

Comments on the Draft Preamble to the IARC Monographs
By Ron Melnick

The draft preamble provides valuable guidance for IARC Working group participants and for those who rely on IARC Monographs for public health decisions. My comments listed below concern clarity of the preamble and some issues that may need additional consideration.

P1, line 41. The labeling of an agent as an ‘occupational carcinogen’ wrongly implies that that agent may not be a carcinogen under other exposure circumstances.

P2, line 9. A ‘carcinogen’ isn’t an exposure; it is an agent for which exposure increases cancer risk.

P2, line 11. What is the meaning of cancer ‘severity’?

P2, line 15. Risk assessment is the ‘evaluation’ of scientific data to describe ‘potential’ adverse health effects...

P2, line 18. Hazard ID is not limited to single agents

P2, lines 21-25. Risk characterization should also address factors contributing interindividual differences in susceptibility. If these issues are not mentioned in NRC 1983 or 1984, then additional citations are needed.

P3, line 33. How does IARC become aware of new scientific information? Can individuals nominate agents or topics? If so, that should be noted.

P3, line 37. How are decisions made to update or re-evaluate a monograph? Who decides how much or what types of new data warrant a re-evaluation?

P3, line 50. Who judges whether studies are inadequate or irrelevant and therefore can be omitted? Intentionally omitted studies should be listed to distinguish them from studies that may not have been found in literature searches.

P4, line 6. How does a Working Group decide what mechanistic data are relevant and should be included in an evaluation? This could be problematic. For example, the DEHP Working Group ignored critical mechanistic information on the role of Kupffer cells even though a co-author of much of that work was member of the Other Relevant Data subgroup. How will future reviews prevent the suppression or omission of critical, relevant information?

P4, line 47. I strongly recommend adding ‘interpretation’ before the words ‘cancer data’. This would indicate that invited specialists with conflicts of interest would not be allowed to draft the mechanistic sections.

P5, line 6. How will you achieve a balance of observers when only industry-sponsored observers can afford the travel expenses necessary to attend these meetings?

P5, lines 29. Sentence should be rewritten to note that it is not acceptable for Observers to contact Working Group members. [Observer is a category of participants]. What happens if contact is made? Is the working Group member disqualified?

P8, line 1. For occupational exposures, do you accept models that provide estimates of past exposures? If so, what are your requirements for validation?

P8, lines 21-22. Regarding studies of cancer in humans, a comment should be made on the reliability of mortality versus incidence data.

P10, lines 47-48. I suggest replacing 'affecting gene-environment interactions' with 'in levels of enzymes affecting metabolism or repair.' I don't think most readers of the monographs will understand 'gene-environment' jargon.

P11, lines 14-16. This sentence needs explaining.

P13, lines 9-13. I don't understand this assessment and how it reflects human relevance or irrelevance.

P13, line 43. Between adequately and reported, add 'analyzed and'

P14, lines 11-19. Why are DNA damage and cell proliferation highlighted. Why aren't cell death rates, receptor mediated changes in gene expression, etc. also noted? This paragraph over emphasizes DNA damage; receptor mediated processes can also produce nonlinearities, including non-monotonic dose-responses.

P14, line 40. The poly-k test used by NTP is another survival adjustment method worth citing.

P14, lines 45-47. More guidance is needed on the utility of historical control data for sites with a high degree of variability. If an author discounts a tumor response that is significant compared to concurrent controls because it falls within the range of historical controls, should the IARC Working Group reverse that conclusion?

P15, line 11. I think you should add 'biological activity of' before 'the agent being considered.'

P15, line 12. How does the working group decide what data are relevant (see comment for P4, line 6)?

P15, line 19. Non-genotoxic pathways should also be mentioned.

P15, line 28. Are human samples (e.g., hepatocytes) also considered?

P15, line 38. Change bioassays to 'cell-based assays'

P15, line 49. Although it is mentioned later, it might be worth noting here that responses may differ as a function of age of exposure, genetics, other exposures, etc.

P16, line 8. Because all cancer mechanisms are actually hypotheses, shouldn't more weight be given to those in which predictions were tested experimentally?

P16, line 12. Regarding experimental model systems derived from animals and humans, some caution should be noted in differences in harvesting and storage that might impact differently on the functional quality of these samples.

P16, line 47. Consideration should also be given to consequences of exposure at different life stages.

P17, line 2. Comment is also needed on the responsiveness of the biological test system.

P17, lines 30-31. Peroxisome proliferation is not a mechanism of carcinogenicity. I would change 'act through other mechanisms' to induce other biological changes.'

P21, line 29. What kinds of physicochemical parameters add relevance to an evaluation?

P21, line 36. Should add 'high quality' before 'biological specimens'

P21, lines 45-47. Strong support may also come from studies that test predictive dose-responses of other compounds that act by the same mechanism.

P22, lines 22 and 36. Depending on available data, why wouldn't IARC list a chemical as 'probably carcinogenic to humans' based solely on mechanistic data? Do we really need to test every benzidine-based dye in animals? Wouldn't pharmacokinetic data be adequate?