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ENVIRONMENT DIRECTORATE
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Task Force on Harmonisation of Classification and Labelling

Ad Hoc Expert Group on Target Organ Toxicity

ISSUE DOCUMENT NO 3: GENERAL OR ORGAN SPECIFIC CRITERIA

2nd Meeting of the ad hoc Expert Group on Target Organ Toxicity,
9th - 10th September 1999, Bethesda, Maryland, beginning at 9:30 a.m. on 9th September

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ISSUE DOCUMENT NO 3: GENERAL OR ORGAN SPECIFIC CRITERIA

ISSUE

1. Should the organ or organ system primarily affected by a substance be specified when such data are available or a general term "toxic" be used in all cases? Or, is it important to have organ-specific criteria, when needed, to identify primary target organ of toxicity in classification, which can be communicated to workers/consumers clearly? (This may be seen as an issue for HAZCOM, rather than classification.)

BACKGROUND

2. A number of substances primarily produce toxicologically significant (physiological impairment and or pathological) changes to a specific organ or organ system. These substances may also produce changes in other organs, which may not be functionally as important or may be secondary to the changes in the primary affected organ. On other hand, a number of substances produce toxicologically significant changes in more than one organ system over time or modulated by concentration or physiological status of subjects (age, pregnancy, etc.,). Further, there are some substances that produce toxicity of nearly all critical organ systems.

3. Would it be useful to inform the worker or consumer, when data indicates, that a organ(s) or organ system is primarily affected or simply to identify substances as a target organ toxicant (Toxic, class 3, 4, or 5)?

CURRENT PRACTICE

Canada

WHMIS

4. Under the Canadian workplace system, the supplier decides the level of specificity required for hazard communication of target organ effects.

EU

5. The substance is classified as "Toxic". However, there are some risk phrases that allow for statement of effects on skin and nervous system.

6. In the EU system substances that meet the criteria for classification are classified either as 'Toxic' or 'Harmful', depending upon the degree of effect and the dose/concentration at which the effect has been observed. The warning phrase attached to these classifications, regardless of 'Toxic' or 'Harmful', is R48/(indicating route of exposure), for which the harmonised text is "Danger of serious damage to health by prolonged exposure". Specific effects or target organs/tissues are not indicated in the warning phrase (R48) for several reasons- e.g. insufficient space on a label, use of scientific terminology may be meaningless or confusing for the initial purpose of the phrase, such reference may misleading especially in circumstances of multiple organ/tissue toxicity. Nevertheless, a more detailed explanation of

toxic effects is expected to be included in the Safety Data Sheet (paragraph 11 – Toxicological information) to provide relevant information for individuals who may need to use this information.

7. NB. Reference to R-phrases that refer to organs/tissues, e.g. Skin, eye or respiratory irritancy, is not relevant here since they deal with short-term or local effects. Effects on the nervous system can range from short-term transient effects, e.g. Drowsiness, narcosis, through to long-term irreversible effects, e.g. neurotoxicity/neuropathy. Serious damage to the nervous system following repeated exposure is included under R48 classification (Danger of serious damage to health by prolonged exposure). Serious damage to the nervous system following single exposure is addressed under R39 or R40 classification (Danger of (very serious) irreversible effects).

US

8. **OSHA** provides a list of specific organs hepatotoxins, nephrotoxins, neurotoxins, agents which act on blood or hematopoietic system, irritate or damage lung, cutaneous hazard, and eye hazard. This list is indicated to be not all-inclusive. [Is the organ identified on the label?]

9. **CPSC** as specific criteria for neurotoxicity and allows for identification of specific organ system toxicity.

10. In the US, pesticides are not given hazard warning labels for target organ toxicity. However, pesticides used in the workplace are provided with MSDS under OSHA authority.

CONSIDERATIONS

11. It is important for the end user of the hazard identification/classification information to know what specific effects may occur, to compare substances and to look out for the expected effects and take appropriate action. The evaluation of available data, both human and animal (acute, sub-chronic and chronic), does include identification of organ or organ systems that are affected. Providing this information would not entail additional work. Furthermore, specifying organ specific criteria for target organ toxicants would lead to consistent identification of the hazard, facilitate classification, and provide basis for uniform hazard communication.

12. alternatively, one could question whether it is important for the end user to know what <u>specific</u> effects may occur. Considering the wide range of potential users, it seems that the first objective is to provide a warning that the chemical is dangerous – and this must be done in as short, clear, understandable and unambiguous a message as possible. In any event, the label of a package/container may not permit lengthy discourse, and most people don't want to read lengthy text – so the message must be conveyed quickly and clearly. Thereafter, for those with more specialist interest and responsibility, more detail regarding the specific effects seen in humans or in animal studies can be clearly described in the Safety Data Sheet.

13. Available human evidence of systemic (target organ) toxicity more often than not comes from clinical presentations wherein the actual nature and extent of damage to specific organs/tissues cannot be deduced.

14. If the hazard is 'Serious damage to health' then specifying the possible target organ, and criteria for classification, seem to add unnecessary complication and potential for error. I suggest we keep it simple, for the purpose of being able to communicate the simplest but most reliable warning of danger.]

OPTIONS

15. Identify specific organ(s) or organ system(s) of primary toxicological importance. In those cases when there a general systemic toxicity, identify as “Toxic”.

16. Identify only as “Toxic”. However, may provide for organ specific precautionary statement during hazard communication.

DISCUSSION

17. The objective of the classification scheme is fundamentally to identify if a chemical has properties hazardous for human health. It is important, for harmonisation to have criteria for specific target organ effects so there is consistency in identification of hazard especially in cases when effects in humans are not documented, i.e. when hazard identification would be based on animal data. It is recognised that for certain substances the primary affected organ (signs/symptoms, metabolism, or pathology) can be identified while for others this may not be possible and just “Toxic” would be appropriate.

18. However, it could be erroneous and misleading to identify a single toxic effect, e.g. hepatotoxicity, in the classification for a chemical which may express multiple organ toxicity at different doses/concentrations. The simplest classification to communicate to users would be Toxic.

19. How this is communicated seems to be outside of the current remit and more in the remit of the hazard communication working group’. If information is available, from human experience or animal studies, that a chemical is neurotoxic or hepatotoxic, then clearly this information can be included in the safety data sheet and as a statement on a label.

20. All body systems and organs are of primary toxicological importance, and so it would be presumptuous to try to specify which are of primary toxicological importance. Furthermore, to discriminate cases between ‘general systemic toxicity’ and more specific ‘target organ toxicity’ could be very difficult and complicated, since adverse effects on some organs can lead to consequential adverse changes in others. I believe we should avoid any likelihood of complication or confusion that could arise due to different interpretations of which is a ‘primary’ effect and which ‘secondary’.

21. Some experts favour this (identify as ‘toxic’) more simple and uncomplicated approach. The question of using an organ specific precautionary statement during hazard communication relates to risk reduction/management, follows after hazard identification, and