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Memorandum

TO: Russ Henshaw, M.S., Epidemiologist

FROM: Jonathan M. Samet, M.D., M.S., Professor and Chair

SUBJECT: Review of Lung Cancer Risk Models

Attached please find my review of the materials concerning the two models for lung cancer prediction. I have also attached an invoice for my time in preparing this report.
Evaluation of Two Models for Projecting Lung Cancer Risk: NIOSH-IREP and NIH-IREP

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**Background:**

This report, prepared at the request of the National Institute for Occupational Safety and Health (NIOSH), addresses two models used for projecting lung cancer risk, one prepared by NIOSH and the other by the National Institutes for Health (NIH). Both models have their origins in work initially carried out in the 1980s following a congressional request to the NIH to prepare tables of estimated probabilities that cancers were caused by radiation. Over time, these models have been modified as additional information became available and the conceptual basis for modeling lung cancer risk evolved. For lung cancer, two bodies of epidemiological evidence have been particularly critical: 1) the data from studies of the atomic bomb survivors; and 2) the data from the studies of uranium and other underground miners exposed to radon. The former data have been analyzed over time by investigators at the Radiation Effects Research Foundation (RERF) as well as by the Biological Effects of Ionizing Radiation (BEIR) Committees of the National Research Council. Similarly, the data from underground miners have been evaluated by the individual investigators, by a pooling group convened by the National Cancer Institutes and by the BEIR IV and BEIR VI Committees.

The NIOSH and NIH models have recently diverged, with a modification of the NIH model to incorporate the most recent analysis of the atomic bomb survivor data. As demonstrated in an assessment of the two models prepared by Apostoaei and Trabalka, the models give divergent
predictions for some scenarios of age at exposure, attained age, and smoking. The differences reflect specifications of the underlying models, and also differences in the data used for model estimation. As a reviewer, I have been asked to indicate which model, or models, should be used in estimating probability of causation for compensation under the Energy Employees Occupational Illness Compensation Program Act of 2000 (EEOICPA).

Comments:

In providing comments, I initially offer my evaluation of the most recent analysis of the atomic bomb survivors data carried out by Pierce et al. and reported in Radiation Research in 1993. This analysis included follow-up for the years 1950 – 1994 and was incorporated into the NIH-IREP, while the NIOSH-IREP model is based only on follow-up from 1950 – 1990. With regard to the new analysis by Pierce et al., I have the following comments pertinent to its use in NIH-IREP:

- Pierce et al. note that the dataset has become more informative because of rising relative risks for lung cancer in Japan, likely reflecting patterns of smoking. With colleagues, I have recently prepared an extensive report on smoking and disease risks in Japan. I am attaching information concerning the smoking profile in Japan, which supports the premise, albeit undocumented, of Pierce et al. Of note, a high proportion of Japanese men were smoking following World War II, but the numbers of cigarettes smoked did not reach the current pattern of approximately one pack per day until the late 1960s and early 1970s. While Pierce et al. are correct in regard to rising lung
cancer relative risks, the temporal profile of smoking and its age-birth cohort
dependence complicate interpretation of models with time-dependent factors.

- While extension of the follow-up interval by four years has added further cases, and
  included coverage of a time period with a higher relative risk, the increment to the
  total database in terms of follow-up time and number of cases must be modest. I
  would thus be surprised if there was strong evidence supporting a departure from
  earlier analytic findings.

- The information available on smoking is limited and the manuscript gives only limited
  attention to measurement error in the assessment of smoking and the possibility of age
  and birth-cohort dependent measurement error.

- Pierce et al. recognize that the lung cancer model for smoking is limited, reflecting in
  part data availability. Would inadequate model specification tend to bias assessment
  of effect modification towards additivity?

I have additional comments concerning the general approach of relying primarily on the data
from the atomic bomb survivors.

- Others have commented on uncertainty in extrapolating risk models from the atomic
  bomb survivors to other populations. For lung cancer, there is the particular concern
  of the different pattern of smoking among Japanese males, compared to U.S.
populations exposed to radiation. There is some evidence indicative of lower lung cancer risks at any particular level of smoking among Japanese smokers, compared to U.S. smokers (see attached report).

- There is a larger body of literature on combined effects of smoking with other agents, e.g., asbestos. This evidence was reviewed in the 2004 monograph of the International Agency for Research on Cancer (IARC 2004) with the general conclusion that synergism between smoking and some other agents has been demonstrated for cancer.

**Conclusions and Recommendations:**

The materials provided demonstrate sensitivity of risk predictions to choice of underlying model and to the data from which the models parameters are estimated. Model sensitivity is to be anticipated and is an indication of the uncertainty in the general approach to estimating the probability of causation. In this setting of model uncertainty and the impossibility of selecting one model as “correct”, maintaining the two models seems warranted, particularly to assure that the decision to provide compensation would tend to be inclusive rather than exclusive. I would not weight the finding of the new analysis by Pierce et al. so heavily as to use only the NIH model. My rationale for this view is given in my comments on the paper by Pierce et al.

For these reasons, I favor the retention of both models, with decision-making based on the higher probability of causation. Consideration should be given to updating the NIOSH model using the updated RERF data.