Poisonous Substances as Defined by the *Transportation of Dangerous Goods Regulations*

50. A pure substance or tested mixture falls into Subdivision B of Division 1 of Class D - Poisonous and Infectious Material if it is included in Packing Group III of Division 1 of Class 6 in Part III of the *Transportation of Dangerous Goods Regulations*.

DISCUSSION of SECTION 50

This section is analogous to section 47. It links the criteria described in section 49 of the *CPR* to the equivalent TDG class, division and packing group, i.e., if a substance is included in Packing Group III of TDG Class 6.1, that substance is included in WHMIS D1B.

The TDG Regulations specify TDG packing groups for primary but not subsidiary TDG classifications. Therefore, where a substance has a subsidiary TDG classification of 6.1, it cannot be determined if the substances falls into WHMIS D1A versus D1B without assessing the substance against the LD_{50}/LC_{50} criteria specified in sections 46 and 49 of the *CPR*.

The distinction between D1A (*CPR* 47) and D1B (*CPR* 50) is based on the packing group of the 6.1 TDG classification. If the 6.1 classification is the subsidiary classification, it can be concluded that the substance falls within D1. However, the scientific literature must be searched to find the LD_{50}/LC_{50} values that enable the determination of whether a substance falls within the criteria for D1A versus D1B. If available LD_{50}/LC_{50} data do not enable an assessment against the criteria set out in sections 46 and 49 of the *CPR* then the substance would be included in D1B.

Untested Mixtures

51. An untested mixture falls into Subdivision B of Division 1 of Class D - Poisonous and Infectious Material if it contains a product, material or substance that meets any of the criteria applicable to a pure substance or tested mixture referred to in section 49 or 50 and is present at a concentration of one per cent or more.

DISCUSSION of SECTION 51

This section is analogous to section 48 of the *Controlled Products Regulations*.

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 criterion specifies a 1% concentration cut-off for ingredients that meet any of the criteria in section 49 or 50.

A cut-off of 1.0% is also specified in the United States OSHA Hazard Communication Standard.

Division 2: Materials Causing Other Toxic Effects

Subdivision A: Very Toxic Material

Pure Substances and Tested Mixtures

Chronic Toxic Effects

52. A pure substance or tested mixture falls into Subdivision A of Division 2 of Class D - Poisonous and Infectious Material if, in an animal assay for chronic toxic effects, it elicits a response of sufficient severity to threaten life or cause serious permanent impairment in a statistically significant proportion of the test population at

(*a*) a dose not exceeding 10 milligrams per kilogram of body weight of the animal per day when tested in accordance with

(i) OECD Test Guideline No. 408, "Subchronic Oral Toxicity --Rodent: 90-day", dated May 12, 1981,

(ii) OECD Test Guideline No. 409, "Subchronic Oral Toxicity -- Non-Rodent: 90-day", dated May 12, 1981, or

(iii) the oral route test in OECD Test Guideline No. 452, "Chronic Toxicity Studies", dated May 12, 1981;

(*b*) a dose not exceeding 20 milligrams per kilogram of body weight of the animal per day when tested in accordance with

(i) OECD Test Guideline No. 411, "Subchronic Dermal Toxicity: 90-day", dated May 12, 1981, or

(ii) the dermal route test in OECD Test Guideline No. 452, "Chronic Toxicity Studies", dated May 12, 1981; or

(*c*) a concentration not exceeding 25 parts per million by volume of gas or vapour, or not exceeding 10 micrograms per litre or 10 milligrams per cubic metre of dust, mist or fume when tested in accordance with

(i) OECD Test Guideline No. 413, "Subchronic Inhalation Toxicity: 90-day", dated May 12, 1981, or

(ii) the inhalation route test in OECD Test Guideline No. 452, "Chronic Toxicity Studies", dated May 12, 1981.

DISCUSSION of SECTION 52

The term "chronic toxic effect" is defined in section 32 of the *CPR*. The criteria in paragraphs (*a*), (*b*) and (*c*) deal with results of animal testing by the three routes of exposure - oral, dermal and inhalation, respectively. OECD Test Guidelines have been referenced as the criteria.

Although the opening statement in this set of criteria refers only to "chronic" effects, several of the referenced OECD guidelines determine effects from "subchronic" studies which are usually conducted for a period of 90 days. Chronic studies usually involve exposing test animals for 10% or more of their normal life span at various dose or concentration levels to determine at what level chronic toxicity occurs. As indicated below, subchronic studies involve the exposure of test animals for a maximum of 10 per cent of their life span.

Guideline 452 is referenced for all three routes of exposure. The introduction section of this guideline states: "The duration of chronic toxicity studies for effects other than neoplasia is still widely debated. Under the conditions of this test, effects such as carcinogenesis and those which are non-specific life shortening, which require a long latent period or are cumulative, may not become manifest. Except for those, the application of these Guidelines should generate data on which to identify the majority of chronic effects and to determine dose-response relationships. Ideally, the design and conduct should allow for the detection of general toxicity including neurological[1], physiological, biochemical, and haematological effects and exposure-related morphological (pathology) effects."

Redundancy of multiple classifications within WHMIS Class D: Materials falling within the criteria of Section 52 of the *CPR* (Class D2A - chronic toxic effects) do not need to be also classified under Section 59, (Class D2B - chronic toxic effects). The difference between inclusion in those two WHMIS classes relates to the dose in relation to the observation of a specified adverse effect. As such, if a chemical falls within the criteria specified in *CPR* 52 and thereby considered “very toxic”, no additional information would be provided by also including the substance in D2B. Please refer to the discussion of Section 43 of the *CPR* for more information on this issue.

Paragraph (*a*):

OECD guidelines 408 and 409 define "subchronic oral toxicity" as the adverse effects occurring as a result of the repeated daily oral dosing of a chemical to experimental animals for part (not exceeding 10 per cent) of the life span.

1. The U.S. EPA has also issued proposed guidelines "for assessing the risks for neurotoxicity from exposure to environmental agents"; ref.: Federal Register, Vol. 60, No. 192, October 4, 1995, p. 52032.

Paragraph (*b*):

OECD guideline 411 defines "subchronic dermal toxicity" as the adverse effects occurring as a result of the repeated daily dermal application of a chemical to experimental animals for part (not exceeding 10 per cent) of a life span.

Paragraph (*c*):

OECD guideline 413 defines "subchronic inhalation toxicity" as the adverse effects which follow repeated daily exposure by inhalation for part (not exceeding 10 per cent) of a life span.

Teratogenicity and Embryotoxicity

53.(1) A pure substance or tested mixture falls into Subdivision A of Division 2 of Class D - Poisonous and Infectious Material, in an animal assay for teratogenicity and embryotoxicity, it is shown to cause injury to the embryo or fetus 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

(*a*) OECD Test Guideline No. 414, "Teratogenicity", dated May 12, 1981;

(*b*) OECD Test Guideline No. 415, "One-Generation Reproduction Toxicity", dated May 26, 1983; or

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

(2) In this section, "injury" includes death, malformation, permanent metabolic or physiological disfunction, growth retardation or psychological or behaviourial alteration that occurs during pregnancy, at birth or in the postnatal period.

DISCUSSION of SECTION 53

These criteria encompass controlled products which cause various injuries to the embryo and fetus that may occur under conditions that would have no effect on the pregnant female.

In OECD Test Guideline No. 414, teratogenicity is defined as "the property of a chemical which causes permanent structural or functional abnormalities during the period of embryonic development". The test substance is administered daily beginning soon after implantation and continuing through organogenesis. One day prior to term, foetuses are delivered by hysterectomy and examined for visceral or skeletal abnormalities.

The oral dose of 1000 mg/kg mentioned in the guideline is **not** intended to serve as a “limit dose” for developmental toxicity testing. Rather, the 1000 mg/kg is intended to aid in the prioritization of developmental toxicity testing by indicating that *if* no adverse fetal or maternal effects are observed at 1000 mg/kg, no further testing at higher doses is required to establish the level at which such effects might be produced. However, if in an existing study adverse fetal or maternal toxicity at dose(s) greater than 1000 mg/kg is observed, such data should be evaluated and used to establish the hazards of the material and ultimately the WHMIS classification. Section 4.2.3.3 of Annex VI of the EU Dangerous Substances Directive (4.5.93, No L 110A/45) states the following:

> "Annex V to the Directive specifies a limit test in the case of substances of low toxicity. If a dose level of at least 1000 mg/kg orally produces no evidence of effects toxic to reproduction, studies at other dose levels may

not be considered necessary. If data are available from studies carried out with doses higher than the above limit, this data must be evaluated together with other relevant data. Under normal circumstances it is considered that effects seen only at doses in excess of the limit dose would not necessarily lead to classification as 'toxic to 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. Studies carried out in accordance with these guidelines may also provide preliminary information about developmental toxic effects of the test substance, such as neonatal morbidity, mortality, behaviour and teratogenesis. They also serve as a guide for subsequent tests.

Maternal toxicity: When developmental effects are found in the presence of maternal toxicity, the primary cause is often left to speculation. Without sufficient evidence to support the premise that developmental toxicity is always a secondary toxic effect in the presence of maternal toxicity, a default is needed.

Inconsistency in the manner by which maternal toxicity data are evaluated has lead to variance in the WHMIS classification of and MSDS disclosure for several substances. The term "maternal toxicity" is not defined in the *CPR*. The Intergovernmental WHMIS Coordinating Committee (IWCC) has adopted the following as policy regarding maternal toxicity:

Indicators of Maternal Toxicity

Guidelines for developmental toxicity evaluation have been published by the US EPA [1] and the California EPA [2]. Both of these documents provide specific guidance concerning the assessment of maternal toxicity in teratology and reproductive toxicity bioassays.

Developmental toxicity can occur in the presence or absence of maternal toxicity. In addition, toxic effects on the female reproductive system in the pregnant female may also be direct or secondary to other toxic effects. Since the prenatal environment for the conceptus is provided by the maternal reproductive system, the developing organism is potentially subject to direct toxic effects of the agent; to toxic effects which directly impair the supportive functions of the female reproductive system; and to other toxic effects in the dam which secondarily affect the conceptus or female reproductive system. Where effects occur both in the developing organism and in the mother, developmental effects may be caused by any of these factors, or by some interaction between them [2].

In its assessment of developmental toxicity hazard, California EPA has adopted the following position regarding maternal toxicity in teratology or reproductive toxicity bioassays:

> Developmental effects which occur in the presence of maternal toxicity are considered to be evidence of developmental toxicity, unless it can be unequivocally demonstrated that the developmental effects are secondary to maternal toxicity [2].

The IWCC Guidelines for the Disclosure of Toxicological Information on MSDSs [3] state that:

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. For the purpose of hazard disclosure, any indication of an adverse effect on fetal development or reproductive parameters should be disclosed on the MSDS. Such disclosure is required because 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 purposes of section 53(1) and subitem 7(9) of Schedule I of the *CPR*, the following indicators of maternal toxicity [1,2] shall be evaluated when determining whether embryo-fetal or developmental toxicity has occurred at "a concentration that has no adverse effect on the pregnant female":

a. *Mortality* - The observation of an increase over the control in the incidence of maternal mortality among the treated dams should be considered evidence of maternal toxicity if the increase occurs in a dose-related manner, and is attributed to the systemic toxicity of the test material (with disease being ruled out). In the case of gavage studies, care must be taken in determining if maternal deaths were due to errors in the dosing procedure rather than the systemic toxicity of the test material.

b. *Maternal Body Weight* - The observation of a statistically significant decrease in the average maternal body weight of the treated dams relative to those in the control group during the treatment period, or on the day of necropsy, may be considered evidence of maternal toxicity. It should be stressed that body weight changes may provide more information than does daily body weight measured during or following treatment [1]. Consideration of the maternal body weight change and/or corrected maternal body weight should be included in the evaluation of maternal toxicity whenever such data are available. Body weight data may not be as useful an indicator of maternal toxicity in rabbits as it is for other species because rabbit body weight changes are usually more variable. Also, in some strains of rabbits, bodyweight is not a good indicator of pregnancy status [1].

c. *Maternal Body Weight Change* - The observation of a statistically significant decrease in the average maternal body weight gain in the treated dams relative to those in the control group over the gestation period and/or during the treatment period, may be considered evidence of maternal toxicity. However, consideration of the corrected maternal body weight change should be included, whenever possible, in the evaluation. Changes in maternal body weight corrected for gravid uterine weight at sacrifice may be a better indicator of whether an effect is primarily maternal or intrauterine. For example, a significant reduction in maternal body weight gain throughout gestation, without a concomitant change in corrected maternal weight gain, would indicate an intrauterine effect in the absence of maternal toxicity. An alternate, although less desirable, estimate of corrected maternal weight change during gestation can be obtained by subtracting the sum of the weights of the fetuses (however, this weight does not include the uterine and placental tissue nor the amniotic fluid)[1].

d. *Organ Weights* - The observation of a statistically significant change in the average weight (absolute or relative) of suspected target organ(s) of treated dams, relative to those in the control group, may be considered evidence of maternal toxicity. Whenever possible, changes in organ weights should be supported by findings of adverse histopathological effects in the affected organ(s), and/or changes in other biologically relevant parameters, such as hematology or clinical chemistry.

e. *Food and Water Consumption* - The observation of a statistically significant decrease in the average food or water consumption in treated dams relative to the control group may be useful in evaluating maternal toxicity, particularly when the test material is administered in the diet or drinking water. Changes in food or water consumption should be evaluated in conjunction with maternal body weights when determining if the effects noted are reflective of maternal toxicity.

f. *Clinical Observations of Toxicity* - The observation of a statistically significant increase in the incidence of significant clinical signs of toxicity in treated dams relative to the control group may be useful in evaluating maternal toxicity. If this is to be used as the basis for the assessment of maternal toxicity, the types, incidence, degree and duration of clinical signs should be reported in the study. Examples of significant clinical signs of maternal intoxication include: coma, prostration, loss of righting reflex, ataxia, or laboured breathing.

References cited in the IWCC policy on maternal toxicity:

[1] US EPA. Guidelines for Developmental Toxicity Risk Assessment. Federal Register 56(234):63798-63826, Dec. 5. 1991.

[2] California Department of Health Services, Health Hazard Assessment Division. Draft Guidelines for Hazard Identification and Dose-response Assessment of Agents Causing Developmental and/or Reproductive Toxicity. April 3, 1991.

[3] IWCC Guidelines for the Disclosure of Toxicological Information on a Material Safety Data Sheet; (accessible from “MSDSs” page on the Health Canada WHMIS website: www.hc-sc.gc.ca/whmis).