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Detailed Review Document on Classification Systems for Reproductive Toxicity in OECD Member Countries

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Detailed Review Document on Classification Systems for Reproductive Toxicity in OECD Member Countries

Environment Directorate

ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT

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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 joined 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 (DRD) on classification sytems for reproductive toxicity in OECD Member countries was prepared 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 the United Kingdom (Health and Safety Executive) and Australia (Worksafe Australia).

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

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SUMMARY

In the countries surveyed, four systems for the classification of chemicals for reproductive toxicity were found. The four systems identified are those of the European Union (EU), Canada and the United States (the Federal Hazardous Substance Act and the Federal Hazard Communication Standard). Of these, the EU system has the most widespread use. It is being used throughout the EU and in a number of other countries, notably Australia.

The systems are broadly similar. All are hazard-based, classifying chemicals on the basis of their intrinsic properties, and involve the consideration of reproductive effects seen in humans and effects shown in suitable animal tests. There are, however, differences between the systems: for example, in the specific reproductive effects covered, the number of classification categories for each type of reproductive effect, the possibility of classifying on the basis of limited evidence, and concentration cut-offs for classifying mixtures/preparations.

With regard to labelling requirements and other regulatory consequences of classification, principal differences exist. Thus, harmonization is likely to be a bigger task in these areas than in the case of harmonization of classification.

INTRODUCTION

As part of the OECD/IPCS initiative on harmonization of chemical classification systems, UK and Australia agreed at the 20th Joint Meeting of the OECD's Chemicals Group and the Management Committee of the Special Programme on the Control of Chemicals, (Joint Meeting) in May 1993 to gather information from OECD Member Countries on existing systems for reproductive toxicity and to prepare a report describing the systems and highlighting their differences and similarities. Australia investigated the situation in Australasia and North America, and the UK covered Europe. Information was obtained either by questionnaire or telephone contact. European Union (EU) Member States were not approached since all are expected to be using the EU classification system.

A report on existing systems was provided to the November 1994 Joint Meeting. Comments received in August 1995 from Canada, France, Germany, Greece, the Netherlands, Sweden and the United States have been addressed and the Report revised as a consequence. Further comment received in May 1996 from the United States and Ireland have also been incorporated.

OVERVIEW OF SYSTEMS IN USE

European Countries

All EU Member States use a hazard-based classification system defined in Commission Directive 93/21/EEC (Annex VI to Directive 93/32). Substances considered to possess the hazardous property of toxic to reproduction can be classified under the headings of effects on fertility and developmental toxicity. Additionally, substances which may interfere with lactation or be present in the breast milk in significant amounts can be classified as hazardous to breast fed babies.

The EU system currently applies mainly to industrial and household chemicals and is being extended to pesticides and veterinary products. The system is not used to classify medicines, cosmetic products, foodstuffs, animal feeds, radioactive substances, and mixtures in the form of waste.

Norway has introduced a national system, which is very similar to the EU system.

Switzerland currently does not have a classification system for reproductive toxicity, but it may in the future implement a system similar to that of the EU.

Bulgaria has a classification system for pesticides which includes a category for teratogenic hazard, but other forms of reproductive toxicity are not considered. A toxicity classification system for industrial and household chemicals is currently being developed which includes a category for teratogenic hazard based on the now superseded EU classification (Directive 79/831/EEC, 6th amendment) for teratogenicity (R47, may cause birth defects). Experts advising the Bulgarian authorities are considering recommending that classification for reproductive effects be extended in line with the current EU system.

Poland and the Slovak Republic do not have classification systems for reproductive toxicity. No information is available in other Eastern European Countries.

Essentially all European countries which operate a classification system for reproductive toxicity are currently using or are likely to adopt the EU system in the near future. Thus a detailed consideration of European classification systems will be restricted to the EU System.

United States of America

Two systems of classification were found in operation in the United States. Firstly, under the Federal Hazard Communication Standard (29 CFR 1910.1200), manufacturers, importers and employers are required to evaluate available data regarding hazards and make a hazard determination in accordance with the standard. The rule covers all “health hazards”, including reproductive toxins, which affect the reproductive capabilities including chromosomal damage (mutations) and effects on foetuses (teratogenesis) and sterility.

In the second system, guidelines for determining the chronic toxicity of products subject to the Federal Hazardous Substances Act (FHSA) have been published by the Consumer Product Safety Commission (16 CFR Part 1500 October 9 1992.). The FHSA applies to the labelling of substances (either singly or in a mixture or preparation) if they are intended, or packaged in a form suitable for, use

in the household or by children. It is the manufacturers' responsibility to determine if their products are or contain a hazardous substance.

The definition of "hazardous substance" requires that the substance may cause substantial personal injury or illness during or as a proximate result of any customary or reasonably foreseeable handling or use.

A concise definition is not included in the guidelines. However, the term appears to cover developmental toxicity, structural abnormalities, altered growth, functional deficiencies and behavioural deficiencies, fertility, and post-natal development to the time of sexual maturation.

Two main distinctions are drawn: those developmental and reproductive toxins which can be identified from human studies, and those which can be identified from animal studies.

Testing guidelines have been developed for developmental and reproductive toxicity to meet the requirements of both the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) and the Toxic Substances Control Act (TSCA). The testing guidelines are also used by several other federal regulatory agencies, including the Consumer Product Safety Commission (CPSC) and the Occupational Safety and Health Administration (OSHA).

In the US, test guidelines for developmental toxicity testing are designed to provide general information concerning the effects of exposure of the pregnant test animal on the developing organism. Additionally developmental neurotoxicity testing guidelines are designed to address functional and behavioural effects of pre-natal exposure. This may include death, structural abnormalities, or altered growth. Reproduction and fertility testing is designed to cover gonadal function, the oestrus cycle, mating behaviour, conception, gestation, parturition, lactation and weaning, and growth and development of the offspring. Proposed revisions to the developmental and reproductive toxicity testing guidelines should increase the sensitivity of the studies in identifying other effects such as cartilaginous development in foetuses, spermatogenesis, oestrus cyclicity and sexual maturation.

Guidelines for risk assessment for developmental toxicity have been published by the US EPA, and guidelines for reproductive toxicity risk assessment are under development.

Canada

Classification criteria for reproductive toxicity are defined in Part IV the Controlled Products Regulations (CPR) (SOR 88-66) under the authority of the federal Hazardous Products Act. This Act implements the supplier requirements of the Canadian Workplace Hazardous Materials Information System (WHMIS). WHMIS is a hazard-based communication system for chemicals used in the workplace. Risk is not taken into account in the process of classification.

The CPR provide the details of the criteria which define a "controlled product" including criteria for reproductive toxicity as well as teratogenicity and embryo toxicity.

Australia

Classification criteria are used to define teratogenic hazard in relation to occupational health and safety assessments under State and Territory occupational health and safety legislation, and to industrial chemicals under the federal Industrial Chemicals (Notification and Assessment) Act 1989, which

provides for mandatory assessment of all new and selected industrial chemicals. The term *industrial chemical* applies to chemicals not used solely for agricultural and veterinary purposes, pharmaceuticals, food additives, and food intended for consumption by humans and animals.

Japan

Information from the Japanese Ministry of Health and Welfare indicates that no formal classification criteria are in use. However, guidance on reproductive toxicity testing is available.

CLASSIFICATION SYSTEMS

The EU Classification System

The classification criteria are presented, together with detailed guidance, in Directive 93/21/EEC.

In the EU system reproductive toxicity is divided into effects on fertility and developmental toxicity. Effects on fertility includes "adverse effects on libido, sexual behaviour, any aspect of spermatogenesis or on hormonal activity or physiological response which would interfere with the capacity to fertilise, fertilisation itself or the development of the fertilised ovum up to and including implantation."

Developmental toxicity covers any effect interfering with the normal development which may be manifested pre-natally or post-natally. Included are effects such as reduced bodyweight, growth or developmental retardation, organ toxicity, death, structural defects, functional defects, and impaired post-natal mental or physical development up to and including normal pubertal development.

There are three classification criteria for effects on fertility and developmental toxicity. Category 1 is for substances which are known to be human reproductive toxicants and can be assigned only on the basis of positive epidemiological data. Category 2 or 3 classification is made primarily on the basis of data from experiments in laboratory animals. Category 2 is appropriate when there is clear evidence of a specific effect on reproduction, and category 3 is used when the evidence is less convincing or when there are doubts about the relevance of the effects for humans.

Substances are not classified as toxic to reproduction when adverse effects on reproduction are due solely to non-specific secondary consequences of other toxic effects. Normally, effects seen at very high doses (for example, above 1 000 mg/kg orally) would not necessitate classification. Also, chemicals with negative reproductive data or chemicals which have not been adequately tested (where there is no data or poor quality data) for reproductive toxicity are not classified.

Preparations (mixtures of two or more substances) require classification if containing a classified substance at a concentration of 0.5 per cent (for category 1 or 2 substances) or 5 per cent (category 3 substances). Also, lower concentration limits can be specified for substances with high potency.

Canada

The classification criteria for reproductive toxicity are specified in Section 55 of the Controlled Products Regulations.

A pure chemical or a tested chemical mixture is considered to present a reproductive hazard if any one of the following criteria is met:

a) there is evidence that shows that it causes sterility or an adverse effect on reproductive capability in persons following exposure to it in the workplace; or

b) sterility or an adverse effect on reproductive capability is shown in an animal assay for reproductive toxicity carried out in accordance with:

i) OECD Test Guideline 415 (One Generation Reproduction Toxicity) dated May 26, 1983

ii) OECD Test Guideline 416 (Two Generation Reproduction Toxicity) dated May 26, 1983)

An untested chemical mixture is considered to present a reproductive hazard if the mixture contains a product, material or substance that meets the criteria applicable to the pure substance or tested mixture as specified above, if the product, material or substance is present in the mixture at a concentration of 0.1 per cent or more.

The classification criteria for teratogenicity and embryotoxicity are specified in Section 53 of the Controlled Product Regulations.

A pure chemical or tested chemical mixture is considered to present a teratogenic and embryotoxic hazard if, in an animal assay for teratogenicity and embryotoxicity, it is shown to cause injury to the embryo or foetus in a statistically significant proportion of the test population at a concentration that has no adverse effect on the pregnant female when tested in accordance with any of the following tests:

a) OECD Test Guideline 414 (Teratogenicity) dated May 12, 1981;
b) OECD Test Guideline 415 (One Generation Reproduction Toxicity) dated May 26, 1983;
c) OECD Test Guideline 416 (Two Generation Reproduction Toxicity) dated May 26, 1983.

Injury is defined to include death, malformation, permanent metabolic or physiological dysfunction, growth retardation, or psychological or behavioural alteration that occurs during pregnancy, at birth, or in the post-natal period.

An untested mixture is considered to represent a teratogenic or embryotoxic hazard if it contains a teratogenic or embryotoxic substance in concentrations greater than 0.1 per cent

Australia

Classification criteria for hazardous substances are published in the National Occupational Health and Safety Commission's Approved Criteria for Classifying Hazardous Substances. The criteria relating to reproductive toxicity are those for teratogenic hazard from the 6th Amendment of the EU Commission Directive 67/548.

Over the next six to twelve months it is planned to develop the criteria in line with those of the 7th Amendment to cover both fertility and developmental hazard criteria.

United States Of America

The classification criteria used as part of the US Hazard Communication Standard are described in Appendix A to the standard. Essentially if there are statistically significant data available (at least one good study) indicating that a chemical is a reproductive toxin, a Material Safety Data Sheet (MSDS) must be prepared including that information, and appropriate hazard warnings included on the container label. The classification system is hazard-based, and because chemical manufactures do not and cannot know what the exposure situation will be in downstream usage, they cannot factor in "risk" for such workers.

Reproductive and developmental toxicity criteria are discussed in guidelines for determining chronic toxicity of products subject to the Federal Hazardous Substances Act.

Guidelines evaluate reproductive toxicity on the basis of human and animal data and "classify" substances if sufficient or "limited" evidence exists to demonstrate developmental or reproductive toxicity. Substances are categorised into *known*, *probable* and *possible* reproductive toxicants where:

known covers substances with sufficient evidence in humans;

probable covers substances with limited evidence in humans or sufficient evidence in animals; and

possible covers substances with limited animal evidence.

These terms are very similar to the Categories 1, 2 and 3 used in the EU and Australia.

Categories of human evidence

1) The evidence for a substance causing an adverse reproductive or developmental effect(s) is considered sufficient when it is based on quality human epidemiology studies. Positive good quality epidemiological studies would meet the following criteria:

   - no identifiable bias
   - adjustment for confounding factors
   - statistically significant association

2) Evidence is considered limited when human epidemiology meets the criteria for sufficient evidence except that it fails to meet one of the criteria (above).

3) inadequate evidence of developmental or reproductive toxicity in humans is considered when more thant one of the criteria are not met.

Categories of animal evidence

Criteria are established for describing a good quality developmental or reproductive toxicity animal study:

- The study should contain at least one dosed (treated) group and one concurrent control group;
- Maternal toxicity should be evaluated and accounted for;
- Test animals should be randomly selected into dose groups;
- Good historical data should be available for the species/strain tested.
- The number of animals per dose should be adequate

Sufficient evidence of developmental or reproductive toxicity in animals is obtained from a good quality animal study with a statistically significant ($P < 0.05$) treatment related:

- increase in the incidence of multiple endpoints in a single species/strain; or
- increase in the incidence of a single endpoint at multiple dose levels or with multiple routes of administration in a single species/strain; or
- increase in the incidence of a single endpoint in multiple species/strain experiments

Evidence of developmental or reproductive toxicity in animals is considered limited when obtained from a good quality study and

- there is a statistically significant ($P < 0.05$) treatment related increase in the incidence of a single endpoint in a single species/strain/experiment at a single dose level administered through only one route, and such evidence does not meet the criteria defined for sufficient evidence; or
- the evidence is derived from studies which can be interpreted to show positive effects but have some qualitative or quantitative limitations which would prevent classification of the evidence in the category of sufficient evidence.

Evidence of developmental or reproductive toxicity would be considered inadequate if it does not meet the criteria of other categories and there can be no interpretation of the data as showing either the presence or absence of a chemical exposure-related effect.

DATA REQUIREMENTS

The EU System

Only broad guidance on the type and quality of studies required to support a classification is available. The classification guidance uses the term "appropriate" studies, and it is essentially left to expert judgement to decide what studies are appropriate for a given chemical. Data from *in vitro* studies or non-mammalian models are only regarded as secondary evidence and cannot normally support a classification in the absence of mammalian *in vivo* data.

Canada

Only broad guidance is given on the type and quality of studies required to support a classification of reproductive toxicity over and above reference to specified OECD Test Guidelines (414, 415 and 416).

Where results are not available according to OECD Test Guidelines, non-specified tests can be used or extrapolation from products with similar properties for example by using Quantitative Structure Activity Relationship (QSAR) data. In place of the test results described in the criteria sufficient, human data can be used to show that a substance meets or does not meet the criteria.

Professional judgement is used to assess whether data are adequate. Inadequate data should not be used to support a classification.

Australia

There are no legislative requirements for particular tests. Reproductive studies should be performed in accordance with an acceptable Code of Good Laboratory Practice (GLP) and according to an internationally accepted protocol. Australian authorities recognise that some existing chemicals have databases that have been generated pre-GLP which may require special consideration.

Data requirements are specified in a "Registration Requirements" document published by the National Registration Authority for Agricultural and Veterinary Chemicals and include a multi-generation reproduction study and developmental toxicity studies in at least two mammalian species. Tests of functional deficit are desirable.

Protocols commonly regarded as acceptable include OECD Test Guideline 416 (Two Generation Reproductive Toxicity) and US EPA Guideline 83-4 (CFR Part 158).

Otherwise no specific data are required for other chemicals and all relevant available data are used.

United States

Relevant testing guidelines include those for pesticides (e.g. the developmental neurotoxicity test guideline 83-3, 83-4, and 83-6) and for toxics (e.g. the inhalation developmental toxicity guideline and the preliminary developmental toxicity screen 40 CRR 798.4350, 798.4420, 798.4700 and 798.4900).

Two specific testing guidelines are expected to be finalised in 1996, namely OPPTS 870.3700 (Draft) Developmental Toxicity Study and OPPTS 870.3800 (Draft) Reproduction and Fertility Effects.

MECHANISM FOR CLASSIFYING SUBSTANCES

The EU system

All substances which have been considered for classification and for which classification has been officially agreed within the EU are listed in Annex 1 to the Dangerous Substances Directive (67/548/EEC). A listing of chemicals which have been so classified is given in Attachment 1 to this document.

Proposals for classification and new entries to Annex 1 are considered by the European Commission's (DG XI) Working Groups for Classification and Labelling. Substances with concerns for reproductive toxicity may be referred by the Working Groups to the Specialised Experts Group (DG XI), which is a group of experts in the fields of mutagenicity, carcinogenicity and reproductive toxicity nominated by Member States who provide specialised advice. Annex I entries accepted by the Working Groups are submitted to the Commission to be voted on by Member States. The classification confirmed in Annex I is obligatory throughout the EU. For substances which are not listed on Annex I, it is the responsibility of a supplier of a chemical to provisionally classify it on the basis of the available information and according to the criteria defined in Directive 93/21/EEC.

Canada

In Canada the classification criteria are used by manufacturers, suppliers, distributors or importers of hazardous materials as a condition of sale of these products or importation of these products into any workplace in Canada. The supplier must use professional judgement to decide if test results or studies on the product signify evidence of reproductive, teratogenic or embryotoxic effects.

With regard to the classification, the supplier is to use a hierarchical approach to the consideration of test results:

1) by using test results of studies carried out in accordance with OECD Test Guidelines;

2) in the absence of test results from 1), by using test results from relevant but non-specified test methods;

3) in the absence of 1) and 2) by extrapolating from results with similar products;

4) where 1), 2), and 3) are not possible, the product can be considered as not meeting the criteria if the supplier has no information of which they might be reasonably aware.

As an alternative strategy, a search may be undertaken of available information and, if the supplier finds sufficient human data to show the product meets or does not meet a criterion, then this information may be used to classify the product.

Australia

In Australia a range of classification approaches are used depending on the sector the chemical is being marketed and used in. In the case of industrial chemicals (as defined under the Industrial Chemicals (Notification and Assessment) Act 1989), the classification criteria are used by the regulatory authority during its assessment, so that appropriate recommendations are made on labelling and MSDS.

In the case of chemicals used at work under occupational health and safety legislation the classification criteria must be used by the importer or manufacturer of the chemical in order to see whether a chemical is teratogenic before supplying the chemical for use at work.

In the case of agricultural and veterinary chemicals, the occupational health and safety assessment includes classification of the active pesticide ingredient. However, a weight of evidence approach rather than classification criteria is used to determine regulatory actions such as restriction of use or decision regarding registration.

United States

In the USA under the Federal Hazardous Substances Act it is the manufacturer of the substance who must apply the criteria to determine the reproductive toxicity of the substance. Where there is controversy about how the evidence should be evaluated, the Consumer Product Safety Commission may proceed by rule-making or by enforcement actions on a case-by-case basis to resolve the question.

Under the Hazard Communication Standard it is the responsibility of manufacturers, importers and employers to determine the reproductive hazards of the substance in a performance-based system.

REGULATORY CONSEQUENCES OF CLASSIFICATION

The EU system

Suppliers of classified substances are required to inform users of the hazardous properties by means of a label and a safety data sheet. For new (notified) substances which are classified, the competent authority of a Member State (for example, in the UK the Health and Safety Executive and Department of the Environment) is required to conduct a risk assessment. The outcome of this risk assessment will be a declaration that:

i) the substance is of no immediate concern or;

ii) there is concern and further information is required to clarify the risk; or

iii) that the risk is clearly understood and risk reduction measures are required.

The following symbols and risk phrases are applied to substances classified as toxic to reproduction:

Cat	Fertility	Developmental toxicity
1	T; R60 May impair fertility	T; R61 May cause harm to the unborn child
2	T; R60 May impair fertility	T; R61 May cause harm to the unborn child
3	Xn; R62 Possible risk of impaired fertility	Xn; R63 Possible risk of harm to the unborn child

Additionally, substances which are absorbed by women and may interfere with lactation or may be present in breast milk in amounts sufficient to cause concern for the health of the breast-fed child are classified, for example Harmful (Xn), and assigned the risk phrase R64 (May cause harm to breast-fed babies).

Canada

No specific risk phrases are mandated for use on a supplier label to indicate a product's reproductive or developmental toxicity. The supplier is expected, however, to use risk and safety phrases appropriate to the classification of the product and to elaborate further on the MSDS.

Australia

Under Australian occupational health and safety legislation, classification as a teratogen would lead to a wide range of workplace measures including information provision (MSDS and labels) and assessment of workplace controls, etc.

No mandatory risk phrases are required. Manufacturers and importers need to ensure that the product is appropriately labelled. Use of the EU risk phrases would normally be regarded as appropriate.

United States

Under the Hazard Communication Standard and Federal Hazardous Substances Act, substances classified as reproductive toxins are required to have MSDS and labels. In addition, a comprehensive hazard communication programme including employee training is required to be developed by employers for substances classified as
reproductive toxins.

COMPARISON OF SYSTEMS

Attachment 2 to this document provides a summary of the identified systems. All identified classification systems are very similar. All are essentially hazard-based. Both animal and human data are used in arriving at the overall classification. All systems are designed to be applied by manufacturers and suppliers in providing adequate labels and MSDS for their products.

The principal differences between the systems are:

- whether the systems have a graded system of classification e.g. Category 1, 2 or 3; known, probable or possible; or have a simple Yes/No approach

- differences in guidance for assessing whether substances meet the criteria or not. For example, the US guidance for determining good quality studies and being more specific in testing requirements. Also, the Canadian system describes a number of strategies which the supplier can use to classify a particular chemical, whereas the EU system relies on expert judgement in the application of the criteria. Furthermore, under the Canadian system negative human data can be used to justify a non-classification, whereas in the European system a weight-of-evidence approach is taken using both human and animal data.

- concentration cut-offs for determining whether mixtures meet the classification criteria, with the Canadian being generally the strictest system with a generally applied 0.1 per cent cut-off, the US having an intermediate position of 1 per cent, and the EU and Australia adopting different cut-offs for the various categories of classification, with the possibility of individually determining a limit in certain cases.

The other main area of difference is in the regulatory consequences of classification. The Canadian system calls for use of appropriate label statements, whereas in the EU system chemicals classified and listed in Annex 1 have mandated risk phrases.

Furthermore, in the EU system there is the additional requirement of a formal risk assessment to be conducted for chemicals on certain regulatory programmes, which may trigger requests for further testing or risk reduction measures.

Attachment 1: Substances Classified in the EU as Toxic to Reproduction

Substance	CAS Number	Index	Classification
Benzo(a)pyrene	000050-32-8	601-032-00-3	Cat 2; R60/61
Binapacryl (iso)	000485-31-4	609-024-00-1	Cat 2; R61
Bromoxynil (iso)	001689-84-5	608-006-00-0	Cat 3; R63
Bromoxynil octanate	001689-99-2	608-017-00-0	Cat 3; R63
Carbon disulphide	000075-15-0	006-003-00-3	Cat 3; R62/63
Carbon monoxide	000630-08-0	006-001-00-2	Cat 1; R61
C I Pigment Red 104	012656-85-8	082-010-00-5	Cat 1; R61 Cat 3; R62
C I Pigment yellow 34	001344-37-2	082-009-00-X	Cat 1; R61 Cat 3; R62
Dimethyl formamide	000068-12-2	616-001-00-X	Cat 2; R61
Dinoseb	000088-85-7	609-025-00-7	Cat 2; R61 Cat 3; R62
Dinoseb salts and esters of	000000-00-0	609-028-00-2	Cat 2; R61 Cat 3; R62
Dinoseb	001420-07-1	609-030-00-4	Cat 2; R61
Dinotseb salts and esters of	000000-00-0	609-031-00-X	Cat 2; R61
2-Ethoxyethanol	000110-80-5	603-012-00-X	Cat 2; R60/61
2-Ethoxyethyl acetate	000111-15-9	607-037-00-7	Cat 2; R60/61
Lead acetate	001335-32-6	082-007-00-9	Cat 1; R61 Cat 3; R62
Lead alkyls	000000-00-0	082-002-00-1	Cat 1; R61 Cat 3; R62
Lead azide	013424-46-9	082-003-00-7	Cat 1; R61 Cat 3; R62
Lead chromate	007758-97-6	082-004-00-2	Cat 1; R61 Cat 3; R62
Lead compounds except those listed	000000-00-0	082-001-00-6	Cat 1; R61 Cat 3; R62
Lead di-acetate	000301-04-2	082-005-00-8	Cat 1; R61 Cat 3; R62
Lead hexafluorosilicate	025808-74-6	009-014-00-1	Cat 1; R61 Cat 3; R62

Attachment 1: Substances classified in the EU as Toxic to Reproduction (continued)

Lead hydrogen arsenate	007784-40-9	082-011-00-0	Cat 1; R61 Cat 3; R62
Lead methanesulphonate	017570-76-2	082-008-00-4	Cat 1; R61 Cat 3; R62
Lead 2 4 6-trinitroresorcinoxide	015245-44-0	609-019-00-4	Cat 1; R61 Cat 3; R62
2-Methoxyethanol	000109-86-4	603-011-99-4	Cat 2; R60/61
2-Methoxyethyl acetate	000110-49-6	607-036-00-1	Cat 2; R60/61
Methyl-onn-azoxymethyl acetate	000592-62-1	611-004-00-2	Cat 2; R61
Mirex	002385-85-5	602-077-00-1	Cat 3; R62/63-64
Nickel tetracarbonyl	013643-39-3	028-001-00-1	Cat 2; R61
Nitrofen (iso)	001836-75-5	609-040-00-9	Cat 2; R61
Tri-lead bis(orthophosphate)	007446-27-7	082-006-00-3	Cat 1; R61 Cat 3; R62
Warfarin	000081-81-2	607-056-00-0	Cat 1; R61

Attachment 2: Summary of the Identified Systems

	USA Federal Hazardous Substances Act	**USA Hazard Communication Standard**	**European Union**	**Canada**	**Australia**
Human evidence Known - Probable -	Sufficient Positive good quality uuman epidemiology studies Limited positive human epidemiology studies but lacking in "one" quality criteria Inadequate Quality criteria not met	At least one good study indicating a reproductive toxin	Category 1 Positive epidemiology data on either fertility or developmental hazard	Evidence of sterility or an adverse effect on reproductive capability in exposed workers	Category 1 Positive epidemiology data on developmental hazard Consideration being given to including developmental hazard
Animal evidence Known, Probable and Possible	Developmental or reproductive toxicity tests. Sufficient, Limited or Inadequate evidence categorised on the basis of specified criteria defining quality of study	At least one good study indicating a reproductive toxin	Category 2 Clear evidence of a specific effect on either fertility or developmental hazard Category 3 Less convincing evidence or where doubts about relevance	Injury to the embryo or foetus in a statistically significant test population at a concentration which has no adverse effect on pregnant female Sterility or an adverse effect on reproductive capability	Category 2 Clear evidence of a specific effect on hazard. Category 3 Less convincing evidence or where doubts about relevance
Concentration Cut-off		1%	0.5% Cat 1 or 2 5% Cat 3 Specified limits for certain substances	0.1%	0.5% Cat 1 or 2 5% Cat 3 Specified limits for certain substances