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**COMMITTEE OF EXPERTS ON THE TRANSPORT OF DANGEROUS GOODS AND ON THE GLOBALLY HARMONIZED SYSTEM OF CLASSIFICATION AND LABELLING OF CHEMICALS**

**Sub-Committee of Experts on the Globally Harmonized System of Classification and Labelling of Chemicals**
**(Second session, 12-14 December 2001, agenda item 5 (b))**

## OUTSTANDING WORK

## Consideration of the need for work on classification criteria for narcotic effects

**Transmitted by the expert from Sweden**

**Summary**

Narcotic and sub-narcotic effects caused by volatile substances are commonly observed in exposed persons. Adverse effects like reduced alertness, prolonged reaction time and disturbed judgement might impose a risk for accidents which not only the exposed individual may be subject to, but also other persons such as working colleagues. Consequently, there is a strong need to identify substances with such properties and to provide appropriate hazard information on the label. This need has also been recognised for certain drugs with similar central nervous system (CNS) depressant properties. In many countries a specific hazard warning is required for these drugs concerning e.g. reduced alertness, which may have consequences on precision and high attention demanding activities such as car driving.

Narcotic effects, however, are only briefly mentioned within the Globally Harmonised System (GHS) criteria for classification for specific target organ systemic toxicity (TOST) and the guidance for classification of such effects is not sufficiently specified. Also, the proposed hazard statements for TOST (single exposure) "Causes/May cause damage to the central nervous system if inhaled " do not give a sufficiently specified warning of the type of effects that can be expected after exposure, e.g. drowsiness, reduced alertness, lack of co-ordination. Therefore, there is a need 1) to provide criteria within the GHS that give sufficient guidance for classification, including mentioning of clearly specified CNS depression symptoms which may be reported in humans such as narcosis, drowsiness, reduced alertness, loss of reflexes, lack of co-ordination, and vertigo, as well as effects which mainly can be found in animals, such as narcosis, lethargy, lack of co-ordination and ataxia, and 2) to provide a hazard statement on the label clarifying that narcotic effects can be expected and which symptoms that may develop after exposure. The two possible options to meet these needs are either to introduce a well-specified third category for classification within the TOST single exposure criteria, or to develop new separate criteria for acute narcotic effects outside the TOST criteria.

**Background**

1. At the 10th meeting of the Organization for Economic Cooperation and Development (OECD) Task Force on Harmonization of Classification and Labelling, it was agreed that Sweden would prepare a thought starter document which was needed as a first step in order to have a better understanding of the narcotic hazards. "The paper would clearly explain the hazards and, importantly, indicate that these hazards are not sufficiently covered in any of the other systems that are part of the GHS". The paper would be expected to be available for review and discussion after summer 2001. This was endorsed by the 31st and 32nd OECD Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology. Also, the UN Sub-Committee of Experts on the GHS has agreed that it will consider the need for work on classification criteria for narcotic effects at its second session in December 2001.

**Narcotic hazards**

2. Organic solvents have multiple uses and can be found in a variety of products, also available for consumers. Their production volume worldwide is large and several of the solvents are produced in high volumes. In many countries, the health effects of organic solvents have been recognised, and control measures have been taken to reduce exposure levels at the work place, but a large number of people are still frequently exposed at work and/or in their homes.

3. Although the levels of organic solvents in general have been reduced at many workplaces, there still are occasional evidences of relatively high acute exposures in consumer as well as workplace settings, where the exposure sometimes may be markedly above the occupational threshold limit values. Cases of acute toxicity after solvent exposure continue to be observed. During the first eight months of this year (2001), 60 cases of solvent intoxication of various severity after occupational inhalation exposure were reported to the Swedish Poison Information Centre. In all cases primary symptoms like dizziness, headache, nausea, vomiting, and a "fainting-like" feeling were reported. Several occupational accidents related to narcotic effects caused by solvent exposure have been reported to the Swedish work environment authority.

***Observed effects and symptoms***

4. In humans, short-term solvent exposures can induce symptoms such as mucous membrane irritation, headache, nausea, and slight incoordination even at fairly low air concentrations. These relatively mild toxic effects are often reported subjectively and adaptation may be developed (which should not be regarded as a normalisation). Increasing levels may cause e.g. reduced vigilance followed by disturbed judgement, dizziness, irritability, fatigue, impaired memory function, deficits in perception and co-ordination as well as prolonged reaction time. Higher levels may produce sleepiness and the initial stages of anaesthesia. These effects on function and behaviour may have adverse consequences that motivate precautions e.g. a reduction in vigilance and impaired judgement may lead to an increased risk of mistakes and errors as well as risk of accidents.

5. Although some overt narcotic effects such as lethargy, ataxia, loss of righting reflex, ataxia and narcosis, may be reported at relatively high levels in acute toxicity studies in animals, animal studies cannot reveal all relevant neurotoxic effects such as cognitive effects. Thus, they have often failed to show effects that are comparable to the findings reported in humans. This may at least partly be explained by the fact that there still are only a few validated animal test methods to identify CNS alterations. Furthermore, the few existing methods may have limited acceptance. It could be mentioned that, in the recently adopted OECD TG 424 on neurotoxicity, narcotic and sub-narcotic effects are to be considered.

**Prediction of narcotic hazards**

6. Most organic solvents have some general characteristics; they are volatile, lipid soluble and have a common non-specific depressant action on the central nervous system. Already a hundred years ago, it was suggested that the narcotic effects of organic solvents were related to their lipophilic character (the Meyer-Overton correlation; see review by P B Larsen, 2000). Numerous studies have since then shown that the narcotic potency of organic solvents in general increases with increasing lipophilicity. In fact, a close correlation has been shown between anaesthetic activity and oil/gas partition coefficient for a heterogeneous group of volatile substances. Thus, depending on its physical properties (volatility and lipophilicity) an organic solvent may have a certain potential to cause acute non-specific symptoms of CNS depression.

7. Within the GHS, structure activity relationships (SAR) should be taken into consideration and may contribute to classification for several endpoints. Because of the close correlation between narcotic activity and lipophilicity, SAR should also be possible to take into consideration for classification for narcotic properties, especially within homologues series of organic solvents. Furthermore, in view of the lack of test guideline methods for CNS effects in animals and the lack of human data, structure-activity relationships based on physico-chemical parameters may be an important basis for classification of narcotic effects of single substances. In addition, the use of structure activity relationships is in line with the aim of reducing animal testing.

8. In Annex 2, some volatile organic compounds causing narcotic effects are listed. In Annex 3, existing national criteria for classification of acute narcotic hazards are summarised.

**Coherence with other legislations**

***Drug labelling and information***

9. An analogous situation is the hazard information, which is provided for certain drugs that can induce reduced alertness and attention and thereby affect e.g. driving ability or working tasks which requires high precision and attention. This labelling requirement appears today to be uncontroversial and undisputed. Disturbed judgement in the work environment can evidently cause accidents including both human injuries and material costs. Most drug manufacturers give detailed information about acute narcotic effects that might follow drug ingestion. It may even be more motivated to inform the user of chemicals about the narcotic properties by the use of an appropriate hazard statement than for drugs. The narcotic effects of chemicals are more difficult to assess and quantify than for drugs, due to lack of the clinical trial data for chemicals, which are provided in the drug evaluation process.

*Occupational limit value settings*

10. For some solvents e.g. pentane, hexane isomers, heptane, octane, the occupational limit values are set by the United States of America Occupational Safety and Health Administration (OSHA) to prevent the reversible non-specific narcotic effects on CNS. In a report from NIOSH 1996 (Dick&Ahlers) butane, *sec*- and *tert*-butyl alcohol, cyclopentane, ethyl bromide, gasoline, heptane, hexane isomers, isoamyl alcohol, isophorone, methyl chloride, methyl chloroform, octane, pentane, 2-pentanone, stoddard solvent, styrene, toluene, and trichloroethylene are regarded as acute CNS depressants. Thus, a labelling based on narcotic effects is clearly coherent with the occupational health assessments for these substances.

**Are acute narcotic hazards sufficiently covered in the GHS?**

11. According to the background given above, there is a strong need to protect exposed humans from both narcotic and subnarcotic effects. These kinds of effects are only briefly mentioned in one paragraph within the classification criteria for TOST (single exposure):

> *…Examples of relevant toxic effects in humans and/or animals are provided below:*
> - ….
> - *Significant functional changes in the central or peripheral nervous system or other organ systems, including signs of central nervous system depression and effects on special senses (e.g., sight hearing and sense of smell).*
> - ….

12. These criteria are too unspecific to give sufficient guidance to make it possible to classify for narcotic effects. Reversible symptoms in humans such as drowsiness, reduced alertness, loss of reflexes, lack of co-ordination, and vertigo, need to be mentioned. Also, the possible narcotic effects that may be observed in acute toxicity studies in animals, such as lethargy, lack of co-ordination, ataxia and narcosis should be mentioned for clarification of the criteria and guidance for classification. Thus, for classification and labelling purposes, there is a need for a more detailed description of the expression "*signs of central nervous system depression*" used in the TOST criteria.

13. In the GHS criteria for TOST (single exposure) an upper guidance value of 20 mg/l/4hr is mentioned. It has been shown that less volatile organic solvents have the highest narcotic potency (P B Larsen, 2000). Thus, an absolute concentration limit restricts classification to the most potent substances. However, the risk for exposure by inhalation may increase with increasing volatility. Thus, substances with low volatility and a high narcotic potency show similar narcotic effects (within homologous groups) as substances with a high vapour pressure but with a lower narcotic potency. Therefore, it is also important that the GHS criteria include the possibility to classify somewhat less potent, but considerably more volatile substances that may cause effects at levels above 20 mg/l/4hr, but still substantially below the saturated vapour concentration[1]. Acetone may, for example, induce unconsciousness at concentration from 29 mg/l, a level that is easily obtained since it is only 5% of the saturated vapour concentration. Substances with an effect concentration well below their saturated vapour concentration are important to consider since the effect levels may easily be obtained during normal handling and use. Accordingly, substances with effect concentrations close to their saturated vapour concentrations are not of equal concern. For non occupational users, the risk of exposure to high levels of volatile substances may even be higher than for workers, since e.g. the ventilation is often poor or non-existent and respiratory protective equipment not available.

14. The suggested hazard statements for TOST which reads *"Causes/May cause damage to …if inhaled"*, can not be considered appropriate for narcotic effects since the symptoms of CNS depression like drowsiness and reduced alertness can hardly be characterised as "damage". Most likely, the user probably does not interpret the hazard statements for TOST, as warnings of acute narcotic effects. Thus, there is an obvious need for a specific hazard statement that is more informative in this respect, such as e.g. "May cause dizziness, drowsiness and reduced alertness".

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[1] *The saturated vapour concentration of a volatile substance is the vapour concentration obtained at equilibrium between the liquid (or solid) and its gas phase at a given temperature. That is, the saturated vapour concentration of a substance is directly proportional to its vapour pressure (at equilibrium). An effective concentration may be expressed in absolute figures, e.g. in mg/l, irrespective of the volatility of the substance or it may be expressed relative to its volatility i.e. the effect concentration is expressed as a certain % of the saturated vapour concentration of a substance.*

As previously outlined, this would be in analogy with the requirements for a specific hazard information for drugs with similar properties.

**Possible approaches/options**

15. If the need for more detailed criteria and a specific hazard statement is generally agreed, there are at least two options that seem possible. One option may be the introduction of a third category for classification within TOST single exposure criteria (c.f. the subcategory of substances which cause effects on or via lactation within the reproductive toxicity endpoint of GHS). Narcotic volatile substances with high vapour pressures should also be considered for this category. The hazard statement should be informative about possible narcotic effects as outlined above.

16. Another option is the introduction of an entirely new endpoint for health classification and set of criteria outside TOST.

## Annex 1

## References

Arlien-Soborg A. Solvent Neurotoxicity. CRC Press, Inc.; 1992.

Dick R B. Short Duration Exposures to Organic Solvents: The Relationship Between Neurobehavioral Test Results and Other Indicators. Neurotoxicology and Teratology, vol. 10; p. 39-50; 1988.

Dick R B and Ahlers H. Chemicals in the workplace incorporating neurobehavioral test results into the regulatory process. Department of Health and Human Services. Public Health Service. CDC; NIOSH;1996.

ECETOC. Technical Report No. 70. Chronic Neurotoxicity of Solvents. Brussels, Feb. 1996.

Iregren A et al. Acute effects from exposure to organic solvents: Experimental approaches and methods. Proceedings from a workshop.....March 7-9, 1990. Arbete och Hälsa 1991:35. National Institute of Occupational Health, Sweden. 1991.

Larsen P B.Narcotic effects of organic solvents in relation to physico-chemical properties. TemaNord 2000:590, Nordic Council of Ministers.

Neurotoxicology, a review of definitions, methodology and criteria. Miljöprojekt nr 282, Environmental Protection Agency, Denmark; 1995.

Test methods and criteria for neurotoxic substances and preparations with special weight on organic solvents. TemaNord 1996:557. Nordic Council of Ministers.(In Danish).

World Health Organization/Commission of the European Communities. Neurobehavioral Methods in Occupational and Environmental Health: Symposium Report.WHO Regional Office for Europe, Copenhagen, 1985; cited in Dick R B, 1988.

World Health Organization/Nordic Council of Ministers. Chronic effects of organic solvents on the central nervous system and diagnosic criteria. Report on a Joint WHO/Nordic Council of Ministers Working Group. Copenhagen 10-14 June 1985.

## Annex 2

### Examples of substances with narcotic effects (and ascribed the hazard statement "Vapours may cause drowsiness and dizziness", R67, within the EU system)

pentane
cyclohexane
methylcyclohexane
1,4-dimethylcyclohexane
n-hexane and hexane isomers
n-heptane and heptane isomers
octane isomers
and 2-propanol
1-,2- and iso-butanol
diethyl ether
di-iso- and di-n-propyl ether
acetone
butanone (MEK)
diethyl ketone
2-hexanone
methyl acetate
ethyl acetate
n- and iso-propyl acetate
n-butyl acetate

## Annex 3

## Existing national criteria for classification of acute narcotic hazards

***Canada***

Canada has mentioned at least 4 toxic or harmful products of special concern described as having acute CNS effects after single exposure (Canadian consumer chemical requirements).

| Substance of special concern | Concentration | Sub-category |
|---|---|---|
| Diethylene glycol | 5% or more | Harmful |
| Ethyl acetate | 5% or more | Harmful |
| 1,2-Dichloroethane | (a) 5% or more but less than 10% | Harmful |
| | (b) 5% or more[?] | Toxic |
| 1,1,1-trichloroethane | 5% or more | Harmful |

Notes:
- *Substances of Special Concern* - Substances which cause non-lethal serious effects, for example depressed level of consciousness, seizures, muscular weakness or paralysis, acute renal failure, arrhythmia, hypotension, dyspnea, respiratory depression, pulmonary oedema, optic neuritis, methaemoglobinuria and euphoria.
- *Toxic* - refers to acute toxicity GHS category 3
*Harmful* - refers to acute toxicity GHS category 4

***The US***

Narcotic effects are covered by OSHA (Occupational Safety and Health Administration), EPA (Environmental Protection Agency) and CPSC (Consumer Product Safety Commission) under “target organ effects”.

***The EU***

Partly to solve problems related to health effects caused by the use of organic solvents in the work environment, EU in year 1998 developed criteria for labelling such substances with a specific hazard statement. Practical experience had shown that exposure to organic solvents with relatively low toxicity, might constitute a risk of discomfort or mild occupational illness during normal handling or use. These substances are volatile and they therefore have a high potential for exposure. Consequently, for many of these organic solvents with relatively low toxicity, threshold limit values in the work environment have been adopted.
Within the EU the following labelling is required (para. 3.2.8; Annex VI; Dir 67/548/EEC):

Hazard statement (R67): *Vapours may cause drowsiness and dizziness*

> For volatile substances and preparations containing such substances which cause clear symptoms of central nervous system depression by inhalation and which are not already classified with respect to acute inhalation toxicity (R20, R23, R26 , R68/20, R39/23 or R39/26).

[?] *should perhaps be ”10% or more”?*

The following evidence may be used:

(a) Data from animal studies showing clear signs of CNS depression such as narcotic effects, lethargy, lack of co-ordination (including loss of righting reflex) and ataxia either:

- at concentrations/exposure times not exceeding 20 mg/l/4h or;
- for which the ratio of the effect concentration at < 4 h to the saturated vapour concentration (SVC) at 20ºC is < 1/10.

(b) Practical experience in humans (e.g. narcosis, drowsiness, reduced alertness, loss of reflexes, lack of co-ordination, vertigo) from well documented reports under comparable exposure conditions to the effects specified above for animals.

For all hazardous endpoints that should be considered for classification, there is a general paragraph considering structure-activity relationships (SAR) (para. 1.6.1 (b) in Annex VI, Dir 67/548/EEC):

”The results of validated SAR and expert judgement may also be taken into account where appropriate”

There are 24 substances in Annex 1 (Dir 67/548/EEC) which at present have been ascribed R67, which are listed in Annex 2.

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