Reproductive Toxicity

55. A pure substance or tested mixture falls into Subdivision A of Division 2 of Class D - Poisonous and Infectious Material if

(*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 work place; 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 No. 415, "One-Generation Reproduction Toxicity", dated May 26, 1983, or

(ii) OECD Test Guideline No. 416, "Two-Generation Reproduction Toxicity", dated May 26, 1983.

INTERPRETATION / DISCUSSION of SECTION 55

This section deals with human and laboratory animal evidence of adverse effects on reproduction. The OECD Test Guidelines No.s 415 and 416 are designed to provide general information concerning the effects of a test substance on male and female reproductive performance such as:

- gonadal function,
- oestrous cycle,
- mating behaviour,
- conception,
- parturition,
- lactation and
- weaning.

Reproductive toxicity and systemic toxicity: In contrast to the *CPR* criteria specified in section 53 for teratogenicity and embryotoxicity, there are no analogous criteria nor mention of systemic toxicity in relation to the *CPR* criteria for reproductive toxicity. However, in relation to *CPR* Schedule I Subitem 7(8) - “Reproductive toxicity”, and Subitem 7(9) - “Teratogenicity”, The Intergovernmental WHMIS Coordinating Committee’s “Guidelines for the Disclosure of Toxicological Information on a Material Safety Data Sheet” states:

> In animal bioassays, adverse effects on fetal development or parental reproductive functions may occur at doses above or below those producing signs of toxicity in the parent animals. The handling, storage or use of controlled products may occasionally produce exposures resulting in mild parental toxicity thereby resulting in potential developmental or reproductive toxicity hazards. For the purpose of MSDS disclosure, any indication of an adverse effect on fetal development or reproductive parameters must be disclosed on the MSDS irrespective of whether or not there is an adverse effect on the pregnant female. Any relevant epidemiological evidence must also be disclosed.
>
> (**http://www.hc-sc.gc.ca/ehp/ehd/catalogue/psb_pubs/whmis12.htm**)

Therefore, as per the Guidelines, toxicity in the parent animals would address both endpoints. However, since there is no reference to systemic toxicity in Section 55 of the *CPR*, a chemical could be classified as a reproductive toxin in the presence of systemic toxicity. Professional judgement will be required to assess whether the data are adequate and to determine the extent or impact systemic toxicity has on reproductive parameters.

Respiratory Tract Sensitization

56. A pure substance or tested mixture falls into Subdivision A of Division 2 of Class D - Poisonous and Infectious Material if there is evidence that shows that it causes respiratory tract sensitization in persons following exposure to it in the work place.

INTERPRETATION / DISCUSSION of SECTION 56

For the purposes of classification, "respiratory tract sensitization" is a term which is defined by section 32 of the *CPR*. The criteria in this section, therefore, exclude substances that only cause respiratory tract sensitization in persons who are "atopic".

This section deals with a limited class of substances that cause moderate to serious (i.e., life-threatening) effects in the lungs and airways of some individuals when they have become previously sensitized.

Atopy / atopic: Atopy is a genetic predisposition toward the development of immediate (type I) hypersensitivity reactions against common environmental antigens (atopic allergy), occurring in 10 per cent of the general population, 50 per cent of those with one affected parent, and 75 per cent of those with two affected parents[1].

Atopy is a term used clinically to apply to a group of diseases of an allergic nature. They differ from most allergies in that (i) they are inherited, (ii) the antibody produced, called *atopic reagin* or *skin-sensitizing antibody*, is deposited in cutaneous tissues and may enter the blood stream, and (iii) the primary reaction which appears is *edema* as occurs in hay fever or inflammation of the mucous membrane (allergic *rhinitis*);[2] bronchial asthma, atopic dermatitis (or chronic *urticaria*) and food allergy occur less frequently.
"Atopy generally refers to the development of immune responses to foreign antigens that are characterized by the production of antigen-specific immunoglobulin E (IgE). Development of atopic responses has been linked to several genes and gene products. Thus, atopic diseases represent a complex gene-environment interaction in which environmental antigens interact with the immune system, producing atopic (IgE) responses."[3]

Sensitization: Sensitization is an allergic response by the immune system. In contrast to irritation which is a local or topical phenomenon, "sensitization" is a systemic condition. Substances that cause sensitization are known as allergens or antigens. A single exposure or, in some cases, several repeated

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[1] Dorland Illustrated Medical Dictionary.

[2] Taber's Cyclopedic Medical Dictionary, 11th edition, Clarence Wilbur Taber, 1970.

[3] "Development of Atopy and Asthma: Candidate Environmental Influences and Important Periods of Exposure"; David B. Peden; Environmental Health Perspectives Volume 108, Supplement 3, June 2000

exposures to an allergen by inhalation, skin contact or ingestion may cause the person exposed to develop antibodies that will react with the allergen. Once antibodies are formed, the person is "sensitized". After a person has been sensitized, any future exposure to the allergen, even at levels significantly lower than the initial sensitizing dose (or doses) results in an allergic reaction. Allergies may become apparent through the display of such symptoms as sneezing, runny nose, headache, asthma, allergic contact dermatitis and anaphylactic shock, singly or in combination. (Refer to section 61 for criteria specifically relating to "skin sensitization").

Sufficiency of evidence - proportion of affected persons: In contrast to the criteria specified in paragraph 61(*a*) of the *CPR*, neither *CPR* 56 nor 61(*b*) provide any indication as to what proportion of affected "persons" should constitute grounds for inclusion within the respective criteria for respiratory tract sensitization and skin sensitization. This has led to differences in classification.

- In the case of animal studies to assess skin sensitization, paragraph 61(*a*) of the *CPR* specifies a response of 30% of the test population using an adjuvant and 15% without use of an adjuvant.
- In the case of human evidence, the *CPR* criteria for both respiratory tract and skin sensitization specify that the substance causes sensitisation "in persons following exposure to it in the work place" without specifying the proportion of persons exposed. It is probable that any chemical, natural or synthetic, is capable of causing an allergic reaction in some individuals. However there are chemicals such as, for example, isocyanates, that cause sensitization in a "substantive proportion of exposed" individuals who come into contact with these substances.

- The OSHA Hazard Communication Standard specifies "*a substantial proportion of exposed people*" in relation to the criteria for skin and respiratory sensitization.

- The current European Economic Community Council Directive 67/548/EEC relating to the classification, packaging and labelling of dangerous substances and the proposed new criteria for skin sensitization also specify "a *substantial number of persons*". (In response to the proposal it has been suggested that, when there are few cases but a high proportion are sensitized, this should be given special concern.) For respiratory sensitization, the current EEC Directive states "*at a greater frequency than would be expected from the response of the general population*". The proposed new criteria state "the size of the exposed population and the extent of exposure should be taken into account".

- The criteria agreed upon for the Globally Harmonized System (GHS) specify that, when considering human evidence, it is necessary for a decision on classification to take into account, in addition to the evidence from observed cases, the size of the population exposed and the extent of exposure. For a contact (skin) sensitizer, the GHS criteria also specify that sensitization should be observed "*in a substantial number of persons*".

- The question of the number of cases that should constitute a "substantive proportion of exposed persons" has been raised in a number of jurisdictions. No regulatory authority, however, has set a number / percentage when considering case reports and other evidence in humans.

Conclusion: When determining whether or not a chemical falls within the *CPR* criteria for sensitization, the

number of cases reported in relation to the size of the population that has been exposed and the extent of the exposure should be taken into consideration. For example, a high-production-volume chemical, used in large quantities in many workplaces would not warrant classification if only a few cases of sensitization had been reported over a period of several years. On the other hand, 3 cases of asthma amongst a workforce of 20 could result in the inclusion of the substance within the classification criteria for sensitization.

The WHMIS Current Issues Committee agreed to the following regarding the issue of "proportion of affected persons", {ref.: PIS No. 85}:

1. For the purposes of determining whether a product falls within the *CPR* criteria for sensitization, and in order to prevent a chemical being classified on the basis of only one or two cases that may be attributable to an idiosyncratic reaction, when considering case reports and other evidence in humans, "persons" shall be understood to mean "a substantial number of persons exposed" and also "take into account the size of the population exposed and the extent of exposure".

2. If there is evidence that a product, material or substance can induce sensitization, even if it does not fall within the *CPR* classification criteria, this information should be disclosed on the MSDS.

Mutagenicity

57.(1) A pure substance or tested mixture falls into Subdivision A of Division 2 of Class D - Poisonous and Infectious Material if

(*a*) there is epidemiological evidence that shows a causal connection between exposure of persons to the substance or mixture and heritable genetic effects; or

(*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, or

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

(2) The evidence referred to in paragraph (1)(*b*) shall be obtained

(*a*) in accordance with test methods described in the "Introduction to the OECD Guidelines on Genetic Toxicology Testing and Guidance on the Selection and Application of Assays", dated March 1, 1987, published in the Third Addendum to the *OECD Guidelines for Testing of Chemicals*; and

(*b*) using testing strategies described in the *Guidelines on the Use of Mutagenicity Tests in the Toxicological Evaluation of Chemicals*, dated 1986, published under the authority of the Minister of National Health and Welfare and the Minister of the Environment.

INTERPRETATION / DISCUSSION of SECTION 57

The criteria in this section encompass human epidemiological evidence as well as results from laboratory animal studies showing a causal connection between exposure to a substance and heritable genetic effects. The criteria include evidence that a genetic change (mutation) has been transmitted to offspring by exposure of eggs or sperm (i.e., germ cells) and evidence of chemical interaction with germ cells when genetic effects occur in cells *other* than germ cells (i.e., somatic cells).

Redundancy of multiple classifications within WHMIS Class D: Materials falling within the criteria of Section 57 of the *CPR* do not need to be also classified under Section 62. A germ cell mutagen also has the potential to induce somatic cells mutations that may be associated with the subsequent development of cancer or other diseases. Therefore, it would be redundant to classify a chemical in both subclasses i.e. meeting criteria for Section 57 (Class D2A - heritable genetic effects) and Section 62 (Class D2B -

somatic cell mutagenicity). The distinction between the two subclasses relies very often on the amount of evidence (i.e test results) available. Please refer to the discussion of Section 43 of the *CPR* for more information on this issue.

Which mutagenicity assays should be considered?: Paragraphs 57(2)(*a*) and 62(*a*) of the *CPR* reference OECD test guidelines for genetic toxicology testing. Some of the OECD test methods (OECD test guidelines 474, 475, 478, 483, 484, and 485) list *intra peritoneal* as one of the route of administration of the chemical which is not considered a normal route of occupational exposure.

- As specific assays are not listed in the *CPR*, this has lead to differing application of the Regulations. For example, the applicability of test data acquired via the *intra peritoneal* route has led to disputes and/or inconsistences in the classification of controlled products.

- The "Harmonized Integrated Hazard Classification System for Human Health and Environmental Effects of Chemical Substances" (November 98) states that the "relevance of the route of exposure of the study of the chemical compared to the route of human exposure should also be taken into account".

For the purpose of determining which assays should be considered when assessing mutagenicity, it is recommended that results from the assays listed in the following chart[(1)(2)] be adopted as a general minimum guideline:

Assay	Gene Mutation	Chromosome Aberrations	*in vitro* Test	*in vivo* Test	*CPR* 57- Criteria for Germ Cell Effects [(3)] WHMIS - D2A	*CPR* 62- Criteria for Somatic Effects[(4)] WHMIS - D2B
Dominant Lethal Assay		x		x	x	
Mammalian Germ Cell Cytogenetic		x		x	x	
Heritable Translocation Assay		x		x	x	
Mouse Spot Test	x			x		x
Micronucleus Test		x		x		x
Cytogenic Assay in Animals		x		x		x
Unscheduled DNA Synthesis in Animals				x		x

	Gene Mutation	Chromosome Aberrations	*in vitro* Test	*in vivo* Test	*CPR* 57- Criteria for Germ Cell Effects (3) WHMIS - D2A	*CPR* 62- Criteria for Somatic Effects(4) WHMIS - D2B
DNA Adduct Formation in Animals				x		x
Sister Chromatid Exchange in Animals				x		x
Salmonella typhimurium Reverse Mutation (AMES) (5)	x		x			
Gene Mutation in Yeast or Mammalian Cells (5)	x		x			
Cytogenic Assay in Cultured Cells (5)		x	x			

(1) Adaptation from *Regulatory Toxicology and Pharmacology* 27, 61-74 (1998)
(2) These are recommended minimum guidelines which do not preclude consideration of other assays not referred to in this table
(3) If present in concentration $\geq$0.1%
(4) If present in concentration $\geq$1.0%
(5) While these tests do not explicitly relate to WHMIS classification for mutagenicity, the results should be disclosed on the MSDS. Regarding, for example, the Ames as a stand alone test, Appendix 10-1 “Basis for Development of the WHMIS Ingredient Disclosure List” of the Report of the WHMIS Project Steering Committee states the following:

> “if sufficient evidence exists to indicate a potential and justifiable cause for concern, then the material in question will be included in the list, subject to:
>
> 1) peer review to confirm that the evidence is sufficient to warrant a justifiable cause for concern; and
>
> 2) the evaluation of any subsequent more definitive information which indicates that the earlier cause for concern is not justified
>
> Notes: (1) Justifiable cause for concern means a technical assessment according to scientific principles of a multiplicity of tests covering a range of effects which takes into account the naturally occurring defence mechanisms which exist in mammals.
>
> (2) A positive result in any one short-term bioassay, e.g., a single Ames Test does not constitute justifiable cause for concern.

(3) The result of any short term bioassay, e.g., a single Ames test (positive or negative), shall not be considered in deciding whether anything is known about the toxicological properties of the material.

(4) In deciding whether or not a chemical ought to be on the WHMIS list, the principle should be to take a conservative approach, i.e. to ensure that reasonable doubt about a chemical will result in its exclusion...."

Untested Mixtures

58. An untested mixture falls into Subdivision A of Division 2 of Class D - Poisonous and Infectious Material if it contains a product, material or substance that meets the criteria applicable to a pure substance or tested mixture referred to in

(*a*) any of sections 53 to 57, if the product, material or substance is present at a concentration of 0.1 per cent or more; or

(*b*) section 52, if the product, material or substance is present at a concentration of one per cent or more.

INTERPRETATION / DISCUSSION of SECTION 58

Where a mixture has not been tested as a whole to determine its health hazards, for the purposes of classification under the *CPR*, the mixture is assumed to present the same hazards as the components comprising a specified percentage of the mixture. The percentage specified (0.1 versus 1.0%) depends upon the hazard under consideration. This section specifies a 0.1% concentration cut-off for ingredients that meet any of the criteria for teratogenicity and embryotoxicity, carcinogenicity, reproductive toxicity, respiratory tract sensitization and mutagenicity specified in sections 53 to 57, respectively, and 1.0% for ingredients that meet any of the criteria for chronic toxicity specified in section 52.

Cut-offs of 0.1 and 1.0% are also specified in the United States OSHA Hazard Communication Standard (HCS). Under the HCS, however, a cut-off of 0.1% is limited to carcinogens.