

**APPENDIX F TO §1910.1200 – GUIDANCE FOR HAZARD  
CLASSIFICATIONS  
RE: CARCINOGENICITY (NON-MANDATORY)**

The mandatory criteria for classification of a chemical for carcinogenicity under HCS (§1910.1200) are found in Appendix A.6 to this section. This non-mandatory Appendix provides additional guidance on hazard classification for carcinogenicity. Part A of Appendix F includes background guidance provided by GHS based on the Preamble of the International Agency for Research on Cancer (IARC) “Monographs on the Evaluation of Carcinogenic Risks to Humans” (2006). Part B provides IARC classification information. Part C provides background guidance from the National Toxicology Program (NTP) “Report on Carcinogens” (RoC), and Part D is a table that compares GHS carcinogen hazard categories to carcinogen classifications under IARC and NTP, allowing classifiers to be able to use information from IARC and NTP RoC carcinogen classifications to complete their classifications under the GHS, and thus the HCS.

**Part A: Background Guidance<sup>1</sup>**

As noted in Footnote 6 of Appendix A.6. to this section, the GHS includes as guidance for classifiers information taken from the Preamble of the International Agency for Research on Cancer (IARC) “Monographs on the Evaluation of Carcinogenic Risks to Humans” (2006), providing guidance on the evaluation of the strength and evidence of carcinogenic risks to humans. This guidance also discusses some additional considerations in classification and an approach to analysis, rather than hard-and-fast rules. Part A is consistent with Appendix A.6, and should help in evaluating information to determine carcinogenicity.

*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 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.
- (b) **Limited evidence of carcinogenicity:** A positive association has been observed between exposure to the agent 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.

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<sup>1</sup> The text of Appendix F, Part A, on the IARC Monographs, is paraphrased from the 2006 Preamble to the “Monographs on the Evaluation of Carcinogenic Risks to Humans”; the Classifier is referred to the full IARC Preamble for the complete text. The text is not part of the agreed GHS text on the harmonized system developed by the OECD Task Force-HCL.

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 and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in two or more species of animals or two or more independent studies in one species carried out at different times or in different laboratories or under different protocols. An increased incidence of tumors in both sexes of a single species in a well-conducted study, ideally conducted under Good Laboratory Practices, can also provide sufficient evidence.

Exceptionally, a single study in one species and sex 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 when there are strong findings of tumors at multiple sites.

- (a) **Limited evidence of carcinogenicity:** The data suggest a carcinogenic effect but are limited for making a definitive evaluation because, e.g. the evidence of carcinogenicity is restricted to a single experiment; there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the studies; the agent increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential; or the evidence of carcinogenicity is restricted to studies that demonstrate only promoting activity in a narrow range of tissues or organs.

*Guidance on how to consider important factors in classification of carcinogenicity (See Reference Section)*

The weight of evidence analysis called for in GHS and the HCS (§1910.1200) is an integrative approach that 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), 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 Preamble to the IARC Monographs (2006; Section B.6. (Scientific Review and Evaluation; Evaluation and Rationale)) provide a basis for systematic assessments that 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 above 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 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  $\alpha$ 2u-globulin nephropathy (IARC, Scientific Publication N° 147<sup>2</sup>). Even when a particular tumor type may be discounted, expert judgment must be used in assessing the total tumor profile in any animal experiment.

### **Part B: International Agency for Research on Cancer (IARC)<sup>3</sup>**

IARC Carcinogen Classification Categories:

#### **Group 1: The agent is *carcinogenic to humans*.**

This category is used when there is *sufficient evidence of carcinogenicity* in humans. Exceptionally, an agent may be placed in this category when evidence of carcinogenicity in humans is less than *sufficient* but there is *sufficient evidence of carcinogenicity* in experimental animals and strong evidence in exposed humans that the agent acts through a relevant mechanism of carcinogenicity.

#### **Group 2:**

This category includes agents for which, at one extreme, the degree of evidence of carcinogenicity in humans is almost *sufficient*, as well as those for which, at the other extreme, there are no human data but for which there is evidence of carcinogenicity in experimental animals. Agents are assigned to either Group 2A (*probably carcinogenic to humans*) or Group 2B (*possibly carcinogenic to humans*) on the basis of epidemiological and experimental evidence of carcinogenicity and mechanistic and other relevant data. The terms *probably carcinogenic* and *possibly carcinogenic* have no quantitative significance and are used simply as descriptors of different levels of evidence of human carcinogenicity, with *probably carcinogenic* signifying a higher level of evidence than *possibly carcinogenic*.

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<sup>2</sup> While most international agencies do not consider kidney tumors coincident with  $\alpha$ 2u-globulin nephropathy to be a predictor of risk in humans, this view is not universally held. (See: Doi et al., 2007)

<sup>3</sup> Preamble of the International Agency for Research on Cancer (IARC) "Monographs on the Evaluation of Carcinogenic Risks to Humans" (2006)

**Group 2A: The agent is *probably carcinogenic to humans*.**

This category is used when there is *limited evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals. In some cases, an agent may be classified in this category when there is *inadequate evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals and strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans. Exceptionally, an agent may be classified in this category solely on the basis of *limited evidence of carcinogenicity* in humans. An agent may be assigned to this category if it clearly belongs, based on mechanistic considerations, to a class of agents for which one or more members have been classified in Group 1 or Group 2A.

**Group 2B: The agent is *possibly carcinogenic to humans*.**

This category is used for agents for which there is *limited evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals. It may also be used when there is *inadequate evidence of carcinogenicity* in humans but there is *sufficient evidence of carcinogenicity* in experimental animals. In some instances, an agent for which there is *inadequate evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals together with supporting evidence from mechanistic and other relevant data may be placed in this group. An agent may be classified in this category solely on the basis of strong evidence from mechanistic and other relevant data.

**Part C: National Toxicology Program (NTP), “Report on Carcinogens”, Background Guidance**

*NTP Listing Criteria*<sup>4</sup>:

The criteria for listing an agent, substance, mixture, or exposure circumstance in the Report on Carcinogens (RoC) are as follows:

**Known To Be A Human Carcinogen:** There is sufficient evidence of carcinogenicity from studies in humans<sup>5</sup> that indicates a causal relationship between exposure to the agent, substance, or mixture, and human cancer.

**Reasonably Anticipated To Be A Human Carcinogen:** There is limited evidence of carcinogenicity from studies in humans that indicates that a causal interpretation is credible, but that alternative explanations, such as chance, bias, or confounding factors, could not adequately be excluded,

*or*

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<sup>4</sup> See: <http://ntp.niehs.nih.gov/go/15209>

<sup>5</sup> This evidence can include traditional cancer epidemiology studies, data from clinical studies, and/or data derived from the study of tissues or cells from humans exposed to the substance in question that can be useful for evaluating whether a relevant cancer mechanism is operating in people.

there is sufficient evidence of carcinogenicity from studies in experimental animals that indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors in multiple species or at multiple tissue sites, or by multiple routes of exposure, or to an unusual degree with regard to incidence, site, or type of tumor, or age at onset,

*or*

there is less than sufficient evidence of carcinogenicity in humans or laboratory animals; however, the agent, substance, or mixture belongs to a well-defined, structurally-related class of substances whose members are listed in a previous Report on Carcinogens as either known to be a human carcinogen or reasonably anticipated to be a human carcinogen, or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.

Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information. Relevant information includes, but is not limited to, dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub-populations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance. For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals, but there are compelling data indicating that the agent acts through mechanisms that do not operate in humans and would therefore not reasonably be anticipated to cause cancer in humans.

#### **Part D. Table Relating Approximate Equivalences among IARC, NTP RoC, and GHS Carcinogenicity Classifications**

The following table may be used to perform hazard classifications for carcinogenicity under the HCS (§1910.1200). It relates the approximated GHS hazard categories for carcinogenicity to the classifications provided by IARC and NTP, as described in Parts B and C of this Appendix.

Approximate Equivalences Among Carcinogen Classification Schemes		
IARC	GHS	NTP RoC
Group 1	Category 1A	Known
Group 2A	Category 1B	Reasonably Anticipated (See Note 1)
Group 2B	Category 2	

Note 1:

*Limited evidence of carcinogenicity from studies in humans (corresponding to IARC 2A / GHS 1B);*

*Sufficient evidence of carcinogenicity from studies in experimental animals (again, essentially corresponding to IARC 2A / GHS 1B);*

*Less than sufficient evidence of carcinogenicity in humans or laboratory animals; however:*

*The agent, substance, or mixture belongs to a well-defined, structurally-related class of substances whose members are listed in a previous RoC as either "Known" or "Reasonably Anticipated" to be a human carcinogen, or*

*There is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.*

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