



Hazardous Materials Information
Review Commission

Conseil de contrôle des renseignements
relatifs aux matières dangereuses

Service Standard for Referencing and Summarizing Toxicological Information in Advice Documents and Toxicity Profile Summaries



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March 2000

Canada

INTRODUCTION

The objective of this Service Standard is to improve the consistency of advice and improve the efficiency of the Material Safety Data Sheet (MSDS) Compliance Division in the production of Advice Documents (AD) and Toxicity Profile Summaries (TPS).

Part I of this Service Standard describes the information which must be included when summarizing a toxicological study for inclusion in an AD or TPS. The information indicated as “mandatory” must be present in a study or the study is considered as not meeting the criteria of the Service Standard and the study is not evaluated further. The information which is indicated as “if available” is to be included in the summary in order to give the reader a better understanding of the nature and scope of the investigation.

Part II of this Service Standard outlines the referencing requirements for various toxicological endpoints under circumstances which will or will not result in a change in classification for the controlled product. Primary sources referred to in this section should be available in English or French and if foreign sources are used they must be fully translated.

Appendix I provides a list of reliable secondary references to be used in AD and TPS. The criteria applied in compiling the list of reliable secondary references included those that reference the primary source of information and those which based on experience and professional judgement, generally provide reliable information. The list should not be considered “all inclusive” and may change from time to time, as more secondary references become available.

PART I: Toxicology Summary Information to be Included in AD and TPS

1. LD₅₀ (Oral, Dermal) Studies

The mandatory information to be included:

- ▶ LD₅₀ value and units as given in the study
- ▶ species
- ▶ route of administration
- ▶ if the study is to be used for classification purposes state if it conforms to an OECD test guideline e.g. 401, 402, 420

Information to be included if it is available:

- ▶ number of decedents/total when a “> or <” value is reported
- ▶ convert units to mg/kg when ml/kg values are given, and provide the density or specific gravity used for the calculation

2. LC₅₀ (Inhalation) Studies

The mandatory information to be included is:

- ▶ LC₅₀ value and units
- ▶ species
- ▶ duration of exposure in hours
- ▶ conversion of LC₅₀ value to 4 hour equivalent if determined for a different exposure duration (CPR 44)
- ▶ saturated vapour concentration for LC₅₀'s within the classification range for substances tested as vapour (CPR46)
- ▶ if the study is to be used for classification purposes state if it conforms to an OECD test guideline e.g. 403
- ▶ form of chemical – i.e. mist, vapour, dust, aerosol, gas

Information to be included if it is available:

- ▶ number of decedents/total when a “> or <” value is reported

3. Skin/Eye Irritation Studies

The mandatory information to be included is:

- ▶ irritant qualities, severity of effect
- ▶ species
- ▶ volume applied
- ▶ duration of skin exposure
- ▶ concentration of solution

- ▶ specify the protocol or test guideline e.g. Draize
- ▶ if the study is to be used for classification purposes state if it conforms to an OECD test guideline e.g. 404, 405

Information to be included if it is available:

- ▶ irritation score/max. score
- ▶ when classifying skin irritation using OECD test data, separate the available scores into erythema and edema
- ▶ when classifying eye irritation using OECD test data, separate the available scores into corneal, iris, and conjunctival swelling or redness
- ▶ for eye irritation studies include if the eyes were washed or unwashed

4. Corrosion Studies

The mandatory information to be included is:

(A) Human Evidence:

- ▶ describe the report including: brief description of the study and the resultant visible necrosis of the skin, number of persons, duration of skin exposure

(b) Animal Evidence:

- ▶ irritant qualities, severity of effect
- ▶ species
- ▶ volume applied
- ▶ duration of skin exposure
- ▶ concentration of solution
- ▶ if the study is to be used for classification purposes state if it conforms to an OECD test guideline e.g. 404, 405

Information to be included if it is available:

- ▶ irritation score/max. score
- ▶ specify the protocol or test guideline e.g. Draize

5. Chronic/Sub-chronic/Short-Term Toxicity

The mandatory information to be included is:

- ▶ species, sex(es), route, duration of dosing, dose levels, dosing schedule
- ▶ group size
- ▶ brief description of serious adverse effects observed at specific dose(s), and indication if effects occur in a dose-dependent manner
- ▶ if the study is to be used for classification purposes indicate which of the described effects are statistically significant

- ▶ for inhalation studies indicate whether the chemical was respirable, the size of the particles/droplets for aerosols, and the form of the chemical, type of exposure (nose-only, whole body)
- ▶ if the study is to be used for classification purposes state if it conforms to an OECD test guideline e.g. 408, 409, 411, 413, 452

Information to be included if it is available:

- ▶ if the study is to be used for disclosure purposes indicate which of the described effects are statistically significant

6. Carcinogenicity

The mandatory information to be included is:

- ▶ a sentence stating that the ingredient is listed on the ACGIH (A1, A2, A3) or IARC (Groups 1, 2A, 2B) list and specify the category
- ▶ add an italicized Note for ingredients which produce tumorigenic effects (e.g. NTP studies), but are not on the IARC or ACGIH lists, and summarize the information under chronic/sub-chronic/short-term toxicity and include for disclosure

7. Teratology/Fetotoxicity/Developmental

The mandatory information to be included is:

- ▶ species, group size, route, dosing period, dose levels
- ▶ description of maternal toxicity (specify) and at which dose levels it was observed (state if none observed or not discussed)
- ▶ brief description of adverse effects in the fetus (CPR 53) observed in relation to maternally toxic dose
- ▶ if the study is to be used for classification purposes indicate which of the described effects are statistically significant
- ▶ if the study is to be used for classification purposes state if it conforms to an OECD test guideline e.g. 414, 415, 416

Information to be included if it is available:

- ▶ if the study is to be used for disclosure purposes, indicate which of the described effects are statistically significant (both maternal and fetal)

8. Reproductive Toxicity

The mandatory information to be included is:

(a) Human Evidence:

- ▶ describe the report including: specification of the adverse effect or sterility, the sex affected, numbers of persons affected, duration of exposure, occupational environment

(b) Animal Evidence:

- ▶ species, sex(es), group size, route, dosing duration, dose levels, dosing schedule, brief description of the mating procedure
- ▶ brief description of the adverse effects in either or both sex(es) and dose(s) at which effects occur
- ▶ for ingredients that produce fetotoxicity in a reproduction study, refer to the section on teratology/fetotoxicity for summary details required
- ▶ if the study is to be used for classification purposes state if it conforms to an OECD guideline e.g. 415, 416

9. Mutagenicity - *In Vivo* Heritable Mutation

The mandatory information to be included is:

(a) Human Evidence:

- ▶ describe the report including: specification of the heritable mutagenic effect, duration and route of exposure, affected sex, numbers of persons affected (≥ 2 required for classification)

(b) Animal Evidence:

- ▶ species, sex, group size, route, dosing duration, dose level(s), type of assay performed
- ▶ brief description of mutagenic effects produced
- ▶ if the study is to be used for classification purposes state if it conforms to an OECD guideline e.g. 478, 483, 485

10. Respiratory Sensitizers

The mandatory information to be included is:

- ▶ describe the report including: brief description of the study and adverse effect produced, brief description of the occupational history of the worker (e.g. increase in severity of attacks, absence of symptoms away from work), numbers of affected persons (≥ 2 required for classification), duration of exposure, occupational environment
- ▶ indicate whether or not workers were identified as being atopic, or state that atopy was not discussed in the reference

11. Dermal Sensitization

The mandatory information to be included is:

(a) Human Evidence:

- ▶ describe the report including: brief description of the study and the effect produced, number of persons (≥ 2 required for classification), duration of exposure, occupational environment
- ▶ indicate that workers were identified as being non-atopic, or state that atopy was not discussed in the reference

Information to be included if it is available:

- ▶ brief description of the occupational history of the worker (e.g. increase in severity of attacks, absence of symptoms away from work)

The mandatory information to be included is:

(b) Animal Evidence:

- ▶ species, numbers of animals, name of test method used, severity of sensitization reaction, proportion of animals sensitized, if an adjuvant was used
- ▶ if the study is to be used for classification purposes state if it conforms to an OECD guideline e.g. 406

12. Mutagenicity – *In Vivo* Somatic Mutation

The mandatory information to be included is:

- ▶ species, sex, group size, route, dosing duration, dose level(s), type of assay performed.
- ▶ brief description of mutagenic effects produced
- ▶ if the study is to be used for classification purposes state if it conforms to an OECD guideline e.g. 474, 475, 484, 486

13. Mutagenicity – *In Vitro* Mutation (DISCLOSURE ONLY)

The mandatory information to be included is:

- ▶ type (name) of the assay, type of cell (i.e. mammalian, yeast, bacterial), result (positive/negative) with or without metabolic activation (S-9)

14. Human Effects of Acute/Chronic Exposure (SCHEDULE I -DISCLOSURE ONLY)

The mandatory information to be included is:

- ▶ route of exposure
- ▶ symptoms grouped by system affected (e.g. central nervous system; peripheral nervous system; blood/circulatory; gastro-intestinal; liver; respiratory; kidney; ocular; skin)
- ▶ for each grouping, provide a brief summary of the **principal** effects/symptoms that apply (in

- ▶ parenthesis)
- ▶ specify conditions of exposure (e.g. accidental poisoning) if applicable

Information to be included if it is available:

- ▶ dose or amount or level of exposure

15. Animal Effects of Acute Exposure (SCHEDULE I - DISCLOSURE ONLY)

The mandatory information to be included is:

- ▶ route of exposure
- ▶ species
- ▶ to the extent possible, symptoms grouped by system affected (e.g. central nervous system, peripheral nervous system, blood/circulatory, gastro-intestinal, liver, respiratory, kidney, ocular, skin)
- ▶ provide a brief summary of the principal effects/symptoms that apply to each grouping (in parenthesis)

Information to be included if it is available:

- ▶ dose

16. Toxicological Synergisms

The mandatory information to be included is:

- ▶ species, occupational route of exposure of controlled product or ingredient (other chemical in the interaction can be given by any route of exposure)
- ▶ a brief description of synergistic effects (must be greater than the sum of their separate effects) observed

Information to be included if it is available:

- ▶ dose, dosing period

PART II: Referencing requirements for toxicology information from publicly available sources to be included in ADs and TPSs

1. LD/LC₅₀ and Skin/Eye Irritation/Corrosion Studies

(a) Data resulting in a change in WHMIS classification

When the LD/LC₅₀ values or eye/skin irritation results obtained from the literature will result in a change in WHMIS classification (e.g. from unclassified to D1B, D1B to D1A, or to Class E from Class D2B due to eye/skin corrosion), the following approach should be followed:

- ▶ Use and reference the **primary source** if it is available on the CAS file; if it is not on the CAS file request primary source for the CAS file.
- ▶ When the primary source is not available on the CAS file and cannot be obtained, reference at least **two reliable secondary sources** (i.e. those sources which reference the primary source for the data – see Appendix I for details). Add an italicized note explaining why the primary source is not available.

If other applicable but **unverifiable** LD/LC₅₀ values or eye/skin irritation data exist for the chemical, and have not been used in preparing the AD, the rationale for the advice provided in the AD should be included in a **brief** note to the screening officer.

(b) Data resulting in no change in WHMIS classification

When the LD/LC₅₀ values or eye/skin irritation results obtained from the literature result in no change in WHMIS classification the following approach should be followed:

- ▶ Use and reference the **primary source** if it is available on the CAS file; if it is not on the CAS file request primary source for the CAS file.
- ▶ When the primary source is not available on the CAS file and cannot be obtained, reference at least **one reliable secondary source** (i.e. those sources which reference the primary source for the data - see the Appendix I for details). Add an italicized note explaining why the primary source is not available.

If other applicable but **unverifiable** LD/LC₅₀ values or eye/skin irritation data exist for the chemical, and have not been used in preparing the AD, the rationale for the advice provided in the AD should be included in a **brief** note to the screening officer.

2. Human Effects of Acute/Chronic Exposure (DISCLOSURE ONLY)

- ▶ Use and reference the **primary source** if it is available on the CAS file; if it is not on the CAS file request primary source for the CAS file.
- ▶ When the primary source is not available on the CAS file and cannot be obtained, reference at least **one reliable secondary source** (i.e. those sources which reference the primary source for the data - see the Appendix I for details). Add an italicized note explaining why the primary source is not available.

3. All Other Toxicological Endpoints (except carcinogenicity)

(a) Data resulting in a change in WHMIS classification

When the study obtained from the literature will result in a change in WHMIS classification the following approach should be followed:

- ▶ **ALWAYS** use and reference the **primary source** if it is available on the CAS file.
- ▶ When the primary source is not available on the CAS file, request the primary source.
- ▶ **ONLY** when the primary reference is not in the CAS file and it cannot be obtained, reference the advice to at least **two reliable secondary sources** (i.e. sources which reference the primary source and provide adequate information concerning the design, conduct and results of the study, such as: published review articles, IARC monographs, CRC Critical Reviews in Toxicology, WHO or IPCS Reports, EPA or ATSDR Reports, or other highly reputable sources). Add an italicized note explaining why the primary source is not available.

(b) Data resulting in no change in WHMIS classification

When the study obtained from the literature will not result in a change in WHMIS classification the following approach should be followed:

- ▶ **ALWAYS** use and reference the **primary source** if it is available on the CAS file.
- ▶ When the primary source is not available on the CAS file, request the primary source for the CAS file.
- ▶ **ONLY** when the primary reference is not in the CAS file and it cannot be obtained, reference the advice to at least **one reliable secondary source** (i.e. sources which reference the primary source and provide adequate information concerning the design, conduct and results of the study, such as: published review articles, IARC monographs, CRC Critical Reviews in Toxicology, WHO or IPCS Reports, EPA or ATSDR Reports or other highly reputable sources). Add an italicized note explaining why the primary source is not available.

APPENDIX I: List of Reliable Secondary References to Be Used in Advice Documents And Toxicity Profile Summaries

The following criteria have been applied in compiling the following list of reliable secondary reference sources:

1. secondary sources which reference the primary source;
2. secondary sources which, based on experience and professional judgement, generally provide reliable information.

AIHA WEEL (Workplace Environmental Exposure Level) Guides

ATSDR Reports (Agency for Toxic Substances and Disease Registry)

BG Chemie Reviews

BIBRA

Chemical Hazards of the Workplace

CHEMINFO (CCINFO Disk)

Clinical Toxicology of Commercial Products

CSST MSDS sheets

Documentation of the ACGIH TLV and BEI

ECETOC Documents

Ethel Browning's Toxicity & Metabolism of Industrial Solvents

Vol. I - Hydrocarbons

Vol. II - Nitrogen & Phosphorous Solvents

Grant's Toxicology of the Eye

HSDB

IARC Monographs (International Agency For Research on Cancer)

NIOSH, Recommended Standard for Occupational Exposure Reports

Patty's Industrial Hygiene and Toxicology

Royal Society of Chemistry Datasheets

Vol. 1 - Solvents

Vol. 2 - Metal & its compounds

Vol. 3 - Corrosive & Irritants

Vol. 4 a & b - Toxic Chemicals

Vol. 5 - Flammable Chemicals

RTECS (Note: Data is not peer reviewed, caution required)

Sax's Dangerous Properties of Industrial Materials (Note: Data is not peer reviewed, caution required)

US National Toxicology Program (NTP) Reports

WHO Environmental Health Criteria Reports