

Comments
DRAFT Preamble to the *IARC Monograph*

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The International Union, UAW affirms the importance of the IARC monographs on carcinogenicity to humans. The UAW notes two separate important roles of the monographs.

First, the monographs present a scientific consensus evaluating both human and laboratory evidence for cancer causing properties of an agent or exposure circumstance. Of particular importance is evaluation of human evidence, which historically has been based on expert judgment of an IARC working group. This provides a starting point for comparison of the concordance of laboratory and human studies. IARC provides the most authoritative systematic review in the public health community of evidence for carcinogenicity in people.

Second, classification by IARC starts, or may stop, a public health intervention to reduce exposure to a dangerous agent, or to control an exposure circumstance. This role attracts pressure and distortion of the scientific project by economic interests.

These observations respond to IARC's request for comments on the draft revised preamble to IARC monographs. These comments follow the order of appearance in the draft.

Objective and Scope (p.2).

Hazard Identification. The UAW concurs with IARC's recognition of the distinction between hazard identification and full blown risk assessment. This is especially important for those agents deemed "possibly" carcinogenic to humans.

The role of IARC reviews is to determine whether there is any exposure or dose of an agent, by any route, which "possibly, or probably" may cause cancer in humans.

The UAW concurs that exposure-response or dose-response assessment, other than extracting information from the literature reviewed for hazard identification, is a separate enterprise from hazard identification. Therefore the UAW believes that IARC's application of mechanism to downgrade the ranking of an agent is not appropriate, violates the paradigm, and therefore should be deleted.

We will return to this when commenting on the section on overall evaluation, but quote the text here (p.23): "Exceptionally, agents (mixtures) for which the evidence of carcinogenicity is *inadequate* in humans but *sufficient* in experimental animals may be placed in this category [not classifiable] when there is strong evidence that the

mechanism of carcinogenicity in experimental animals does not operate in humans.” Exposure-response evaluation for human risk assessment consists of comparing mechanistic parameters between laboratory animals, typically more or less resistant species, and humans. Logically, a conclusion that a mechanism “does not operate” is simply a limiting case for exposure-response extrapolation.

5. Meeting Participants (p.5)

UAW concurs that no person with an apparent or real conflict of interest should chair a working group or subgroup, draft parts of monograph text related to cancer, or vote on classification. UAW would hope that IARC would reconsider past evaluations where such persons had a material role in the classification.

The UAW remains concerned about “invited specialists” and “observers.” Invited specialists would appear to be primarily scientific personnel who have worked in an area material to a classification, who have been funded or employed by an entity with a commercial interest in the outcome. These persons with a conflict of interest who will be accorded a voice in the working group, and participate in deliberations, but no vote. UAW recognizes this to be an improvement in transparency from past practice. However, UAW urges IARC to balance any such “invited specialist” with persons with expertise relevant to the decision.

Similarly, “observers” are accorded a voice at the discretion of the chair or subgroup chairs. In the past, “observers” have largely been employed by entities with a commercial interest in the outcome. They have participated in much the same way as the new category of “invited specialists” and have been heavily involved in deliberations. A balance of interests among “observers” is important. The UAW urges IARC to seek out and fund public interest or other NGO affiliated observers once it becomes clear that economically interested observers have been granted access.

8. Studies of cancer in humans (p. 8)

This section does not improve the state of the art in assessing epidemiology or provide transparent decision rules, in the manner of evaluation of laboratory studies. The description of types of studies, and the role of chance, confounding and bias is well done.

The UAW urges IARC to more carefully define the term “quality” as applied to weighing studies. The UAW believes that the greatest weight should be given to those studies where the subjects had the highest exposure, longest duration and latency of exposure, and longest period of observation. Size of the cohort as a whole is less important than the level of exposure, duration and latency and the size of the highest exposure strata. Elaborate and quantitative exposure assessments are desirable, but these can’t confer quality where exposures were low, or where the range of exposures was narrow and would impair observing an exposure-response relationship within the cohort. Where quantitative exposure data are lacking, increasing risk ratio with either duration or latency from first exposure are evidence for an exposure-response relationship within a cohort. The UAW believes that latency is a stronger indicator than duration (or cumulative exposure based on duration) because both duration and cumulative exposure may be

limited because of health related termination of employment. Increased risk among manual workers, compared to engineers and supervisors, is evidence for exposure-response. Null studies in which engineers and supervisors are included in cohort should be given little weight because of the more pronounced healthy worker effect in these groups.

The UAW also suggests that the human studies subgroup of the working group in the future include persons with expertise in exposure assessment in the environment to which the subjects were exposed, frequently the occupational environment. The quality and feasibility of the exposure assessment component of epidemiology, and the power to observe an exposure response relationship if it were there should be evaluated at the same time the rest of the study is being considered.

The human studies subgroup should be tasked to abstract whatever exposure level information can be gleaned from epidemiology studies and include these in their summaries.

9. Studies of Cancer in Experimental Animals. (p. 12)

The UAW concurs that an increased incidence of benign tumors of a type known to progress to malignancy shall be considered evidence for carcinogenicity in a laboratory study. Combining benign and malignant tumors in the same cell type or organ is a valid procedure for evaluating carcinogenicity.

The UAW believes that mortality adjusted statistical methods are always preferred for evaluating results of laboratory studies for carcinogenicity. The mortality adjusted tumor rates should be quoted in the summary where these rates are available. Such rates should also be used to estimate the no observed effect level.

10. Mechanistic and other relevant data. (p. 15)

The enumeration of types of data which may be considered is complete and correct. No decision criteria are supplied in this section for invoking the concept of “mechanism of carcinogenicity in experimental animals does not apply in humans. (P.23)” Given the absence of such decision criteria, the language on using mechanism to downgrade classification should be struck.

The discussion of genetic toxicology is incomplete. Agents or exposures which act through gene silencing would likely have similar exposure response properties to those which act by mutational mechanisms – clonal expansion of cells with genes defective or genes silenced. However, the assays cited to detect mutational activity will not detect gene silencing. Thus, mutational activity is evidence for carcinogenic potential, but absence of mutational activity provides no evidence for null carcinogenic potential.

11. Summary and integration (p. 18)

12. Evaluation (p.19)

(a) Carcinogenicity in humans.

The UAW recommends that IARC subdivide the category “inadequate” evidence by adding a level “no adequate studies available.” This will distinguish agents for which there are “suggestive” or “equivocal” epidemiological studies from those where there is no information at all.

(b) Carcinogenicity in experimental animals

The UAW concurs with IARC that a finding of carcinogenicity in “both sexes of a single species in a study conducted under Good Laboratory Practices (e.g. a US National Toxicology Program study)” should be sufficient evidence of carcinogenicity. In a modern bioassay, each gender-species experiment is truly an independent study, evaluated independently. An experiment in one gender may be a null study, the other may find an association. Activity in both genders of a species is stronger evidence than activity in one gender repeated. That the finding is contemporary should not be an issue, only the quality of the study. The proposed change to consider each experiment in a species-gender group is progress, but not enough progress.

The requirement for “two or more independent studies in one species carried out at different times or in different laboratories or under different protocols” is a vestige of the early days of carcinogen bioassays, using developing methods, statistical tests, and other features in small groups of animals. Under GLP, it’s nearly certain the same results would be found if the study were repeated. In other words, the second study would be a waste of effort, conducted or not conducted only to meet the two study criterion. Therefore, the UAW argues that a single species-gender study conducted under GLP should be considered “sufficient.”

(d) Overall evaluation

A very important issue is raised under Category 3, Not Classifiable. At issue is the paragraph (p. 23):

“Exceptionally, agents (mixtures) for which the evidence of carcinogenicity is *inadequate* in humans but *sufficient* in experimental animals may be placed in this category when there is strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans.”

UAW believes this paragraph should be struck. The UAW does not here argue again the wrongly decided instances where laboratory data of carcinogenic risk to humans has been ignored under various ad hoc hypotheses regarding mechanisms. Rather, we address the logic.

UAW argued above that this paragraph contradicts the logic of hazard identification. The notion that a mechanism found in experimental animals does “not operate” in humans, as opposed to operates to a lesser degree in humans, is still quantitative, not qualitative notion. How close to zero the mechanism gets in humans is a quantitative exposure response determination outside the IARC process. UAW notes that in the real world, this exposure response determination is usually the province of public health agencies. But a “not classifiable” rating aborts that analysis.

