MUSC
MEDICAL UNIVERSITY
OF SOUTH CAROLINA

BIOMETRY & EPIDEMIOLOGY
135 RUTLEDGE AVE • STE 1148
PO BOX 250551
CHARLESTON• SC 29425

(843) 876-1100
FAX (843) 876-1126

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Dr. James W. Neton
NIOSH
Fax (513) 458-7125

Dear Dr. Neton:

Sorry to be late in my review which was due November 19, 2001. My specific recommendations are attached and I would be happy to answer any questions.

Sincerely,

David G. Hoel, Ph.D.
Distinguished University Professor

DGH/ps

Review of the NIOSH-Interactive RadioEpidemiological Program

My review consists of additions to the NCI Document on Radio-epidemiological programs and tables. There are well known issues concerning the NCI approach. These include (1) the concept of probability of causation, (2) the use of only the A-bomb data for risk calculations, (3) assigning risks for cancers that have not been shown to be radiogenic, and (4) the use of upper bound confidence intervals which may result in the lower likelihood of compensation for an individual with a cancer that is known to be radiogenic than one which is not radiogenic. I will not comment on these issues but assume that NIOSH is adopting the NCI approach and simply wishes to extend its applicability to additional cancers.

1. Bone Cancer – Although the A-bomb mortality data has a non-significant effect for bone cancer which is not suitable for risk estimation, there is clear evidence from both the radium dial painters and Mayak workers that radionuclides deposited on the bone at high doses over a long period of time will induce bone cancer. Although the dosimetry for the Mayak workers is not available, there is a large body of data from the radium dial painters including risk modeling that is not mentioned in the NIOSH Report. This data indicates that there appears to be a very non-linear dose response and probably a threshold for bone cancers. The recent NCRP report by Upton, et. al. on low dose linearity does state that bone cancer maybe an exception to the low dose, no threshold approach that most radiation cancer data appears to satisfy. I believe NIOSH should take a more careful look at the data and in particular the radium dial painter data and at least

discuss why it does not choose to follow other groups in stating that the dose response is very non-linear with a likely threshold.

2. Non-Melanoma Skin Cancer – With the recent report by Ron, et. al. (1998) there is clear evidence that external radiation can induce basal cell carcinoma. With this data it equally establishes that external radiation does not induce squamous cell carcinoma at the doses received by the A-bomb survivors. I believe that NIOSH is incorrect in combining these two different cancers and should only deal with the basal cell carcinoma. A second point is the differences between black and whites with regard to their background rates of skin cancer. It appeared from the tinea capita studies in Israel that they found a large number of skin cancers among the whites but did not observe them in non-whites. (78 basal cell carcinomas among 1727 whites, and 0 among 500 non-whites and 3 among 1400 white controls (from BEIR V)). If radiation induced basal cell skin cancers are projected as a relative risk, then the background rate for blacks would not enter into the computation. If it is assumed that risks or excess cancers are additive, then of course it would make a great difference. A clear discussion of this is needed in this section since I was not convinced by the arguments for using an additive risk approach by the document particularly in light of the above numbers. With regard to dose response from the Ron analysis, it does appear that the argument for a one sievert threshold that Little had previously had found with RERF data is not the best model to use. The linear spline model with a knot at one sievert appears to be best and is better than a threshold model with a threshold at one sievert. Thus, a linear dose response is reasonable. As part of the evidence

for melanoma, a study by Carpenter was sited that among nuclear workers skin cancer deaths which presumably are primarily melanomas were found to be associated with external radiation in the U.K. This was based on 16 cases. The NIOSH should actually refer to the more recent follow-up which was published in 1999 by Muirhead ("The Second Analysis of the National Registry for Radiation Workers") and reports that there are 30 deaths as supposed to 16 and on a dose response basis is non-significant with a P value of .43. Therefore, it maybe a little deceptive to use the older study with fewer cases. The NIOSH Report mentions that the Ron study shows the relative risk for melanoma similar to the non-melanoma skin cancers. This is probably true but it should be pointed out, it is based only on one case at the high dose category out of the 10 total cases of melanoma. I would not go beyond what even the authors say in their paper on the issue of melanoma. It should be mentioned that the larger study carried out by the Cardis team found in the combined nuclear worker cohorts 46 melanoma deaths. The trend was non-significant with a one-sided P value of .42. It should also be mentioned that the Cardis study observed 11 bone cancer deaths among the workers with a negative dose response trend. Also, the registry of British workers with bone cancers had only 4 cases and that trend was also negative.

3. Male Breast Cancer – This is a curious argument to equate it to female breast cancer which is possibly the most susceptible radiation site. I suppose the same argument could be applied to the prostate cancer and equate it with female breast cancer. Since female breast cancer risk involves critical period of cell division I would be careful assuming the same in males. I would however follow the NCI

here and include it with the mixed cases that they use as opposed to singling out the male breast cancer. The NCI mixed sites also includes bone cancer which allows them to avoid the issue of dealing with radium dial painters. It might be the best strategy for NIOSH to follow the NCI on this for both bone and male breast cancer.

4. Dose rate effects and RBE's – It is first pointed out that the Hiroshima data strongly supports a linear at low dose response for most solid tumors. This is the case if you assume that the alternative to a linear is a linear quadratic. There are certainly other models that suggest non-linearities at low doses. But I believe that this is not the place to argue this issue. It must be remembered that there are quality differences between the incidence data from Japan and the mortality data. For example, the incidence study found no effect for multiple myeloma while the mortality study did. A comparison showed some misdiagnosis on the death certificates which helped explain the differences. Subsequently, Wing, et. al. did a case-control study of DOE workers and essentially found no radiation effect. I assume however, multiple myeloma is in the PC program. With regard to the RBE's it should at least be mentioned that based on theoretical considerations, the RBE's for neutrons will likely increase with decreasing dose so things are not as simple as are mentioned in this section. The smoking category discussion is good.

5. Part III on Cancer Models - I understand the issue with CIS and breast cancer and the fact that Ron in her skin cancer study examined the issue. What is not clear to

me is that CIS will be treated as a neoplasm for some specific sites, will this be for all sites including prostate.