Columbia University
CENTER FOR RADIOLOGICAL RESEARCH
630 West 168TH Street
New York, NY 10032

WORK: (212) 305-9930
FAX: (212) 305-3229
djb3@columbia.edu
Dec 13, 2001

Dr. James Neton
NIOSH

Dear Dr. Neton,

Attached is my review of "Proposed Radiation Weighting Factors for use in Calculating Probability of Causation of Cancer"

FYI, I took about 3.5 days to do the review.

Yours Sincerely,

David Brenner

David J. Brenner, Ph.D., D.Sc.,
Director, Radiological Research Accelerator Facility
Professor of Radiation Oncology and Public Health,
Columbia University

Review of "Proposed Radiation Weighting Factors for Use in Calculating PC of Cancer"

The document under review would be quite appropriately submitted for journal publication, but I do not see it as an appropriate basis for PC tables. The analysis techniques used in it, particularly the use of Eq. 3, are highly non standard, and are inadequately justified, particularly as there is not an established body of peer-reviewed literature to back them up. In fact the only mention of the use of Eq. 3 that I know of in the peer-reviewed literature is in a 1999 paper by Alan Edwards at the UK NRPB; Edwards discusses the advantages of the approach but finally opts for a completely different one. Nor is Eq. 3 applied uniformly, being used only for neutrons, but not for other types of radiation.

In terms of the actual data analysis, the document relies heavily on the rather sparsely documented analysis by Edwards (1999), and almost not at all on documented primary sources. While this might be reasonable if a standard analysis technique was being used, the fact that this is not the case makes the reliance on Edwards of considerable concern. Indeed Edwards (1999) states "the values given ... result from my judgment of the basic data and other equally valid values could be obtained by others considering the same data". While this is perfectly acceptable in the Edwards paper, it is not a good basis for the PC tables.

I did not find the treatment of uncertainly distributions satisfactory. In too many places parameters were simply stated without adequate justification or documentation. Again the issue of not being able to rely on past NCRP or ICRP analyses is a concern.

I note that in section IV-G of the accompanying material (Draft Report of the NCI-CDC Working Group), there is a two page analysis of RBE. While it has aspects that can be criticized and potentially improved (particularly, as discussed below, the rather implausible assumption that photons of all energies have the same biological effectiveness), because it is so grounded in the extensive prior analyses of the NCRP and ICRP, it makes for a more satisfactory basis for use in PC tables than does the report under review.

Finally the use of terminology is somewhat sloppy throughout the paper. For example the term "radiation weighting factor" (clearly defined by ICRP) is sometimes used to refer to $w_{r,L}$, and sometimes to $w_{r,H}$, this latter also sometimes being referred to as the "RBE factor".

In summary, not having the extensive analyses by the ICRP, nor those of the NCRP, as background support, an expert witness would be hard-pressed to defend in court the proposed radiation weighting factor.

Specific Comments follow:

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Page 3. The argument applied in rejecting use of the standard Eq. 2 relates to the question of whether high values of RBE_{max} are associated with larger values of the DDREF than the factor of 2 used in analyzing low-LET A-bomb data. This may or may not be the case, but even if the authors did make a strong case, there are simpler methods to overcome the problem than rejecting the use of Eq. 2, and thus throwing away much of the accumulated analyses of the ICRP and the NCRP.

Page 3. The use of the Eq. 3 is primarily designed to avoid problems associated with dose rate. However the authors still need to add an ad-hoc correction for inverse dose rate effects. Again this argues against changing the basic formalism used from the standard Eq. 2 to Eq. 3.

Page 4. The argument here that the use of Eq. 3 is necessary because the variability in their derived weighting factor ($w_{R,H}$) is "considerably less than the variability in RBE_{MAX}" is weak. In the paper on which the current authors rely heavily (Edwards 1999), Edwards derives a variability of a factor of 5 in derived RBE_{MAX} values, and a variability of a factor of 3⅓ in derived $w_{R,H}$ values.

Page 6. There are more recent data on the RBE of low-energy neutrons, published subsequent to the Edwards (1999) analysis, which should have been considered (e.g. Miller *et al* Int. J. Radiat. Biol. 2000). At this point the weight of evidence is probably that the cancer risk does not decrease with neutron energy from, say, 1 MeV to 50 keV – an important issue since much potential high-LET occupational dose may come from highly scattered low-energy neutrons. Again, the lack of reference to primary sources is a concern here.

Page 7. The treatment of inverse dose rate effects seems inadequate and again does not seem to consider the recent literature adequately. Both theory and experiment (e.g. Lubin *et al* 1995) strongly suggest that the inverse dose rate effect is relevant only for protracted high doses of high-LET radiation. As the analysis nowhere uses risks or weighting factors that refer to protracted high doses of high-LET radiation, it is hard to see why Eq. 5 contains an "enhancement factor".

Page 8. The use of Eq. 2 rather than Eq. 3 for photons, while welcome, makes for considerably inconsistency within the report as a whole. The justification (page 9) that if one makes an "arbitrary assumption", the risks estimated using Eq. 3 would be about the same as the risks estimated using Eq. 2, is itself not self consistent. If one forgets about Eq. 3, however (as the authors do in this section), the analysis is quite reasonable and is the only part of the current report which I found more satisfactory than the material in section IV-G of the accompanying "Draft Report of the NCI-CDC Working Group" - specifically because the latter assumes a radiation weighting factor of 1 for all photons.

Page 10. Again Eq. 2 is used rather than Eq. 3, this time without any comment or discussion. It is hard to see how the authors can justify using a different risk model for neutrons compared with that for alpha particles. The only practical explanation that I can see is that Edwards only produced his analysis for neutron data.

Page 11. Similarly the treatment of the inverse dose-rate effect is inconsistent between neutrons and alpha particles. No rationale is given for this difference.