

APPENDIX F – GUIDANCE FOR HAZARD CLASSIFICATIONS RE: CARCINOGENICITY (NON-MANDATORY)

The mandatory criteria for classification of a chemical for carcinogenicity are found in Chapter A.6. However, as noted in Footnote 5 of that chapter, the GHS also included as guidance for classifiers the following information taken from the International Agency for Research on Cancer (IARC) *Monographs programme on the evaluation of the strength and evidence of carcinogenic risks to humans*. This guidance is consistent with Chapter A. 6, and should help in evaluating information to determine carcinogenicity.

Background guidance

Carcinogenicity in humans

The evidence relevant to carcinogenicity from studies in humans is classified into one of the following categories:

- (a) Sufficient evidence of carcinogenicity: A causal relationship has been established between exposure to the agent, mixture or exposure circumstance and human cancer. That is, a positive relationship has been observed between the exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence; or,
- (b) Limited evidence of carcinogenicity: A positive association has been observed between exposure to the agent, mixture or exposure circumstance and cancer for which a causal interpretation is considered by the working group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.

In some instances the above categories may be used to classify the degree of evidence related to carcinogenicity in specific organs or tissues.

Carcinogenicity in experimental animals

The evidence relevant to carcinogenicity in experimental animals is classified into one of the following categories:

- (a) Sufficient evidence of carcinogenicity: A causal relationship has been established between the agent or mixture and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (i) two or more species of animals or (ii) in two or more independent studies in one species carried out at different times or in different laboratories or under different protocols;
- (b) Exceptionally, a single study in one species might be considered to provide sufficient evidence of carcinogenicity when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumor or age at onset; or,
- (c) Limited evidence of carcinogenicity: The data suggest a carcinogenic effect but are limited for making a definitive evaluation because, for example, (i) the evidence of carcinogenicity is restricted to a single experiment; or (ii) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the study; or (iii) the agent or mixture increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential, or of certain neoplasms which may occur spontaneously in high incidences in certain strains.

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

This section provides some considerations and an approach to analysis, rather than hard-and-fast rules. 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 International Life Sciences Institute (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. The IPCS also convened a panel in 2004 to further develop and clarify the human relevance framework. However, the available documents are not intended to dictate answers, nor provide lists of criteria to be checked off.

Mode of action

Various 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 substances. 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.

Responses in multiple animal experiments

Positive responses in several species add to the weight of evidence that a substance is a carcinogen. Taking into account all of the factors listed in A.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. It should be noted, however, that positive results for one species in at least two independent studies, or a single positive study showing unusually strong evidence of malignancy may also lead to Category 1B.

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.

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.

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 behaviour 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_2 -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.

**References:*

Cohen, S.M., J. Klaunig, M.E. Meek, R.N. Hill, T. Pastoor, L. Lehman-McKeeman, J. Bucher, D.G. Longfellow, J. Seed, V. Dellarco, P. Fenner-Crisp, and D. Patton. 2004. Evaluating the human relevance of chemically induced animal tumors. Toxicol. Sci., 78(2): 181-186.

Cohen, S.M., M.E. Mkke, J.E. Klaunig, D.E. Patton, P.A. Fenner-Crisp. 2003. The human relevance of information on carcinogenic modes of action: overview. Crit. Rev. Toxicol. 33(6), 581-9.

Meek, M.E., J.R. Bucher, S.M. Cohen, V. Dellarco, R.N. Hill, L. Lehman-McKeeman, D.G. Longfellow, T. Pastoor, J. Seed, D.E. Patton. 2003. A framework for human relevance analysis of information on carcinogenic modes of action. Crit. Rev.Toxicol., 33(6), 591-653.

Sonich-Mullin, C., R. Fielder, J. Wiltse, K. Baetcke, J. Dempsey, P. Fenner-Crisp, D. Grant, M. Hartley, A. Knapp, D. Kroese, I. Mangelsdorf, E. Meek, J.M. Rice, and M. Younes. 2001. The Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis. Reg. Tox. Pharm. 34, 146-152.

International Programme on Chemical Safety Harmonization Group. 2004 Report of the First Meeting of the Cancer Working Group. World Health Organization. Report IPCS/HSC-CWG-1/04. Geneva

International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Human. Preambles to volumes. World Health Organization. Lyon, France.

S.M. Cohen, P.A.Fenner-Crisp, and D.E. Patton. 2003. Special Issue: Cancer Modes of Action and Human Relevance. Critical Reviews in Toxicology, R.O. McClellan, ed., Volume 33/Issue 6. CRC Press.

C.C. Capen, E. Dybing and J.D. Wilbourn. 1999. Species differences in Thyroid, Kidney and Urinary Bladder Carcinogenesis. International Agency for Research on Cancer, Scientific Publication N° 147.