OCAS Meeting Report

4/24/01

Topic: Demonstration/discussion of IREP
Date/Location: April 10, 2001; Cincinnati - NIOSH/Ridge
Attendees (Affiliation):

Larry Elliott; Greg Lotz, Jim Neton, Mary Schubauer-Berigan, Randy Smith, Ted Katz (NIOSH)
Owen Hoffman, Brian Thomas (SENES)
Cynthia Lane, Roberta Mosier (DOL)

General summary: SENES provided an overview of the IREP program, which included demonstrations of IREP using hypothetical cases. The group discussed the technical basis of IREP (how various forms of ionizing radiation, different cancers, and other variables are handled; the statistical/analytic methods employed in the underlying models) and a variety of practical issues for adapting IREP to accommodate potential needs of DOL & NIOSH (e.g., changes in the underlying PC models, types of data, approaches to data entry, and development of the web-based version). A general recommendation by SENES with respect to guidelines for POC is to ensure flexibility in the application of IREP to borderline cases, for which special attention to default values of certain variables might be warranted. A general finding by NIOSH is that we may need to fund a formal process to validate the accuracy/reliability of IREP.

Specific findings

Web-based system: SENES is in the process of translating IREP from a PC to a Web-based application. SENES is incorporating all functionality (e.g., sensitivity analyses) and increasing online documentation.

Data entry: (1) NIOSH found the system for dose data entry time consuming and labor intensive, particularly for use with DOE populations who have a high frequency of doses and for whom dose distributions may be used. SENES agreed that IREP could and should be modified to permit entry of dose information in file format and the use of a copy/paste function.

(2) Beta radiation and X-rays are entered as Low LET.

(3) To facilitate data entry and reduce errors, NIOSH suggested the cancer menu should be modified to provide ICD codes and list cancers in ICD code order.

IREP PC Reports: NIOSH needs to evaluate the adequacy of the current IREP report format to adequately document each IREP analysis. IREP output should include all parameters necessary to reconstruct the analysis, including input and default parameters, and the version of the software used. A signature and date line for the performing and reviewing individuals should also be included. This reporting mode could be integrated as a setup option in IREP to be used for official, final analyses and for evaluations of the DOL PC program (e.g., for quality control).

Dose-response assumptions: IREP uses a linear dose-response assumption in the epidemiologic

models for all neoplasms except leukemia (which was modeled as linear-quadratic). However, the shape of the dose-response curve is modified by the use of the "dose and dose-rate effectiveness factor" (DDREF)," which adjusts the dose response curve (in the dose region of importance to most DOE workers) to an expected value that is linear-quadratic, even for acute exposures. This adjustment for "low acute dose" has not been adopted by NCRP, although it has by ICRP and the U.S. EPA (see Fry, R.J.M. 2000. "Dose-rate effects and radiation protection." Radiat. Res. 154(6):735-736.). The 1985 radioepidemiologic tables also used a linear-quadratic model for leukemia and all solid tumors except breast and thyroid, for which a strictly linear dose-response was assumed. There is no justification for this dose adjustment for acute exposures of the breast and thyroid. SENES will clarify whether or not the "low acute dose" adjustment has been applied to these sites.

Use of multiple epi data sets in modeling: SENES suggested NIOSH consider weighting different epidemiologic data sets in a risk model if there is uncertainty in the selection of a fully optimal data set for modeling.

Selection of models where alternatives are incorporated in IREP (e.g., leukemia): Discussion clarified the need for NIOSH consider when to apply dose-risk information from general diagnoses, if epidemiologic information on specific diagnoses is sparse. For example, the IREP model for the class of "all leukemias except CLL" differs from the models of its individual components: acute lymphocytic, acute myelogenous, and chronic myelogenous. The general diagnosis adjusts for age at exposure, while the specific diagnoses do not – possibly because of sparseness of data after stratification by subtype. Because age-at-exposure is an important factor for leukemias, the PC estimates can differ substantially for the general vs. site-specific models. Results of simulations suggest that those exposed at young ages would benefit more from a "general leukemia" model, and those exposed at older ages may benefit more from a site-specific leukemia model.

Alternatively, to improve the models of leukemia subtypes, an improved model could incorporate "expert judgment" about risk modifiers for the leukemia subtypes.

The changing background incidence of cancers: SENES will review how this is presently addressed by IREP. This requires follow-up. Secular changes and ethnic/racial differences could be incorporated into IREP, if warranted, but substantial developmental work might be required.

Time as a factor: IREP only addresses time-since-exposure and age-at-exposure for leukemia,. Attained age or age at exposure is modeled for colon, kidney, stomach, liver, thyroid, and female breast cancers.

Radon: Incorporating the radon-lung cancer models from BEIR VI in IREP is not technically difficult, but developing the epidemiologic models would require consultation with experts (e.g., Jay Lubin, Rick Hornung), and sufficient time for implementation.

RBEs: (1) NIOSH needs to review default values: e.g., alpha irradiation of red bone marrow – assumed REB of 20 was not used. The RBE for alpha irradiation of the lung is greater than 20. The following publication was cited as the basis for these decisions:

> Grogan, HA, Sinclair WK, VoillequePG. Assessing Risks from Exposure to Plutonium. Final Report. Part of Task 3: Independent Analysis of Exposure, Dose and Health Risk to Offsite Individuals. Radiological Assessment Corporation (RAC) Report no. 5, 1999.

NIOSH should assess the applicability of these findings to the DOE workforce.

(2) NIOSH recommended SENES consider modifying the IREP program to accept exposure inputs in units of absorbed dose (Gray), requiring the user to select the RBE of the radiation type. Alternatively, ensure the user is prompted to examine the default RBE value, and has the ability to change it as appropriate.

(3) If dose from required medical x-rays were included in POC, NIOSH would need to incorporate a separate RBE distribution for "soft" x-rays (e.g., photofluorography).

DDREF: (1) Ethel Gilbert developed this element of IREP. SENES questions whether DDREF should ever take a value greater than 1. DDREF equal to one was assumed for high LET radiation (neutrons and alpha particles) – but this is not explictly stated in the relevant documentation.

(2) The current IREP program does not account for an inverse dose-rate effect for high LET radiation. SENES was not planning to add this to IREP (it doesn't relate to veteran exposures), but this could readily be changed in IREP if appropriate for DOE workers. This issue would require scientific development and review.

(3) DDREF is (appropriately) not applied to cases of leukemia.

Acute vs. Chronic Exposures: Due to the DDREF applied to low LET radiation, the specification of acute or chronic exposures can substantially influence the IREP PC result for solid tumors – the characterization as acute exposures producing higher PCs. (SENES considers exposures received over days or longer to be chronic. NIOSH is likely to receive annual summary data for the external doses of many workers, without the ability to document whether exposures were acute or chronic.)

IREP needs testing and validation for this variable. A test case of leukemia, which doesn't employ DDREF, produced substantially different PC results (7.7% higher PC) depending on the selection of acute (1 year) vs. chronic dose, whereas the results should have been identical.

Latency Adjustment Factors: (1) IREP uses latency adjustment factors that are tumor specific. For solid tumors, the ERR is zero or nearly zero for times after exposure until approximately

eight years. NIOSH needs to evaluate these factors.

(2) DOL should consider using these factors as a potential screening tool, eliminating unnecessary dose reconstructions.

Scale Factor: SENES suggested this might warrant special attention – with respect to the appropriateness of the default value – on borderline cases (e.g., 48-52% PC). NCI is currently adopting a GSD of one for the scale factor, as recommended by the National Research Council review panel. This will reduce the probability of causation calculation for claimants.

Dose Variability: This appears not to contribute substantially to PC determinations for certain diseases (e.g., multiple myeloma). Its effects appear to be swamped by other sources of variation.

SENES recommended the following scientific consultants: Duncan Thomas, Ethel Gilbert, Dan Stramm, Roy Shore, Charles Land, Keith Eckerman (Oak Ridge internal dose expert).