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Dear Dr. Neton,

Thank you for the opportunity to review the NIOSH-IREP Program and Technical Documentation. I spent approximately 24 hours (3 days) reading the technical documentation, experimenting with the Web implementation of the program, and writing up my comments. I hope that my attached comments will be useful to you.

Sincerely,

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REVIEW OF NIOSH-INTERACTIVE RADIO-EPIDEMIOLOGICAL PROGRAM TECHNICAL DOCUMENTATION

I served on the recent National Academy of Sciences Committee that reviewed a draft report of the NCI-CDC Working Group to revise the 1985 Radioepidemiological Tables. We also reviewed an earlier version of the IREP program which at the time was implemented as stand alone program rather than being made available on the Web.

One problem that I, and others on our committee, identified at the time of our review was that the draft report failed to acknowledge that there has been significant and continuing debate about the validity of the concept of the probability of causation. In fact partly on this basis an earlier NAS review of the original 1985 Tables, suggested the use of a different name for the concept, i.e. "assigned share" or AS. I note that the NIOSH implementation reverts to the use of the term "probability of causation" rather than assigned share. This may be justified by political or other factors but it strikes me that some description of the assumptions that are being made upon which the utility of the PC in compensation decisions is based should be made a part of the documentation of the IREP program. A critical assumption is that baseline risks of cancer are similar from person to person.

Key to this debate is the fact that the usual definition of PC = (RR-1)/RR, where RR>1 (RR is the relative risk of disease in exposed individuals) only behaves like a probability if the populations from which the relative risk is calculated and for which the PC is being applied are homogeneous with respect to background risks of cancer. In particular, if this assumption is violated, PCs do not in general "average out" the way ordinary probabilities do. That is if there is a population of exposed individuals each one of who are unique in terms of their baseline disease rates then the average of the individual PCs of persons with disease, which will in general be higher than (RR-1)/RR as estimated from an epidemiological study.

In fact, a number of statistical articles (Robins and Greenland, 1989, 1991, Greenland 1999) have gone into a great deal of detail concerning this failure of the PC to average over groups of heterogeneous individuals, and take this as a rationale for abandoning its use in compensation and in the settling of litigation. Further these articles make the generic statement that no epidemiological study can address the variation in individual disease risk and thus even the most extreme models for heterogeneity in baseline risk cannot be invalidated by epidemiological data.

I myself reject as unwarranted the conclusion of Robbins and Greenland that the PC should be removed entirely from the compensation debate. In particular I feel that it is fully appropriate to ignore any truly unmeasureable individual variation in risk. On the other hand we know that baseline risks of cancer are not completely homogeneous from subject to subject in large populations; in particular most or all cancers tend to cluster within families (Goldgar et al1994) implying that either genetic similarities or shared environmental characteristics are responsible for individual variations in background rates. This leads to the conclusion that the application of the PC to the individual case is

wrong to some degree because evidence for heterogeneity in personal baseline risk is being ignored.

In order to deal with this problem I suggest that the IREP program as implemented by NIOSH utilize the "User defined Uncertainty Distribution" (advanced features). The parameters for this distribution are evidently set so that no additional "User defined Uncertainty" is presently included in the calculations. I would rename this from the "User defined Uncertainty Distribution" to something like "Uncertainty in individual baseline risk of disease" and that this parameter be set in a disease-specific way. In particular for diseases (e.g. thyroid cancer, testicular cancer) for which familial clustering in risk appears to be larger than other cancers some additional variation in the PC should be allowed by manipulation of this feature, i.e. by setting the GSD for the uncertainty distribution to a value > 1. Even for the remainder of cancers where more modest familial clustering has been detected to date this source should be included to some degree (GSD>1 but smaller than for thyroid or testicular). Note that this suggestion is my own, and is not incorporated into the NAS review of the IREP report. In fact at the time that we reviewed the report all members of the committee were quite uncertain as to the utility of the "User defined uncertainty distribution" and suggested that it be kept at its null value (GSD=1).

The precise amount of uncertainty to attribute to this source is something that would need further study, In particular further simulation studies similar in spirit to those described by Thomas (2000), would need to be performed. As in Thomas's simulations the general approach would be to estimate a latent variable distribution for individual baseline risk based on observed familial clustering and then to empirically estimate the variation in individual probability of causation around the standard PC applied to the whole population. I do anticipate that the amount of additional uncertainty justified by familial clustering is likely to be relatively modest, but it would be worthwhile to try to pin this down more specifically.

Note that the issue of varying baseline risk is distinct from the question of whether some individuals may be more radiosensitive than others. At present there is only a small amount of information available regarding differences in individual radiosensitivity (much less than there is known about familial clustering of background risk). One exception is the case of the ataxia telangiectasia (AT) gene where homozygotes for the variant have extraordinarily enhanced susceptibility to UV and ionizing radiation risk. However it is not even known presently whether AT heterozygotes (1-2% of the population) have any increased susceptibility to radiation-induced cancer. My own work with the A-bomb survivors' data (Neriishi, et al 1991, Sposto et al 1991, Stram et al 1991, Stram et al, 1993) seemed to indicate little evidence of differential radiosensitivity between individual in multivariate analyses of early and late radiation effects in that cohort. At the present I think that there is little reason to try to account for especially susceptible populations when dealing with the PC (except for those defined by age at exposure and gender which are important covariates in many cases and have already been included in IREP). Therefore I agree with the approach of the NIOSH-IREP implementation, in basically ignoring this issue given present-day knowledge.

Except for skin cancer, no accounting for minority group membership is done in the NIOSH-IREP implementation. The main issue is probably not whether different minority groups vary in their radiosensitivity to radiation (which is certainly possible, but for which little data exists), but again whether baseline risks vary by ethnic group. Many other cancers, besides skin cancer, vary by ethnic group within the US. This is a similar issue as the transport of the risks seen in the Japanese population to the US population as a whole.

I still believe (as did the NAS committee) that a systematic and thorough comparison of the older tables with the IREP program needed. Because so many new diagnoses are considered than covered by the original tables the biggest difference is that many more cancer cases may now be considered for compensation. However it is important to understand whether there are instances where the older Radio-Epidemiology tables would compensate when IREP-based information doesn't. If so then the reasons for the changes (improved relative risk estimates, etc.) need to be especially carefully described.

The NAS committee had suggested an approach towards pooling of relative risk estimates for rare tumors in an effort to reduce the variability introduced into the PC calculation due poor data for estimating relative risks. While in certain instances pooling has been done, there unfortunately is still no systematic approach taken for pooling relative risk estimates across the various subsets of diagnoses and thereby reduce uncertainty. Statistical tools for pooled analyses exist and are partly outlined in the Committee's report, and should be considered in future updates. In particular the problem identified by the committee that individuals with rare tumors (where the excess RR/Sv is poorly known), are more likely to be compensated using the 99% rule than subjects with common tumors, is not addressed, but could be, if a random effects analysis was undertaken (see citations in the NAS report).

Other weaknesses pointed out by the NAS review included a failure to adequately document and rationalize the choices made about the uncertainties of the RBE factors for exposures to electrons, neutrons, or alpha particles and also for the DDREF. This is partially rectified by the technical report provided, however, it is clear that the choices made reflect the judgment of a relatively small group of investigators (the report authors) rather than a true consensus of experts. This is probably unavoidable given the lack of good human data regarding these issues, however, the choices made here are very important, and are likely to be subject to considerable scrutiny and criticism by other experts with a different view: particularly of the DDREF.

The web-based NIOSH implementation of the IREP program appears to be quite satisfactory as a way of implementing the PC calculation for occasional NIOSH usage; I found the web system to be quite a bit easier to use than the stand-alone version that the committee reviewed. One problem with the web-based system is that if there is a reason to run the program repeatedly for a large number of scenarios (perhaps to set up a comparison of the 1985 tables with the IREP output, for example) then this would be very tedious over the web. One way to solve this would be to allow a user to submit

(perhaps by email) a file of input parameters for batch processing and have the output from the program then emailed back to the user.

It probably is not made adequately clear, however, in the descriptions that appear on the web for a lay user, that the probability of causation is something that is calculated for an exposed person already diagnosed with cancer, and is definitely not the same thing as the probability that an exposed person will either get cancer due to his/her exposure in the future.

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