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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

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**UPDATING OF THE GLOBALLY HARMONIZED SYSTEM OF CLASSIFICATION AND
LABELLING OF CHEMICALS (GHS)**

Health hazards

Carcinogenicity

Proposal for guidance on how to consider important factors in classification of carcinogenicity

Transmitted by the Organization for Economic Co-operation and Development (OECD)

Introduction

1. The GHS is hazard-based. Classification for carcinogenicity reflects a chemical's potential for carcinogenicity in humans by means of two GHS categories: 1) known or presumed and 2) suspected. Classification is a one-step process combining strength of evidence criteria, based on IARC definitions (which denote tumor incidence in humans or animals and their level of statistical significance), with consideration of all other relevant information (important factors). Expert judgment must be exercised in order to classify each chemical because the scientific basis of cancer development is not fully understood and data on carcinogenic chemicals are rarely detailed enough to precisely elucidate the mechanism of action of the carcinogen or the complete pathophysiological process for development of tumors in animals or humans. Therefore, classification is a weight of evidence process taking all available information into account.

2. The OECD expert group on carcinogenicity considered how to address the need for guidance on the importance of the different factors noted in subsection 3.6.2.5.2 of the GHS. In 2001, the OECD Integrated Document (OECD Series on Testing and Assessment Number 33) noted, at par. 152: "Guidance on the importance of [these] factors has to be elaborated in order to indicate their effects on the level of concern." Par. 3.6.2.5 of the GHS says: "The full list of factors that influence this determination is very lengthy, but some of the important ones are [listed in GHS Par. 3.6.2.5.2]."

Important factors

3. Some important factors (mentioned in GHS Paragraph 3.6.2.5.2) which may be taken into consideration, when assessing the overall level of concern are:

- tumor type and background incidence;
- multisite responses;
- progression of lesions to malignancy;
- reduced tumor latency;
- whether responses are in single or both sexes;
- whether responses are in single or several species;
- structural similarity or not to a chemical (s) for which there is good evidence of carcinogenicity;
- routes of exposure;
- comparison of absorption, distribution, metabolism and excretion between test animals and humans;
- the possibility of a confounding effect of excessive toxicity at test doses;
- mode of action and its relevance for humans, such as mutagenicity, cytotoxicity with growth stimulation, mitogenesis, immunosuppression.

4. The GHS calls for use of these factors as part of the basic classification decision. Internationally available documents on evaluation of carcinogenicity (IPCS, IARC, ILSI) all cite such factors and recommend that they be considered in basic hazard assessment decisions, by means of expert judgment. IARC publishes generic guidance for assessment of carcinogenicity in the preamble to its monographs on the carcinogenicity of substances. After assessment of carcinogenicity in experimental animals or in human epidemiological studies, IARC (Preamble section 12(b)) calls for description of “Other evidence judged to be relevant to an evaluation of carcinogenicity and of sufficient importance to affect the overall evaluation [including] data on preneoplastic lesions, tumor pathology, genetic and related effects, structure-activity relationships, metabolism and pharmacokinetics, physicochemical parameters and analogous biological agents. Data relevant to mechanisms of the carcinogenic action are also evaluated. ... [Then assess] if that particular mechanism is likely to be operative in humans.”

5. To further the goal of harmonization, IPCS brought together an international group of experts to establish the IPCS “*Conceptual Framework for Evaluating a Mode of Action for Chemical carcinogenesis*” (2001). This framework has been widely adopted and used, including by: IPCS/WHO, JECFA, JMPR, the European Union, Australia, Japan, Canada, the US EPA and in OECD guidance. It is an analytic approach and is consistent with the GHS. It calls for a mode of action to be postulated and key events consistent with the postulated mode of action, based on experimental observations, including sites of action, increased cell growth, specific biochemical events, etc. Postulated modes of action can be mutagenic or non-mutagenic. If directly mutagenic, tumorigenic responses are assumed to be linear. Non-mutagenic responses may be linear or nonlinear.

6. In 2003, ILSI assembled an international panel which developed “*A Framework for Human Relevance Analysis of Information on Carcinogenic Modes of Action*” (Meek et al., 2003; Cohen et al., 2003, 2004). This framework provides an approach to take the IPCS mode of action analysis further by establishing relevance of experimental results for carcinogenicity to humans. This weight of evidence process would then take into consideration many additional factors, including kinetics and dynamics, temporal development of tumors, sex- or species-specificity, etc., which have a bearing on the plausibility of animal results for human responses. In 2004, IPCS convened a panel to further develop and clarify the ILSI human relevance framework.

7. These frameworks are intended to provide a basis for systematic assessments which may be performed in a consistent fashion internationally. However, they are not intended to dictate answers, nor provide lists of criteria to be checked off. The guidance provides an approach to analysis rather than hard and fast rules.

Proposal

3.6.2.5.2 Add the following sentence at the end of the paragraph, after the last sub-paragraph:

“Guidance on how to consider important factors in classification of carcinogenicity is included in 3.6.5.3”.

3.6.5.3 Insert “3.6.5.3.1” before the first paragraph and renumber following paragraphs and sub-paragraphs accordingly.

Insert a new sub-section as follows:

“3.6.5.3.2 *Guidance on how to consider important factors in classification of carcinogenicity**

The guidance provides an approach to analysis rather than hard and fast rules. This section provides some considerations. The weight of evidence analysis called for in GHS is an integrative approach which considers important factors in determining carcinogenic potential along with the strength of evidence analysis. The IPCS “*Conceptual Framework for Evaluating a Mode of Action for Chemical carcinogenesis*” (2001), the ILSI “*Framework for Human Relevance Analysis of Information on Carcinogenic Modes of Action*” (Meek et al., 2003; Cohen et al., 2003, 2004) and the IARC (Preamble section 12(b)) provide a basis for systematic assessments which may be performed in a consistent fashion internationally; the IPCS also convened a panel in 2004 to further develop and clarify the human relevance framework. However, the internationally available documents are not intended to dictate answers, nor provide lists of criteria to be checked off.

3.6.5.3.2.1 Mode of action

The various international documents on carcinogen assessment all note that mode of action in and of itself, or consideration of comparative metabolism, should be evaluated on a case by case basis and are part of an analytic evaluative approach. One must look closely at any mode of action in animal experiments taking into consideration comparative toxicokinetics/toxicodynamics between the animal test species and humans to determine the relevance of the results to humans. This may lead to the possibility of discounting very specific effects of certain types of chemicals. Life stage-dependent effects on cellular differentiation may also lead to qualitative differences between animals and humans. Only if a mode of action of tumor development is conclusively determined not to be operative in humans may the carcinogenic evidence for that tumor be discounted. However, a weight of evidence evaluation for a substance calls for any other tumorigenic activity to be evaluated as well.

3.6.5.3.2.2 Responses in multiple animal experiments

Positive responses in several species add to the weight of evidence, that a chemical is a carcinogen. Taking into account all of the factors listed in 3.6.2.5.2 and more, such chemicals with positive outcomes in two or more species would be provisionally considered to be classified in GHS Category 1B until human relevance of animal results are assessed in their entirety. Note, however, that positive results for one species in at least 2 independent studies, or a single positive study showing unusually strong evidence of malignancy may also lead to Category 1B.

3.6.5.3.2.3 Responses are in one sex or both sexes

Any case of gender-specific tumors should be evaluated in light of the total tumorigenic response to the substance observed at other sites (multi-site responses or incidence above background) in determining the carcinogenic potential of the substance.

If tumors are seen only in one sex of an animal species, the mode of action should be carefully evaluated to see if the response is consistent with the postulated mode of action. Effects seen only in one sex in a test species may be less convincing than effects seen in both sexes, unless there is a clear patho-physiological difference consistent with the mode of action to explain the single sex response.

3.6.5.3.2.4 Confounding effects of excessive toxicity or localized effects

Tumors occurring only at excessive doses associated with severe toxicity generally have doubtful potential for carcinogenicity in humans. In addition, tumors occurring only at sites of contact and/or only at excessive doses need to be carefully evaluated for human relevance for carcinogenic hazard. For example, forestomach tumors, following administration by gavage of an irritating or corrosive, non-mutagenic chemical, may be of questionable relevance. However, such determinations must be evaluated carefully in justifying the carcinogenic potential for humans; any occurrence of other tumors at distant sites must also be considered.

3.6.5.3.2.5 Tumor type, reduced tumor latency

Unusual tumor types or tumors occurring with reduced latency may add to the weight of evidence for the carcinogenic potential of a substance, even if the tumors are not statistically significant.

Toxicokinetic behavior is normally assumed to be similar in animals and humans, at least from a qualitative perspective. On the other hand, certain tumor types in animals may be associated with toxicokinetics or toxicodynamics that are unique to the animal species tested and may not be predictive of carcinogenicity in humans. Very few such examples have been agreed internationally. However, one example is the lack of human relevance of kidney tumors in male rats associated with compounds causing α 2u-globulin nephropathy (IARC, Scientific Publication N° 147). Even when a particular tumor type may be discounted, expert judgment must be used in assessing the total tumor profile in any animal experiment.

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