

Comments on IARC Draft Preamble  
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**Page 2.** Line 10. Might add here the occurrence of "rare tumors". Also rather than waiting until section 9 suggest adding combined occurrence of benign and malignant tumours. Does IARC consider total tumors as does Maltoni et al? I have come to believe these are valid indicators of carcinogenic activity.

Line 28. Nice to explain use of 'risk' in the title. Of course one option would be to change the title. Use 'carcinogenic hazard'.

Line 34. Thanks for not using 'mode-of-action' in the preamble [unless I missed it].

**Page 3.** Lines 12-14. I wonder why this needs to be in bold? To cover your ass? Seems to me to be an over-emphasis to allow industry to misuse your evaluations.

Lines 16 & 18 & 32. Why "topics"? Totally incorrect word.

Lines 18-26. Seems to me you need to add 'exposure circumstances' e.g. for manufacturing processes. Not covered in those given, like 'mixtures'.

Line 36. 'Subjects' not correct word.

Line 42. Why cite only the negative 'does not'. Suggest using "does or does not operate in humans".

Line 47. What does 'intend to' mean? That you will not review all? Suggest delete this cover-up words. Somewhere in this sentence I would add the word 'available' as a better cover-up: 'all pertinent and available. . '

Line 48. What does 'Other studies' mean? Maybe the word 'related' needs to be added between these two words.

Line 50. Those 'inadequate' studies [bioassays and human studies?] must be mentioned only to label them as inadequate for others to realize they were looked at and not simply missed.

**Page 4.** Lines 9-16. Are these general exceptions listed in section 12? I didn't find them, or any mention. Thus why refer readers to section 12? I recall NTP and Prop 65 were once listed as examples of 'unpublished' reports being citable. Has this been removed?

Line 25. Mentions five categories; thus suggest numbering the bullets 1 to 5.

Lines 27-34. I would further suggest that much of #1 [lines 27-34] be placed between lines 23 and 25, because there are "tasks" for the working group. Thus start #1 with line 34.

Line 35 is overly restrictive and often not the case that WGs 'published significant' papers on chemicals being reviewed. This was used before to justify packing the WGs with industry people.

Line 42. #2. I would add here they also 'do not vote'. To simply say they don't 'participate in the evaluations' is almost but not good enough; suggest adding the finality and unambiguous 'do not vote' as well.

**Page 5.** Lines 1 & 5. Why use 'in limited numbers' [lines 5-6] for group #5 and but not for groups #4 or #3? Are observers being treated differently? Why? Are representatives 'allowed to speak'? Why do observers have this restriction and not representatives?

Lines 15-17. Perhaps conflicts ought to be divulged here in #5 as well.

Line 19. How does IARC obtain this information unless a person is 'almost invited'?

Line 32. In this modern era of communication might I suggest adding e-mail address to the listing of participants? Those not so inclined can of course decline to have their e-mail addresses listed.

Line 38. Is 'separate' necessary? Perhaps nothing or use 'unique', 'distinct', or some other more useful word. Or use 'each' for 'a separate'.

Line 41. Sorry but 'topics' don't convey for me.

Line 42. Actually 'invited' seems more accurate than does 'selected'.

Line 43. Why use only 'recognized sources'? Recognized by whom?

Line 44. Does everyone know MEDLINE? Really though should be PubMed who more recognize. Is this where 'unpublished' and 'in press' should be mentioned again? NTP? PROP 65?

Line 46. Suggest replace 'generally' with 'should'. See (i) line 29, page 4.

**Page 6.** Line 7. This is bogus to say production data would 'disclose confidential information'. Like what for goodness sake. This just bows down to industry fake secrets.

Line 14. Does 'sent to all participants' mean representative and observers as well? If so perhaps IARC could make these available to others on request who have much interest but were not lucky enough to get invited.

Lines 20-22. Who does this? Not terribly clear. Isn't this also obvious that the WG will do this?

Line 23. Is 'consensus evaluations' used to avoid the word 'vote'? Are votes no longer taken? And for record completeness perhaps these should be recorded. And even the names of those who voted for or against, one way or the other. The NTP does this and it has worked well for more than 25 years. In fact NTP even records the vote or votes with names in the Peer Review Meeting summaries in the published technical reports.

**Page 7.** Line 12. 'Trades' should be 'trade'.

Line 13. Are 'impurities' the same as 'contaminants'?

**Page 8.** Lines 16-19. Since many occupational carcinogens were first identified by case reports [including vinyl chloride], perhaps these should not be relegated to 'may also be reviewed'. How can one even pretend to ignore these? After all the three types of human data signaled here are most often lacking or absent. Then IARC goes on to slam these case reports in lines 29-38, guaranteeing their non-use. Too bad.

No mention is made of clusters. I guess I can understand that but again these were what were observed for many industrial carcinogens.

Lines 41-42 sure place an insurmountable ['They may, in some instances'] damper on the use of benign tumours as a measure of carcinogenicity for evaluation.

Section 8. Somewhere in here perhaps mention however brief could be made of clues and hints and even correlations from or with animal findings on the human evidence strengthens causality.

Also since almost everyone now cites Hill's Criteria of Causation [1965] perhaps this reference citation might be added:

Hill, B.A. (1965). The environment and disease: Association or causation? Proceedings of the Royal Society of Medicine, 58, 295-300.

**Page 9.** Nothing.

**Page 10.** Line 33 uses the terms 'mechanistic biomarkers' gives much to much credence to the use and value of so-called biomarkers. Then the listings of biomarkers like DNA adducts largely has nothing to do with 'mechanism' but has to do with exposures makers. So to oversell these is a disservice. Likewise line 44 giving 'mechanistic' credibility to 'inflammatory responses' clearly stretches the concept.

**Page 11.** Line 20. Here is where you might reference Hill's Criteria.

Line 42-46. Might I think here as 'hogwash'? Dioxins of course cause multiple tumors in multiple strains and in humans. Yet if one site were only considered than perhaps dioxin would still not be judged a human carcinogen [mechanism notwithstanding]. Also different tumors types from similar exposure circumstances in males and females are rift in bioassays and not uncommon in humans especially for hormonal 'mechanisms'. So to discount this decreases sensitivity for identifying carcinogens.

**Page 12.** First paragraph. Here again one might mention how to deal with or consider solid animal cancer data with a purported 'lack' of carcinogenicity in epidemiologic studies. Likewise I wonder when epidemiologists will begin to increase 'public health' sensitivity by using 90% confidence intervals instead of the indefensible and strict 95% CLs. Simply put this means that in reality a P value of 0.25 is needed to believe in a borderline positive finding. In bioassay one uses one-tailed tests for carcinogenicity again simply because a positive [and not negative] effect is 'anticipated' and 'hypothesized'. Nothing galls me more than to see study and after study discounted because the lower limit is 0.9 or 0.95 and thus 'not statistically significant'. Here again animal data should impact on this rote conclusion.

Line 32. Suggest adding the first reference to declare this concept of first evidence in animals:

Tomatis L. The predictive value of rodent carcinogenicity tests in the evaluation of human risks. *Annu Rev Pharmacol Toxicol.* 1979;19:511-30.

Lines 37-39. Perhaps the word 'possibility' needs strengthening. For instance before 'species-specific' add 'purported' the word 'does' in line 38 would better be 'may'. Without this adjustment the certainty and finality of the existing clearly go beyond what we really know about this 'topic'.

Line 44. Does IARC still place the 'hyperplasias' in the 'other' section or as stated here place these relevant findings with the bioassay findings?

Lines 47-2 [page 13]. Might add here as well chemicals of the same class that have been studied: e.g. anthraquinones to impact on an evaluation. This is somewhat mentioned in page 13, line 11.

**Page 13.** Line 24. What does 'duration of follow-up' mean. This could mean observing animals after exposure has ceased, as is done at times by the Ramazzini Foundation. Should this be stated as 'duration of exposure'? Perhaps 'duration' should be added after 'schedule'. If I may say so, a detailed reference to this issue is:

Haseman J, Melnick R, Tomatis L, Huff J. Carcinogenesis bioassays: study duration and biological relevance. *Food Chem Toxicol.* 2001 Jul;39(7):739-44.

Line 27. What are 'modifying factors'?

Line 29. As mentioned the word 'intend' is fuzzy at best.

Lines 30-31. Might add 'exposures were too low' and 'incomplete or limited pathology'. This was the case most vivid for the lack of carcinogenicity of benzene in earlier studies; only leukemia was sought.

Line 32. 'May be omitted' is a disservice because these may be cited by others perhaps as 'adequate' to support their particular agenda. And yet not even mentioned by IARC as inadequate continues to 'promote' other to cite them.

Line 33. Certainly Montsano et al., 1986 is good to cite, but perhaps one or both of these more current references by the two key players in bioassays could be added here:

Soffritti M, Belpoggi F, Minardi F, Maltoni C. Ramazzini Foundation cancer program: history and major projects, life-span carcinogenicity bioassay design, chemicals studied, and results. *Ann N Y Acad Sci.* 2002 Dec;982:26-45.

Bucher JR. The National Toxicology Program rodent bioassay: designs, interpretations, and scientific contributions. *Ann N Y Acad Sci.* 2002 Dec;982:198-207.

Lines 39-40. Even if survivals for controls and exposed were similar does not mean they were adequate for evaluation, if both were too short. [Incidentally 'treated' seems to indicate a 'benefit' whereas 'exposed' is really what is going on; I also don't cotton to 'dosed'].

Line 42. Again not sure what 'duration of observation' means. Is it different than line 39: 'duration of treatment' [re exposure]?

Lines 50-51. Good. And added weight if these benign lesions are known to progress from other studies [especially those of longer duration than the NTP truncation at 2 years], though not necessarily the one being evaluated. For example mammary fibroadenomas in Fischer rats progress in about 2% or so of the lesions observed and sometime only benign tumors are found in an individual experiment.

And as mentioned before does IARC consider total malignant tumors as does Maltoni et al? I have come to believe these are valid indicators of carcinogenic activity.

**Page 14.** Lines 13-14. To balance the view of Cohen [cell proliferation 'causes' cancer] you might consider this reference:

Melnick RL. Does chemically induced hepatocyte proliferation predict liver carcinogenesis? *FASEB J.* 1992 Jun;6(9):2698-706.

Or this one:

Melnick RL, Huff J, Barrett JC, Maronpot RR, Lucier G, Portier CJ. Cell proliferation and chemical carcinogenesis: a symposium overview. *Mol Carcinog.* 1993;7(3):135-8.

Line 13. Perhaps 'is a strong' could be replaced with 'may be a'.

Line 15. Would 'ultimate carcinogen' be better than 'reactive intermediates', as the latter is not precise enough, as the topic here is carcinogenesis.

Line 27. As NTP has been using the Poly-k statistical method for years, perhaps one or both of these references might be considered:

Portier CJ, Bailer AJ. Testing for increased carcinogenicity using a survival-adjusted quantal response test. *Fundam Appl Toxicol.* 1989 May;12(4):731-7.

Bailer AJ, Portier CJ. Effects of treatment-induced mortality and tumor-induced mortality on tests for carcinogenicity in small samples. *Biometrics.* 1988 Jun;44(2):417-31.

Line 28. Again simply seeing 'no difference in survival' does not mean the study was adequate.

Lines 46-50. Another 'good' among many 'goods' in the preamble.

**Page 14.** Line 20. I know there are some who correlate carcinogenesis with teratogenesis but I remain uncertain why the IARC monographs on carcinogenic 'hazard' continue to devote time and energy not only to 'reproductive and developmental effects' but also to other irrelevant 'toxic' effects.

Lines 24 & 33. Interesting to introduce 'concise' here.

Line 34. Really. Do we have a clue to this certainty?

Lines 33-49. Whew. One of those 'sound good' paragraphs with little applicable meaning.

Sorry.

**Page 16.** Lines 1-2. Whew again.

Line 41. Should a period or semi-colon [colon] come after 'dimensions'?

**Page 17.** Line 31. Consistent findings on 'cellular toxicity and regenerative proliferation' as being 'mechanistic' are clearly lacking. Likewise with 'peroxisome proliferation'.

Line 49-51. Wonder why? Perhaps iarc could state why these are important in the context of carcinogenesis.

**Page 18.** Line 17-18. 'Summaries' of what will appear on the monographs website? All that follows?

Line 22. Is 'as appropriate' necessary?

Line 25. Likewise 'when available'. Either or both of these could be used many times throughout, but are not necessary. These 'phrases' are taken for granted.

Line 31. How about using 'pertinent epidemiologic studies' rather than 'that are considered pertinent' etc? And then

Line 32 'When relevant' etc. Is this necessary? Of course they should be summarized/mentioned.

Line 39. Same necessary comment.

Lines 43-45. Two sentences should be combined. Reads as if the former is always available and the latter may be. Combine the 4 items together ending with 'are also summarized'.

**Page 19.** Lines 3-4. Somewhere iarc should indicate why these 'are considered important' to carcinogenesis.

Lines 19-20. Is this a timid effort to indicate 'votes'?

Line 22. For this whole Evaluation section suggest deleting in all places the use of 'the Working Group'. Not needed, and could then imply that where not used means the WG should not pay attention? Silly, yes. For example what is lost if in line 40 'the WG' is deleted? Nothing. Likewise in line 30 [but here the sentence needs to be slightly re-structured.

Line 25. What does 'using standard terms' mean? Delete this?

Line 28. Surely we can do without 'it is recognized that'. Redundant and besides how do you know?

**Page 20.** Lines 18-21. Seems to me that available studies being inadequate are not near the same as no studies/data available. To combine these two different cases does not send a precise informed message. In the former one could say 'inadequate evidence' [although what does that really mean?] but not for the latter. In fact I would hazard a suggestion that the category should be 'inadequate study of carcinogenicity', not 'inadequate evidence' which makes little sense. As

described the study[ies] evaluated are inadequate to decide on the presence or absence of an effect. Further, and a separate category for 'no data on cancer in humans available'.

Line 23. Instead of 'there are' consider 'several adequate studies are available covering' etc'

Line 28. As is evident, forgive my lack of statistical expertise [and others as well] but why must the upper limit value be close to 1.0. And how close to 1.0 is close? Seems to me the CI should be 'tight' and below 1.0

Line 33. What is the difference between 'very little' and little? Suggest delete 'very'.

Lines 35-36. What? Not only comes out of the 'blue' but is redundant with lines 10-11. Suggest delete.

Line 40 [as in line 2]. 'The evidence' should be 'Evidence'.

Line 43 [as in line 5]. 'The Working Group considers that' is unnecessary. And alternatively could be used to introduce each category. Suggest delete.

Line 47. Why limit GLPs to only group (b)? And why even mention it here. Seems defensive and out of place here.

**Page 21.** Lines 11-12. Not sure what this last phrase really means. And does it matter? That is given there is a relatively 'high' background' for leukemia [e.g.] in Fischer rats, then the exposed groups must have a considerably and statistically higher incidence to be considered due to the chemical exposure. Regardless of the 'high background'. Does this phrase mean that if 'high' [whatever that means] backgrounds are true, then one can not call it a carcinogen'. That is what it reads like. Also, one could read this as if 'certain strains' have a high bkg then this could be used to negate a strain with 'not a high bkg'; silly I know but it could be read that way. Thus I don't see the need for this phrase at all.

Line 14. Please, the study is not 'inadequate evidence' but is an 'inadequate study[ies]'. There is no evidence in the study so how can it be inadequate evidence? NTP uses

'Inadequate Study of Carcinogenic Activity is demonstrated by studies that because of major qualitative or quantitative limitations cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.'

Also here [line 14 and page 20 line 18] iarc uses 'studies' and might this be better as 'study or studies'.

Lines 26-27. What if the mechanistic evidence does not 'affect' the overall evaluation? Is it still 'highlighted'?

Line 28. What does 'tumour pathology' mean in this mechanistic context? Surely one has already evaluated the chemically induced tumours and used that information to decide on a level of evidence. So why mentioned here as mechanism? Likewise 'preneoplastic lesions'.

**Page 22.** Lines 8-11. No idea what this says/means. Or lines 7-8.

In fact almost all that is included in '(c) mechanistic and other relevant data' [pages 21-22] is wishful thinking/hoping about things we know little or nothing about. Or that some of what we know relates somehow to mechanism. Reading this leads one to think we know much much more about MECHANISM[S] than we really do. Just overwhelms me that it is this clear and confirmed. Guess I have not been paying attention.

Line 21. Is 'Finally' needed? And that line could be easily shortened to simply read: 'All evidence is considered to make an overall . . . .'

Line 25. Full stop after 'agents'. What is the rest of that sentence for?

Line 27. What does 'evidence of capacity' mean? If the 'of' should be 'or' it still makes little sense. Just drop 'capacity to induce' and it becomes clear.

Line 33. 'And the designated group is given' could be deleted.

Line 43. Suggest replacing 'placed in this category' with 'considered carcinogenic to humans' when etc.

Line 44. Does 'less than sufficient' mean limited? Or also 'no evidence'?

Line 45, of course the word 'strong' is too strong. Delete. The rest of the sentence makes no doubt about relevancy.

Line 46. Having said that, what does 'relevant' mean?

**Page 23.** Line 1. After 'category' consider inserting 'comprises two levels of evidence' and etc to let the reader know there are two. In fact better to simply switch sentence 1 and 2. With some re-write and definite shortening.

Line 2. Amusing to read 'almost sufficient' [reminds me of a professor who used to tell us that one does not get 'almost pregnant', but I digress]. So, what does 'almost sufficient' mean? More than limited? How is that possible? If I get the meaning, then suggest replacing 'almost sufficient' with 'limited'.

Lines 7-10. Suggest delete 'have no quantitative significance and' [what does this mean any how?]. If compelled you could replace this with 'indicate a qualitative difference' and etc. but even that is not necessary or even useful.

Lines 9-10. Confusing and contradictory [to lines 1-4] because this clearly indicates that there is human evidence for both grades, one a higher level than the other. And yet one can have no evidence in humans and get 'into' 2A or 2B. So more clarity and thought is needed.

Lines 12-36. Overall I find this stuff interesting and confusing. As an example for 2A I am surprised that 'exceptionally' a chemical may be in 2A with 'limited evidence in humans', but for 2B it takes 'limited evidence in humans' AND 'less than sufficient evidence of carcinogenicity in experimental animals'. Wonder if anyone else feels this way. Thus it seems to me that 'limited' and 'limited' should be considered for 2A. Right? In my opinion if there is evidence in both humans and animals it almost ALWAYS should be 2A.

Line 20. Delete 'strong' as virtually meaningless.

Lines 20-21. To insist on this level of mechanistic certainty in humans and animals is way overboard. If one has a flaming carcinogen like butadiene in animals [and no human evidence] this alone should get it to 2A, without any mechanism information.

Lines 30-32. Turn this around because it is written is a slight negative connotation: Category 2B is also used when there is sufficient evidence of carcinogenicity in experimental animals in the absence of human evidence. Makes it more 'positive feeling' that animal data are valuable. Why no mention of getting a 2B with limited evidence in humans and no animal data? Or did I miss this some how?

Lines 40-43. Too bad IARC does not have an 'equivocal evidence category' for those with evidence but not enough for 2B.

**Page 24.** Lines 1-2. Wow. No idea what this means. What then goes here? Makes no sense to me.

Line 6. What does this mean? The WG should clear up differing interpretations.

**End.** jehuff-