# The Application of Dose Reconstruction Results to NIOSH-IREP (NIOSH's Version of the Interactive Radio-Epidemiological Program) in Estimating the Probability of Causation of Radiogenic Cancer

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# What is NIOSH-IREP?

- Computerized application of the 1985 radio-epidemiological tables, as updated by NCI
- Based on NCI methods and risk models, modified by NIOSH to fit exposures and risks of EEOICPA-covered workforce
- Two different versions of IREP - NIOSH and NCI versions are similar but not identical

# What is NIOSH-IREP? (Con't.)

- Web-based interactive software program
- NIOSH version is freely available to public; requires no password
- Calculates probability that a worker's cancer was caused by on-the-job exposure to ionizing radiation
- Created for NIOSH by SENES Oak Ridge, Inc. to implement "Probability of Causation" guidelines

# Probability of Causation (PC)

- Procedures outlined in 42 CFR Part 81 ("Guidelines for Determining the Probability of Causation…")
- Reflects "as likely as not" statutory requirement; PC must be ≥ 50% (at upper 99% credibility limit)
- Methods designed to err on the side of claimants
- Incorporation of uncertainty factors
- PC guidelines/results are not intended to impact radiation protection standards

# More on PC

- Derived from epidemiological concept called "assigned share"
  - sometimes referred to as "attributable risk" or "attributable fraction"
- Traditionally applied to populations, not individuals
- Refers to the proportion of disease in a population caused by the exposure of interest

# The 5 Determinants of PC

1. Cancer risk models
2. Radiation dose
3. Dose response factors
4. Personal characteristics
5. Uncertainty factors

- Inputs may be entered manually, or uploaded via an Excel spreadsheet (template available online)

# Cancer Risk Models in NIOSH-IREP

- Risk coefficients derived from cancer incidence
- Based primarily on the Japanese Life Span Studies (A-Bomb survivors), adjusted for U.S. workers
- Modified by individual risk, based on reconstructed dose and personal attributes unique to each claim

# Cancer Risk Models (Con't.)

- 32 separate cancer risk models in NIOSH-IREP
- Some cancers require running more than 1 IREP model
- Each model falls into 1 of 4 broad groups
- ERR/Sv for each group has an uncertainty based on statistical analysis of epidemiological data

# Cancer Groups in NIOSH-IREP

- Group 1: includes liver, breast, & others
  - ERR/Sv depends on both age at exposure and age at diagnosis
  - Cancers in this group are of relatively high incidence
- Group 2: lymphoma, bladder, & others
  - ERR/Sv similar to Group 1, but with more "uncertainty" factored in
  - Cancers in this group are of relatively low incidence

# Cancer Groups (Con't.)

- Group 3: lung (except from radon exposure) & female genitalia (excluding ovary)
  - ERR/Sv not dependent on age
  - Uncertainty considered constant at all ages

- Group 4: lung (from radon exposure), skin, thyroid, leukemia
  - Each cancer in this group has a unique risk model

# Dose Inputs (Except Radon)

- Year of exposure
- Radiation type (and energy range)
  - Electrons (<15 keV, >15 keV)
  - Photons (<30 keV, 30-250 keV, >250 keV)
  - Neutrons (<10 keV, 10-100 keV, 100 keV-2 MeV, 2-20 MeV, >20 MeV)
  - alpha

# Dose Inputs - Non-Radon (Con't.)

- Radiation rate
  - acute or chronic
- Exposure distribution and dose (in cSv)
  - Can be a point estimate or a probability distribution
  - Choices are normal, log-normal, triangular, log-triangular, uniform, log-uniform, constant
  - Choice of distribution depends on "best fit"

# Dose Inputs (Radon Only)

- Radon exposures apply only to lung cancer (lung model includes trachea and bronchus)
- Risk model based on studies of uranium miners

<u>Inputs:</u>

- Year of exposure
- Exposure distribution and dose
  - Dose entered in Working Level Months (WLM)
  - Distributions: Same as non-radon exposures

# Dose Response Factors

- Japanese cohort exposed primarily to high doses of gamma radiation at high dose rates
- U.S. workers exposed mainly to low doses at low dose rates
- Background cancer incidence in U.S. is different than Japan, and varies by cancer site

# Dose Response Factors (Con't.)

Japanese cancer risk "transferred" to U.S. workers

- Adjustment for varying background cancer rates
- Use of "dose and dose rate effectiveness factor" (DDREF)

- Use of radiation effectiveness factors (REFs)
  - Purpose is to model the biological effectiveness of different radiation types in causing cancer
  - Developed by Kocher, et. al., under contract with NIOSH

# Personal Characteristics Required for NIOSH-IREP

- Gender
- Year of birth
- Year of cancer diagnosis
- Type of cancer (primary organ site, ICD-9 code)
  - Determines correct IREP cancer model to run, based on tables in *NIOSH-IREP Technical Documentation*
- Smoking history, if lung cancer
- Ethnicity, if skin cancer

# Uncertainty Factors

- Statistical uncertainties associated with epidemiological studies
  - measurement error, response bias, possible effects of confounding variables, etc.
- Uncertainty of radiation exposures
- Uncertainties of dose-response assumptions
- Uncertainty in transfer of risk from exposed populations to target population

# Effect of Uncertainty on PC

- Uncertainty is built into nearly every part of the process of estimating causation
  - Uncertainty distributions used in dose reconstruction, cancer risk models, etc.
  - Distributions "sampled" via Monte Carlo simulations
- "Credibility limits" are placed around the point estimate; upper 99$^{th}$ percentile determines PC
- Uncertainty is often the major contributor to PC

# Credibility Limits in Action

- Example:
  - Male exposed to 3 rem at age 40 (electrons, E<15keV)
  - Diagnosed with leukemia at age 50
- Best estimate of PC is 27% (before placing credibility limits around the point estimate)
- Apply credibility limits
- PC at upper 99$^{th}$ percentile credibility limit = 54%

# Examples of PC Results for Acute Exposure to Photons (E<30 keV)

IREP Inputs (Applies to next 7 slides)

- Gender = Male (female for breast, ovary, female genitalia)
- Age at exposure = 20
- Age at diagnosis = 35
- Smoking status = Never smoked
- Ethnicity = White, non-Hispanic
- Simulation sample size = 2,000
- Random seed number = 99

# Compensable at Dose of 3 cSv*

| NIOSH-IREP Cancer Model | PC |
|---|---|
| Liver | 62% |
| Leukemia, excl. CLL | 61% |
| Malignant melanoma; Non-melanoma skin-Basil cell | 56% |
| Thyroid; Gallbladder | 53% |
| Acute myeloid leukemia; chronic myeloid leukemia | 50% |
| **Acute exp to photons (E<30 keV) at age 20; diag at age 35; male; white non-Hisp; never smoked* | |


# Compensable at Dose of 5 cSv*

| NIOSH-IREP Cancer Model | PC |
|---|---|
| Acute lymphocytic leukemia | 53% |
| Stomach | 51% |
| **Acute exp to photons (E<30 keV) at age 20; diag at age 35; male; white non-Hisp; never smoked* | |

# Compensable at Dose of 10 cSv*

| NIOSH-IREP Cancer Model | PC |
|---|---|
| Colon; Esophagus | 64% |
| Ovary | 62% |
| Urinary organs, excl. bladder | 60% |
| Other endocrine glands; Breast | 59% |
| Bladder | 58% |

**Acute exp to photons (E<30 keV) at age 20; diag at age 35; male (except Ovary & Breast); white non-Hisp; never smoked*

# Compensable at 10 cSv* (Con't.)

| NIOSH-IREP Cancer Model | PC |
|---|---|
| Bone | 58% |
| Eye | 57% |
| Connective tissue; Other and ill-defined sites | 56% |
| Lymphoma & multiple myeloma; All digestive; All male genitalia | 50% |

**Acute exp to photons (E<30 keV) at age 20; diag at age 35; male; white non-Hisp; never smoked*

# Compensable at Dose of 15 cSv*

| NIOSH-IREP Cancer Model | PC |
|---|---|
| Lung | 57% |
| Pancreas | 51% |
| Oral cavity and pharynx; Nervous system | 50% |
| **Acute exp to photons (E<30 keV) at age 20; diag at age 35; male; white non-Hisp; never smoked* | |

# Compensable at Dose of 20 cSv*

| NIOSH-IREP Cancer Model | PC |
|---|---|
| Other respiratory | 53% |
| Rectum | 51% |
| **Acute exp to photons (E<30 keV) at age 20; diag at age 35; male; white non-Hisp; never smoked* | |

# Not Compensable Even at 60 cSv*

| NIOSH-IREP Cancer Model | PC |
|---|---|
| Non-melanoma skin-squamous cell | 39% |
| Female genitalia, excl. ovary | 9% |
| **Acute exp to photons (E<30 keV) at age 20; diag at age 35; male (except Female genitalia); white non-Hisp; never smoked* | |

# How to Access NIOSH-IREP

- Linked to NIOSH/OCAS Web page
- Navigate to:

  http://www.cdc.gov/niosh/ocas/ocasirep.html
- Click on NIOSH-IREP
- Links also provided to *NIOSH-IREP Technical Documentation*, *NIOSH-IREP User's Guide*, & related material