Comments on the radio-epidemiological tables, and the supporting interactive computer program (IREP), developed under the EEPICPA by NIOSH.

Introduction

The 1985 NIH radioepidemiological tables were based on analyses of mortality among atomic bomb survivor data at Hiroshima and Nagasaki. An update was prepared the National Cancer Institute-Centers for Disease Control in May 2000. The primary quantitative basis for these updated radioepidemiological tables is a study of cancer incidence among atomic bomb survivors in Hiroshima and Nagasaki. NIOSH has proposed certain modifications to these updated tables as a basis for determining probability of causation under the EEOICPA.

The order of these comments is as follows: specific comments about assumptions underlying the IREP model; points for clarification in the Technical Documentation; and, lastly, general comments.

Specific Comments

1. Following the approach outlined in NCRP Report no. 126, radiation risk estimates derived from the study of atomic bomb survivors have been modified by applying adjustment factors in order to account for uncertainties in DS86 dose estimates ENRf8(1). The proposed uncertainty distributions for these adjustment factors offer no possibility that gamma or neutron exposure measurement error in DS86 would lead to underestimation of radiation effects (and therefore adjustment for these errors in dosimetry will necessarily de*crease* the probability that a workers cancer was caused by radiation). The IREP model divides estimates of the excess relative risk per unit dose by a factor with a distribution centered around 1.1 in order to account for errors in DS86 gamma dose estimates and by a factor centered around 1.1 in order to account for errors in neutron dose estimates. The radiation risk estimate is therefore diminished; the uncertainty distribution for these factors range from 1.0-1.4, and 1.0-1.3, respectively (that is, there is no possibility that measurement error led to downward bias in estimates). This assumption is not supported by empirical evidence (e.g., ENRf8(2)); furthermore, given the complexities of problems of non-random measurement error in gamma and neutron dose estimates this is not a valid approach to dealing with exposure measurement error in the DS86.

   DS86 doses should be treated as the best estimate of the A-bomb survivors' true doses for the purposes of compensation unless appropriate revisions in dose estimates for A-bomb survivors are produced. Uncertainties in radiation risk estimates due to uncertainties in gamma and neutron doses should be accounted for in calculation of probability of causation by use of a factor centered at unity with an error distribution in which exposure measurement error could lead to inflation or attenuation of risk estimates.

2. While uncertainty and bias in LSS risk estimates due to ascertainment and misclassification of cancer cases is recognized, no account is made of the uncertainty in LSS risk estimates due to selection effects. Several recent studies have concluded that there is evidence that mortality following the bombings of Hiroshima and Nagasaki left a select group of healthy survivors ENRf8(3, 4). There is evidence that selection was dose-related; overall mortality rates, for example, in the first 15 years after the bombing, are negatively associated with dose ENRf8(5). Such a pattern is consistent with a healthy survivor effect in the cohort, and would lead to a downward bias in radiation risk estimates ENRf8(3, 4). It is reasonable to consider that this may be a select group of survivors, and that bias could arise due to this selection. While previous authors have identified the potential for bias and uncertainty to arise due to health-related selection, no allowance has been made for bias that might arise because the LSS study population is unrepresentative due to selection. NIOSH should develop and include a correction factor that at least accounts for uncertainty in the magnitude of estimates derived from the LSS due to selective survival ENRf8(6).

3. The distribution of values for the DDREF (applied to acute doses less than 0.2 Sv and to chronic exposures) is skewed towards unrealistically *large* values. The uncertainty distribution of the DDREF is described as a modified triangular distribution similar to that in NCRP (1997) and described in Kocher et al. (2001). The decision to center this distribution around a value of 2.0 (with the 90^{th} percentile as high as

4.1) is not consistent with current epidemiological literature, nor is it logically consisted with statements in the Technical Document (page 21). The Document notes that the latest A-bomb survivor data (Pierce 2000), which are the quantitative basis for these tables, strongly support a linear over a sub-linear model in the low dose range ENRf8(7). This strongly supports the conclusion that there is no reduction in effectiveness at causing cancer at low doses. ICRP (1991) and NCRP report no 126 were cited as evidence justifying this distribution. The epidemiological evidence in those documents has been largely superceded by more recent analyses of the LSS. Analyses of leukemia among atomic bomb survivors have been interpreted as supporting a DDREF greater than unity, although there is substantial uncertainty in estimates of the excess relative risk for leukemia in the low dose range of the LSS data; and, when broader groups of solid cancers are examined there is strong evidence of linearity. Studies of breast cancer among tuberculosis patients who were exposed to multiple chest fluoroscopies have been considered in evaluations of the effect of fractionation of low-LET radiation doses. There is no evidence in these studies of a reduction in breast cancer risk with protracted exposure ENRf8(8). Some have argued that a lack of a dose-related excess of lung cancer among the tuberculosis patients suggests a DDREF greater than unity for that cause of death ENRf8(9); however, necrosis and surgical removal of lung tissue among tuberculosis patients (related to risk of lung cancer and duration of treatment) precludes any clear interpretation of dose, or dose-rate, effects on lung cancer ENRf8(10, 11). Evidence from studies of chromosomal damage, and animal experimentation (often evaluating non-cancer outcomes), is of less relevance to decisions about the distribution of DDREF values for radiation-induced cancer in humans. In the face of the epidemiological findings of linearity in the atomic bomb survivor study ENRf8(7), which is used as the quantitative basis for the risk estimates in these tables, there is little support for a distribution of DDREF that leads to reduction of radiation risk estimates by a factor of 2 or more for purposes of compensation. Evidence from the LSS supports the use of an uncertainty distribution for DDREF with a central value at 1.0. Since there is the possibility that at low doses (and dose rate) the exposure-response association is super- or supra-linear, such uncertainty should be accounted for by an uncertainty distribution centered around 1.0.

4. The method used to adjust the lung cancer radiation risk estimate for workers who smoked should be re-evaluated. Studies of A-bomb survivors have failed to discriminate between additive and multiplicative interaction models; and, evidence from uranium miner studies may be of limited relevance given the differences between exposures and questions of smoking-effects on lung function. For many occupational exposures, the carcinogenic effect of the exposure among non-smokers is small and would be difficult to detect if the occupational cohort were entirely composed of non-smokers. Therefore, the magnitude of interaction is hard to evaluate. However, for some occupational hazards where attention has been given to this question, for example asbestos exposure, examination of lung cancer-asbestos associations within stratum of smoking status indicate effects are relatively close to multiplicative but may be somewhat greater among non-smokers. Estimates of asbestos effect among non-smokers, while less precise than estimates for smokers, tend to about twice as large as estimates of asbestos effect among smokers (Liddell, 2001). Workers would be given the benefit of the doubt in a situation where the science is unclear, by applying the radiation effect estimates for lung cancer from the LSS cohort (which includes a mixture of smokers, former smokers, and non-smokers) to the US cohort. Uncertainty should be accounted for by adjustment factors for smoking status, allowing that the central value of the adjustment factor for non-smokers may be greater than unity.

5. The examination of age-at-exposure needs to be re-evaluated. The IREP model uses data from Japanese survivors who were exposed to ionizing radiation from very young ages to old age. A linear term is used to describe changes in sensitivity to the effects of ionizing radiation with age-at-exposure (Draft report of the NCI-CDC Working Group, page 29). The young are especially vulnerable to ionizing radiation when compared to adults; consequently, the slope of this age at exposure term tends to negative. However, for issues of workers compensation, we are concerned with variation in sensitivity to the effects of ionizing radiation at adult ages. The slope of the age-at-exposure term may be predominantly influenced by the

relatively high radiosensitivity of children, which is not relevant to the issues under consideration ENRf8(11). Furthermore, for many cancers studied in the LSS (and other cohorts) there is departure from linearity in change with age-at-exposure in radiation effects. The effect of age-at-exposure should be modeled as a categorical term.

Similar to other factors in these analyses for which expert opinion and evidence from the epidemiological literature are used to inform the development of adjustment factors to account for uncertainty, the IREP model should include a factor (which may have a central value of 1.0) that allows for uncertainty in risk estimates with age-at-exposure. Several epidemiological studies of US nuclear workers suggest that among sensitivity to the carcinogenic effects of radiation increases in adulthood with older ages at exposure ENRf8(12-16). This evidence from occupational cohort studies of US nuclear workers raises uncertainty about the transport of risk estimates from the LSS to US nuclear worker populations specifically with respect to variation in radiation effects with age-at-exposure; an adjustment factor should be included to allow for the possibility that there is greater radiosensitivity of nuclear workers to ionizing radiation at older ages-at-exposure.

Points for clarification in the Technical Document

Page 2 – Propose revising the text to read "… is the use of risk models developed from data on cancer incidence rather than cancer mortality among Japanese atomic bomb survivors." Some discussion of the strengths of incidence data should be included (eg., "Incidence data may be superior to mortality data because they offer information on cancers of low or delayed fatality and are based on more detailed diagnostic information than death certificate data.") and some discussion of the limitations of incidence data should be included (e.g, "Estimates of the denominator for the tumor registry data are imprecise and only include A-bomb survivors still residing within the catchment of the tumor registries; and, the potential for bias associated with surveillance may be greater than analyses based on mortality data.")

Page 20 – The document cites an investigation of radiation-CLL association among ankylosing spondylitits patients; only two cases of CLL occurred in that cohort, it is inappropriate to draw any conclusion about the exposure-response association in a cohort with such a minimal power to detect an association.

Page 21 – The document notes that DDREF for low LET radiation differs for leukemia, breast and thyroid cancer. It is not specified how these distributions differ.

While there is great deal of discussion of variation in effect estimates by specific radiation types, there is little discussion about how this will be applied in practice to workers with limited historical radiation dosimetry records.

General Comments

The primary quantitative basis for these updated radioepidemiological tables is the study of atomic bomb survivors. The study of atomic bomb survivors has a number of important strengths to it. It is a study of a large number of people, many of whom had received relatively large doses of radiation, and with follow-up that has continued over a long period of time. However, there are important concerns about the validity of conclusions drawn from this study.

One set of concerns relates to limitations of the A-bomb data. Radiation dose estimates for the survivors are based on questionnaire information about where people were at the time of attack, along with models of radiation shielding. This questionnaire study was conducted under extreme conditions: it was directed by occupying forces, and people were asked to recall information from five or more years previously about a wartime event. Some people did not want admit that they were A-bomb survivors or report how close they were to ground zero, because in Japan at the time there was prejudice against the radiation exposed. The

complexities of radiation shielding within a city raise a whole different set of questions about exposure misclassification-- since slight differences in location, even within a room or in relation to an open window or piece of machinery, led to differences in exposure. Inability to accurately classify people by their level of exposure means that a study will have an inability to accurately estimate the effects of exposure, because people who had high exposures are classified in the low dose group, and vice versa. Under the proposed model, dosimetric errors lead to a reduction in estimates of radiation effects. The overall factor for uncertainty in risk estimates due to dosimetrical uncertainties should have a central value of 1.0 since the direction of bias that will occur in estimates is complex and uncertain at this point; uncertainties in radiation risk estimates due to uncertainties in DS86 should be accounted for by use of an adjustment factor with an error distribution that is not be bounded at unity since exposure measurement error could lead to inflation or attenuation of risk estimates.

There is also concern about selection bias. Prior to the attacks on Hiroshima and Nagasaki, it was estimated that about 580,000 people lived in the two cities. In the first year after the bombing over one hundred thousand people died from the lingering effects of radiation, infectious epidemics, and the destruction of food, housing, and medical services. Five years after the attack, in 1950, this survey of atomic bomb survivors began. A number of studies have concluded that there is convincing evidence that mortality following the bombings of Hiroshima and Nagasaki left a select group of healthy survivors. There is evidence that this selection was dose-related, such that people in the high dose categories were more select than people in lower dose categories. Overall mortality rates, for example, in the first 15 years after the bombing, are negatively associated with dose ENRf8(3). Such a pattern is consistent with a healthy survivor effect in the cohort, and would lead to a downward bias in radiation risk estimates ENRf8(3, 4). It is reasonable to consider that this may be a select group of survivors, and that bias could arise due to this selection. While previous authors have identified the potential for bias and uncertainty to arise due to health-related selection, no allowance has been made for bias that might arise because the LSS study population is unrepresentative due to selection. NIOSH should incorporate a correction factor that accounts for uncertainty in the magnitude of estimates derived from the LSS due to selective survival ENRf8(6).

For the purposes of workers' compensation, radiation effect estimates from the LSS are to be applied to decisions about probability of causation among US nuclear workers. There are important differences in the conditions of exposure: A-bomb survivors received an acute blast of radiation, while in environmental and occupational settings, exposures are typically chronic and low level. As noted in the Specific Comments above, the justification for an adjustment factor (DDREF) with a central value equal to 2.0 is not supported by epidemiological findings from the LSS. There are also significant differences in the types of radiation exposure received by US workers. Discussions of RBE should give greater attention to the paucity of epidemiological data upon which RBE central values and uncertainty distributions are based.

These radiation effect estimates from the LSS are to be applied to US nuclear workers. The population of US workers has substantially different baseline cancer incidence rates than the studied population of Japanese atomic bomb survivors. Since a purely multiplicative RR model was not used in these tables, estimates of baseline US cancer incidence rates were required. As noted in the Limitations section of the technical document, large changes have occurred in cancer incidence rates, and these have not been incorporated in the probability of causation calculations. Therefore there is the possibility that PC is underestimated for some claimants (and overestimated for others). Another issue in applying radiation-cancer effect estimates from the LSS to US nuclear workers is the potential effect of differences in factors other than occupational radiation dose that may modify the radiation exposure-effect. Smoking is considered in these analyses as a factor that may influence the radiation-lung cancer association; and race is discussed as a factor that may influence the radiation-skin cancer association. However, nuclear workers have been exposed to a variety of other agents (solvents, asbestos, silica, etc) that may play a role in carcinogenic processes and lead to modification of radiation-cancer incidence associations. This raises questions about the transfer of risk estimates between populations. Therefore, it is appropriate that NIOSH incorporate a correction factor that accounts for uncertainty in the transfer of risk estimates from the LSS to US nuclear workers. Epidemiological evidence of

increasing radiation-cancer associations with increasing age-at-exposure in US nuclear workers may reflect differences between the LSS population and US nuclear worker populations where cancer initiation occurs due to exposures accrued at earlier ages. Accounting for uncertainty in the transfer of cancer risk estimates from the LSS to US nuclear worker populations by an uncertainty factor that varies with age-at-exposure provides a way for NIOSH to use data from occupational cohort studies of US nuclear workers to inform calculation of probability of causation.

Finally, it should be noted that the exclusion of CLL, while often made in analyses of radiation-cancer associations, is not consistent with the logic spelled out for examining categories of cancer. Whole body exposure to external sources of ionizing radiation is a well-established carcinogen and may lead to all cancers. The choice of cancer types examined was not based on positive dose-response coefficients in the LSS. In the limitation of analyses to rare causes of death, lack of evidence of an association may occur even if true positive association exists. There appears to be inconsistency in the use of cited materials to support this exclusion. For example, in the IARC analyses of US and European nuclear workers, which was cited as an empirical example in which no trend was observed for CLL, it is noteworthy that the coefficient for CLL is similar to the coefficient for ALL, and the upper 90% CI for CLL (ERR/Sv =9.4) is slightly larger than the upper 90% CI for ALL (ERR/Sv =7.3). However, ALL is included in the IREP models while CLL is not.

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