reviewed here are based on evidence derived from studies in experimental animals and cultured cells, and other relevant data (e.g. structure-activity relationships). If relevant human data were available, they would also be used in some of the schemes. Described below are the key elements of schemes from Canada, Japan and the EU and the mutagenicity risk assessment guidelines of the United States.

Canada

Part IV of the Controlled Products Regulations (CPR-SOR 88-66), under the authority of the federal Hazardous Products Act, implements the supplier requirements of the Canadian Workplace Hazardous Materials Information System (WHMIS). Mutagenicity criteria fall into Division 2: “Materials Causing other Toxic Effects”. Within this division there are two subdivisions, namely:

A: “Very Toxic Material”; CPR section 57 criteria determine whether a substance falls into this subdivision, and

B: “Toxic Material”; determined by CPR section 62.

According to CPR 57, a chemical or chemical mixture is considered to present a hazard to man if:

57 (1)(a) There is epidemiological evidence that shows a causal connection between exposure of persons to the substance or mixture and heritable genetic effects, or

57 (1)(b) There is evidence of mutagenicity in mammalian germ cells *in vivo*, as shown by:

(i) positive results in a study that measures mutations transmitted to offspring,

(ii) positive results in an *in vivo* study showing chemical interaction with the genetic material of mammalian germ cells and positive results in an *in vivo* study assessing either gene mutation or chromosomal aberration in somatic cells.

According to CPR 62, a pure chemical or a chemical mixture is considered to present a hazard if evidence of mutagenicity in mammalian somatic cells is obtained in a test to assess either gene mutations or chromosomal aberrations.

Japan

The Japanese Industrial Safety and Health Law (Article 57-2) addresses the mutagenicity classification of substances in the workplace. Under this legislation, Japan does not classify mutagenic substances according to a weight of evidence approach but rather recognizes one category: "mutagenic". A substance is classified as mutagenic when the results of a "Mutagenicity Test Using Micro-Organisms" are positive and the relative activity is higher than 1 000 revertants/mg.

United States

For the evaluation of chemicals with respect to their ability to induce mutations in mammalian germ cells, a classification in three categories was proposed by the EPA in 1984 (ref 2).

Category I is based on sufficient evidence obtained from at least one *in vivo* mammalian germ cell mutation test or from at least two somatic cell mutation tests (point mutation/chromosomal aberrations), plus sufficient *in vivo* evidence that the chemical interacts with mammalian germ cells.

Category II is based on suggestive evidence provided from positive results of somatic cell mutation tests plus evidence for interaction of the chemical with mammalian germ cells, but the evidence is insufficient to place the substance in Category I.

Category III is based on limited evidence of mutagenic activity or interaction of the chemical with mammalian germ cell DNA or other chromatin constituents.

In 1986, guidelines for a "weight-of-evidence" approach to human germ cell mutagenicity were established by adapting the approach of 1984, leading to eight categories with a decreasing order of strength of evidence. In addition, a "non-mutagen" category and a category for substances with inadequate evidence were described (ref 3). The eight categories of evidence are as follows:

1. Positive data derived from human germ cell mutagenicity studies.

2. Valid positive results from studies on heritable mutational events (of any kind) in mammalian germ cells.

3. Valid positive results from mammalian germ cell chromosome aberration studies that do not involve transmission from one generation to the next.

4. Sufficient evidence for a chemical's interaction with mammalian germ cells, together with valid positive mutagenicity test results from two assay systems, at least one of which is mammalian (*in vivo* or *in vitro*). The positive results may be both for gene mutation or both for chromosomal aberrations; if one is for gene mutation and one for chromosomal aberrations, both must be from mammalian systems.

5. Suggestive evidence for a chemical's interaction with mammalian germ cells, together with valid positive mutagenicity evidence from two assay systems as described under 4 above. Alternatively, positive mutagenicity evidence of less strength than defined under 4 above, when combined with sufficient evidence for a chemical's interaction with mammalian germ cells.

6. Positive mutagenicity test results of less strength than defined under 4 above, combined with suggestive evidence for a chemical's interaction with mammalian germ cells.

7. Although definitive proof of non-mutagenicity is not possible, a chemical could be operationally classified as a non-mutagen for human germ cells if it gives valid negative test results for all endpoints of concern.

8. Inadequate evidence bearing on either mutagenicity or chemical interaction with mammalian germ cells.

The European Union

The criteria for classification of mutagens is described in Directive 93/21/EEC, which is the 18th adaptation to technical progress of Directive 67/548/EEC. There are three categories:

Category 1: Substances known to be mutagenic to man

There is sufficient evidence to establish a causal association between human exposure to a substance and heritable genetic damage.

Category 2: Substances which should be regarded as if they were mutagenic to man

There is sufficient evidence to provide a strong presumption that human exposure to the substance may result in the development of heritable genetic damage, generally on the basis of:

appropriate animal studies

other relevant information

Category 3: Substances which cause concern for man owing to possible mutagenic effect

There is evidence from appropriate mutagenicity studies, but this is insufficient to place the substance in Category 2.

Criteria for placing a substance in category 1, 2 or 3:

Category 1:

To place a substance in category 1, positive evidence from human mutation epidemiological studies will be needed. Examples of such substances are not known to date. It is recognized that it is extremely difficult to obtain reliable information from studies on the incidence of mutations in human populations, or possible increases in their frequencies.

Category 2:

To place a substance in category 2, positive results are needed from assays showing (a) mutagenic effects, or (b) other cellular interactions relevant to mutagenicity, in germ cells of mammals *in vivo,* or (c) mutagenic effects in somatic cells of mammals *in vivo* in combination with clear evidence that the substance, or a relevant metabolite, reaches the germ cells.

Evidence from the following assays is needed for placement in Category 2:

2(a) *in vivo* heritable germ cell mutagenicity assays:

specific locus mutation test

heritable translocation test

dominant lethal mutation test

These assays actually demonstrate the appearance of affected progeny or a defect in the developing embryo.

2(b) *in vivo* assays measuring relevant interaction with germ cells (usually DNA):

assay for chromosomal abnormalities as detected by cytogenetic analysis,

including aneuploidy caused by malsegregation of chromosomes

test for sister chromatid exchanges (SCEs)

test for unscheduled DNA synthesis (UDS)

assay for (covalent) binding of mutagen to germ cell DNA

assaying other kinds of DNA damage

These assays provide evidence of a more or less indirect nature. Positive results in these assays would normally be supported by positive results from *in vivo* somatic cell mutagenicity assays. in mammals or in man. [See Category 3, preferably methods as under 3(a).]

2(c) *in vivo* assays showing mutagenic effects in somatic cells of mammals [see under 3(a)], in combination with toxicokinetic methods or other methods capable of demonstrating that the compound or a relevant metabolite reaches the germ cells.

For 2(b) and 2(c), positive results from host-mediated assays or the demonstration of unequivocal effects in *in vitro* assays can be considered as supporting evidence.

Category 3:

To place a substance in Category 3, positive results are needed in assays showing

(a) mutagenic effects in mammalian somatic cells *in vivo,* or

(b) other cellular interaction relevant to mutagenicity, in somatic cells in mammals *in vivo*.

The latter especially would normally be supported by positive results from *in vitro* mutagenicity assays.

For effects in somatic cells *in vivo,* at present the following methods are appropriate:

3(a) *in vivo* somatic cell mutagenicity assays:

bone marrow micronucleus test or metaphase analysis

metaphase analysis of peripheral lymphocytes

mouse (coat colour) spot test

3(b) *in vivo* somatic cell DNA interaction assays:

test for SCEs in somatic cells

test for UDS in somatic cells

assay for the (covalent) binding of mutagen to somatic cell DNA

assay for DNA damage, e.g. by alkaline elution, in somatic cells.

Substances showing positive results only in one or more *in vitro* mutagenicity assays should normally not be classified. Their further investigation using *in vivo* assays, however, is strongly indicated. In exceptional cases, e.g. for a substance showing pronounced responses in several *in vitro* assays, for which no relevant *in vivo* data are available, and which shows structural resemblance to known mutagens/carcinogens, classification in Category 3 could be considered.

REGULATORY CONSEQUENCES OF MUTAGEN CLASSIFICATION

Labelling. safety data sheets and restrictions

Table 6 summarizes the regulatory consequences of mutagenicity classification. The countries which require labelling use differentiated labelling symbols and explanatory phrases for the different categories. In EU countries, the Czech Republic, Norway and Switzerland, category 1 and 2 mutagens are

assigned the danger symbol T ("toxic") with phrase R46, "may cause heritable genetic damage". For category 3 mutagens the danger symbol Xn ("harmful, noxious") and phrase R40, "possible risk of irreversible effects", are given. In Canada a single hazard symbol is used for Workplace Hazardous Materials Information System (WHMIS) Division 2, where the criteria for occupational mutagens are found.

The EU countries and countries with EU-related classification systems generally allow 0.1 per cent as the concentration limit of substances in preparations for Category 1 and 2 mutagens unless specific concentration limits are given. For Category 3 mutagens, a limit of 1.0 per cent applies. Canada applies a limit of 0.1 per cent and 1.0 per cent for mutagens in CPR section 57 and 62, respectively.

Nearly all countries require the use of material safety data sheets. Category 1 and 2 mutagens may not be used in the EU (and EU-following) countries as substances, or in preparations, which are placed on the market for sale to the general public (Directive 76/769/EEC). In addition, the packaging of such substances and preparations requires the label "restricted to professional users".

Classification of carcinogens

From the responses received, it is clear that substances classified as germ cell mutagens are not automatically classified as carcinogens. However, in the EU system substances classified as mutagens are considered for classification as carcinogens.

OVERALL COMPARISON OF EXISTING SYSTEMS

The main conclusions that can be drawn after comparing the different systems are as follows:

- Canada, the United States and the EU have a system in which (the classification for) germ cell mutagenicity is the toxicological endpoint, whereas the Japanese system focuses on the inherent potential of a chemical to be a mutagen.

- The Japanese system is not directed towards identifying substances mutagenic to (germ cells of) humans.

- The Canadian and EU classification systems and the risk assessment guidelines of the United States have similar sets of criteria. In each case they include categories for proven human germ cell mutagens, established animal germ cell mutagens, and possible germ cell mutagens (i.e. somatic cell mutagens). In contrast, industrial chemicals in Japan are classified on the basis of *in vitro* data.

- The United States has developed a "weight of evidence" approach which contains elements that play a major role in the Canadian and EU systems for classification of substances for mutagenicity.

- In the Canadian and EU systems a compound can be classified on the basis of *in vivo* somatic data, whereas in the US system additional evidence of relevant interaction in germ cells is required for classification.

- In the EU system evidence of the presence in the germ cells of a substance known to be a somatic cell mutagen is sufficient to classify it in category 2, while in the US system evidence of a relevant interaction with the germ cells is required.

- In the EU system, classification of a substance as a mutagen can influence the classification for carcinogenicity.

References

1. Carere. A., G.R. Mohn, J.M. Parry, A.I. Sors and C.V. Nolan, *Methods and testing strategies for evaluating the gentoxi properties of chemicals.* Luxembourg: Office for Official Publications of the European Communities.

2.. Federal Register 49 (1984) 46313-46321

3. Federal Register 51 (1986) 34005-34012.

Table 1. OECD Working Group on "Harmonization of Classification and Labelling of Germ Cell Mutagenicity"

Name	Institution	Location	Country	Telephone	Telefax
Ms. A. Auletta	US EPA, Office of Pesticides and Toxic Substances	Washington	USA	1-202-260 1513	1-202-260 1279
Mr. D. James	Health and Safety Executive, Toxicology Unit	Bootle	United Kingdom	44-151-951 3342	44-151-951 3317
Mr. S. Madle	Federal Institute for Health Protection of Consumers and Veterinary Medicine	Berlin	Germany	49-30-8412 3700	49-30-8412 3264
Mr. G. Mohn	National Institute of Public Health and Environment (RIVM)	Bilthoven	The Netherlands	31-30-274 2140	31-30-274 4446
Mr. H. Roelfzema	Ministry of Health, Welfare and Sports	Rijswijk	The Netherlands	31-70-340 6965	31-70-340 5177
Mr. A. Smith	Health and Safety Executive, Toxicology Unit	Bootle	United Kingdom	44-151-951 3404	44-151-951 3317
Ms. J. de Stoppelaar	National Institute of Public Health and Environment (RIVM)	Bilthoven	The Netherlands	31-30-274 3647	31-30-274 4446

Table 2. Summary of the Questionnaire

Question No.	
1	Is there (inter)national legislation based on classification of mutagenic substances?
	- consumers
	- general population
	- occupational population
	Please enclose copies or descriptions of the legislation
2	Which national authorities/organisations are responsible for legislation systems?
3	Have these authorities developed criteria and/or guidelines for classification?
4	Have scientific/advisory groups been appointed for identification/evaluation of mutagenic substances?
	Do these groups produce documents to explain the basis for their decisions?
5	Have authorities/organisations produced lists of substances classified as mutagenic?
6	Are there regulatory consequences of classification: concentration limits?
	Are there regulatory consequences of classification: additional classification for carcinogenicity?
	Are there regulatory consequences of classification: labelling?
	Are there regulatory consequences of classification: safety data sheets?
	Are there regulatory consequences of classification: special restrictions on consumers/work place/export?
	Are there regulatory consequences of classification: official register?
7	Are any changes foreseen in mutagen classification/legislation in the next two to three years?

Table 3. Overview of Replies

Questionnaire to:	Institution	Country	Date replied	Reply from	Institution	Reminder	Acknowledged
Mr. K. Wettig	BgVV	Germany	19-Dec-95	S. Madle	BgVV		18-Jan-96
Ms. K. Dal Bon	EPA	Australia				18-Jan-96	
Ms. K. Kratz	FEA	Austria				18-Jan-96	
Mr. G. Del Bino	CEC-DG XI	EU	27-Dec-95	G. Del Bino	EC-DG XI		18-Jan-96
Ms. T. Lakhanisky	Hygiene	Belgium	19-Dec-95	A. Pauwels	Maîtrise des Risques		18-Jan-96
Ms. M. Taylor	Environment	Canada	11-Nov-95	K. Headrick	Products Safety		18-Jan-96
Ms. L. Seedorff	Danish EPA	Denmark	10-Jan-96	L.S. Tobiassen	Danish EPA		18-Jan-96
M. E. Tacoronte	Salud Publica	Spain				18-Jan-96	
Ms. A.S. Rispin	US EPA	USA	25-Apr-96	A. Auletta	US EPA	18-Jan-96	
Mr. E. Nikunen	Environment	Finland				18-Jan-96	
Mr. J. Pyotsia	Health	Finland				18-Jan-96	
Ms. S. Bially	BIAC*	France				18-Jan-96	
Mme F. Briens	Environnement	France				18-Jan-96	
Mr. J. Evans	TUAC*	France				18-Jan-96	
Mr. P. Chamikiotis	Chemical	Greece	7-Feb-96	Chamikiotis	Chemical State Lab.	18-Jan-96	7-Feb-96
Ms. M. Iconomou	Chemical	Greece				18-Jan-96	
Ms. A. Tsatsou-Dritsa	Chemical	Greece				18-Jan-96	
Mr. F. O'Mahony	Health & Safety	Ireland				18-Jan-96	
Ms. I. Pratt	Health & Safety	Ireland	23-Jan-96	I. Pratt	HSE	18-Jan-96	23-Jan-96
Mr. R. Binetti	ISS	Italy				18-Jan-96	

continued next page

Table 3. Overview of Replies (continued)

Questionnaire to:	Institution	Country	Date replied	Reply from	Institution	Reminder	Acknowledged
Mr. Y. Kimura	Environment	Japan	18-Dec-95	K. Ofuchi	Ministry of Labour		18-Jan-96
Mr. M. Yoshimura	Agriculture	Japan					
Mr. C. Hurtado	OECD	Mexico				18-Jan-96	
Ms. S. Hardeng	Pollution	Norway	16-Jan-96	K.R. Villars-Dahl	Pollution Control		18-Jan-96
Ms. P. Wilkinson	OECD	New Zealand	12-Mar-96	Jim Waters	Ministry of Health	18-Jan-96	
Mr. H. Roelfzema	VWS	Netherlands	15-Dec-95	H. Roelfzema	VWS		18-Jan-96
Mme A. Moura	Ambiente	Portugal				18-Jan-96	
Mr. J. Hasa	Environment	Czech Republic	25-Jan-96	J. Hasa	Environment	18-Jan-96	25-Jan-96
Mr. R. Woodward	HSE	UK	21-Dec-95	A. Smith	HSE		18-Jan-96
Mr. N.G. Lindquist	Chemicals	Sweden	20-Dec-95	N.G. Lindquist	Chemicals Inspectorate		18-Jan-96
Mr. M. Mercier	WHO/IPCS	Switzerland				18-Jan-96	
Mr. I. Obadia	Occupation	Switzerland	11-Jan-96	H. Reust	Toxic Substances		18-Jan-96
Mr. A. Weber	Environnement	Switzerland					
Ms. N. Besbelli	Poison	Turkey				18-Jan-96	

**BIAC and TUAC are the Business and Industry Advisory Committee to the OECD and the Trade Union Advisory Committee to the OECD, respectively.*

Table 4. Responsible National Authorities/Organisations

Australia	
Austria	
Belgium	Mr. A. Pauwels, Maîtrise des Risques, Cité Administrative, Brussels
Canada	Ms. Kim Headrick, Chemicals Hazards & WHMIS Division, Hull, Quebec. Phone: 1-819-994-4669
Czech Republic	Mr. Z. Koutecky, Ministry of Health, Prague. Phone: 42-2-24972586
Denmark	Ms. Lea Tobiassen, Danish EPA, Copenhagen. Phone: 45-32 66 01 00
Finland	
France	
Germany	Dr. T. Neustadt, Bundesanstalt für Arbeitsschutz, Dortmund; Dr. S. Madle, BgVV, Berlin. Phone: 49-30-8412-3700
Greece	Ministry of Finance, General Chemical State Laboratory, Athens. Phone: 30-6428211
Ireland	Dr. Iona Pratt, Health & Safety Authority, Dublin. Phone: 353-1-6620400
Italy	
Japan	Ms. K. Ofuchi, Ministry of Labour, Tokyo. Phone: 81-3-3502 6756
Mexico	
Netherlands	Dr. H. Roelfzema, Ministry of Health, Welfare and Sports, Rijswijk. Phone: 31-70-340 6965
New Zealand	Dr. Jim Waters, Ministry of Health, Wellington. Phone: (04) 4962121
Norway	Directorate of Labour Inspection, Oslo. Phone: 47-22-957000; SFT, Pollution Control, Oslo. Phone: 47-22 57 34 00
Portugal	
Sweden	Prof. Nils-Gunnar Lindquist, Swedish National Chemicals Inspectorate, Solna. Phone: 46-87 30 57 00
Switzerland	Dr. H. Reust, Federal Office of Public Health, Division of Toxic Substances, Bern. Phone: 41-31-322 96 25
Turkey	
United Kingdom	Mr. Robert Woodward, Health Directorate, Health and Safety Executive, London. Phone: 44-171-717 6261
United States	Dr. A.S. Rispin, US EPA, Washington, D.C.; Dr. AE Auletta, US EPA, Washington, D.C. Phone: 1-202-260 1513
European Union	Mr. G. Del Bino, European Commission, DG-XI/E/2, Brussels. Phone: 32-2-299 11

Table 5. Replies to Questions 1, 3, 4 and 5

Question	1a	1b	1c	1d	1e	3	4a	4b	5
	legisl.	**legisl. consumer**	**legisl. general**	**legisl. occup.**	**legisl. EC/nat.**	**criteria**	**advisory group**	**advisory docs.**	**national list of substances**
Australia									
Austria									
Belgium	yes	yes	yes	yes	EU	yes	yes	yes	yes (EU)
Canada	yes	yes	yes	yes	Canada	yes			no
Czech Republic	no					no	no		no
Denmark	yes	yes	yes	yes	EU/Denmark	yes (EU)	no	no	yes (EU)
Finland									
France									
Germany	yes	yes	yes	yes	EU/Germany	yes (EU)	yes	yes	yes (EU & TRGS-905)
Greece	yes	yes	yes	yes	EU/Greece	yes (EU)	no	no	yes (EU)
Ireland	yes	yes	yes	yes	EU	yes (EU)	no	no	yes (EU)
Italy									
Japan	yes			yes	Japan	yes	yes	yes	yes
Mexico									
Netherlands	yes	yes	yes	yes	EU/Neth.	yes (EU)	yes	yes	yes (EU)
New Zealand	no	no	no	no		no	no	no	no
Norway	yes	yes	yes	yes	EEA	yes (EU)	yes	yes	yes (in revision)
Portugal									
Sweden	yes	yes	yes	yes	EU	yes (EU)	yes	yes	yes (EU)
Switzerland	yes				Switzerland	no	no	no	no
Turkey									
United Kingdom	yes	yes	yes	yes	EU/UK	yes (EU)	yes	yes	yes (EU)
United States									
European Union	yes	yes	yes	yes	EU	yes	yes	yes	

Table 6. Replies to Questions 6 and 7

	What are the regulatory consequences of this classification?					Expected changes
Question	6a	6c	6d	6e	6f	7
	concentration limits	**labelling**	**safety data sheets**	**special restrictions**	**official register**	**changes in next 2-3 years**
Australia						
Austria						
Belgium	yes	yes	yes	yes	no	no
Canada		yes	yes	yes		no
Czech Republic						yes (EU)
Denmark	yes	yes	yes	yes	yes	no
Finland						
France						
Germany	yes	yes	yes	yes	no	no
Greece	yes	yes	yes	yes	no	no
Ireland	yes	yes	yes	yes	no	no
Italy						
Japan	no	yes	yes	yes	no	no
Mexico						
Netherlands	yes	yes	yes	yes	no	no
New Zealand	no	no	no	no	no	yes (legisl.)
Norway	yes	yes	yes	yes	yes	yes (EU)
Portugal						
Sweden	yes	yes	yes	yes	yes	no
Switzerland	no	no	no	no	no	yes (EU)
Turkey						
United Kingdom	yes	yes	yes	yes	no	no
United States						
European Union	yes	yes	yes	yes		no