Utility of NIOSH-IREP for Evaluating Probability of Disease Causation for McMurdo Station Veterans

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Interactive RadioEpidemiological Program (IREP) is an online computer code

- Estimate uncertainty in Excess Relative Risk (ERR)
  - For an individual diagnosed with cancer and formerly exposed to radiation
  - Given either a point estimate or an uncertain estimate of absorbed organ dose
- Estimate uncertainty in the Probability of Causation, more correctly known as "Assigned Share", (PC/AS)
  - The fraction of the total cases of disease in excess of the expected baseline cases of disease, is "assigned" to each individual in the subgroup diagnosed with disease
  - The total cases of disease are for a subgroup of like individuals exposed at the same dose

PC/AS is merely an arithmetic transformation from the excess relative risk (ERR)

$$PC/AS = \frac{ERR}{ERR + 1}$$

$$ERR = \left[\frac{R + B}{B}\right] - 1 = R/B$$

- Whereby, R is the excess risk from radiation, B is the baseline risk to an unexposed population of individuals (with attributes of age and sex similar to the exposed person).
- [R + B/B] is the relative risk (RR), ERR = RR-1, and ERR + 1 = RR; thus, PC/AS = ERR/RR
- PC/AS varies between 0 and 1.0, ERR may be <0 or >1.0

IREP is a substantial, but interim, 2003 update of the 1985 NIH Radioepidemiological Tables

- Authors
  - Charles E. Land and Ethel S. Gilbert , National Cancer Institute (NCI)
  - A. Iulian Apostoaei, Brian Thomas, David C. Kocher, and F. Owen Hoffman of SENES Oak Ridge, Inc.,
  - Mary Schubauer-Berigan, Russell W. Henshaw, and Daniel O. Stancescu of NIOSH.
- Two versions online
  - NIH-IREP https://www.irep.nci.nih.gov/irep/
  - NIOSH -IREP http:www.niosh-irep.com/irep_niosh/

ESSENTIAL FEATURES OF IREP

[1] Intended as state-of-the-art tool to provide unbiased estimates of ERR and PC/AS

[2] Accounts for uncertainties to represent state of knowledge in estimating ERR and PC/AS for any exposure situation

Calculates probability distributions of ERR and PC/AS to represent uncertainty

Accounts for some uncertainties not considered in other risk assessments (i.e., BEIR VII, EPA, ICRP, UNSCEAR)

Problem

- To what extent can NIOSH-IREP reliably quantify the probability of causation/assigned share (PC/AS)
  - For a veteran diagnosed with cancer who was formerly exposed to radiation while working in McMurdo Station?
- Radiogenic cancer risk coefficients in NIOSH-IREP mostly originate from the 1994 epidemiological evaluation of cancer incidence within the LSS cohort of Japan.
  - The LSS cohort composed of Japanese survivors of US atomic bombings of Hiroshima and Nagasaki.
- Radiation exposures to veterans at McMurdo Station fundamentally different than acute exposures received by the LSS cohort.

BASIC ELEMENTS OF CALCULATION OF ERR AND PC/AS

[1] ERRs for all potentially radiogenic cancers estimated from epidemiologic studies

[2] Application of ERRs from epidemiological studies (mostly LSS cohort of Japan) to exposure conditions for specific individual with diagnosed cancer

Generally requires several adjustments

[3] Evaluation of uncertainties in both components and in absorbed organ dose (specified as probability distributions) to represent state of knowledge in ERR and PC/AS

Adjustments in IREP to estimate ERR and PC/AS for veterans diagnosed with cancer

- Differences in baseline risk between Japan and the US population
- Extrapolation from acute exposure to exposures received at low doses and low dose rates
- Bias in risk estimates resulting from random and systematic uncertainty in 1985 LSS dose estimates
- Exposure to radiation types other than high energy gamma
- Risk reduction and uncertainty due to minimum latency
- Effect of smoking on radiogenic risk of lung cancer
- Ethnicity affecting the baseline risk for radiogenic skin cancer

USE OF PC/AS IN U.S. COMPENSATION PROGRAMS

- Compensation awarded when
  - Upper 99th percentile of probability distribution of uncertain PC/AS ≥ 0.5 (50%)
- PC/AS ≥ 50% means –
  - risk due to radiation (R) ≥ baseline risk (B)
  - ERR ≥ 1.0
- Upper 99th percentile of PC/AS ≥ 0.5 means
  - At least a 1 % chance that baseline risk of cancer is at least doubled

Application of PC/AS in U.S. Compensation Programs

[1] PC/AS ≥ 50% – "At least as likely as not" that individual's cancer was caused by radiation (Subpart B of EEOICPA)

- Important assumption: Radiogenic cancer initiation functions independently from other (baseline) causes, without affecting rates of baseline cases

[2] Use of upper 99th percentile of PC/AS ≥ 50% to decide compensation

- Provides "benefit of the doubt to the claimant" in the presence of uncertainty (under Subpart B of EEOICPA)
- DOL definition of "substantial contributing factor" (Subpart E of EEOICPA)

Is Calculation of PC/AS Biased?

- In IREP modeling of risk, bias not intended
- Bias introduced via policy decisions
  - Present in “high-sided” dose estimation
  - Decision to use upper 99th percentile of uncertain PC/AS for the award of claims
- Use the most favorable outcomes among multiple models for lung and leukemia (NIOSH-IREP)
- Assumption of statistical independence for multiple primary cancers (NIOSH-IREP)

Bias Introduced via Policy

- Inclusion of cancer sites for which epidemiological evidence is inconclusive
  - i.e., bone, CLL, all male genitalia, malignant melanoma
  - For other organs and cancer sites, the full range of uncertainty in the ERR/Gy is taken into account
    - Negative values of ERR are set to zero when calculating PC/AS

IREP Needs to be Updated

- To account for advances in the state of knowledge about radiogenic cancer since 2003
  - Discussed further in following slides on “Limitations of IREP”
- Interim adjustments to IREP estimation of PC/AS can be implemented via the “user justifiable uncertainty factor”
  - This factor, although in IREP, is yet to be activated by NIOSH, DOL, or VA

LIMITATIONS OF IREP (1)

[1] Dependencies of ERR on dose (or WLM for radon) assumed to be correct

- No uncertainty to account for plausible alternatives (model uncertainty)

[2] Combining data for several cancer types may underestimate uncertainties in ERRs for specific cancers (precision vs accuracy)

LIMITATIONS OF IREP (2)

[3] Dependence of ERRs on *age at time of exposure, attained age, and time since exposure* assumed to be correct

- No uncertainty to account for plausible alternatives (e.g., assumptions used by others)

[4] Modeled ERRs in LSS cohort now outdated

- Effects of updated cancer incidence data and DS02 probably small for many cancers

[5] Uncertainties in modeled ERRs due to different definitions of exposed and unexposed LSS cohorts not considered (should be small)

LIMITATIONS OF IREP (3)

[6] Modeling of ERRs for thyroid cancer

- Modeled ERRs in adult males tend to be higher than RERF estimates for LSS cohort
- No accounting of uncertainty in assuming DDREF = REF for fractionated x rays

[7] Treatment of minimum latency period

- Representation of adjustment vs. *t* and uncertainty based largely on judgment
- Recent analyses suggest nominal period for most solid cancers should be reduced

LIMITATIONS OF IREP (4)

[8] Modeling of risk transfer

- Substantial changes in baseline risks of many cancers in LSS cohort and U.S. population over past two decades not accounted for
- Modeled using age-averaged baseline risks; may misrepresent $(ERR)_{US}$ and uncertainty to extent that B_{LSS}/B_{US} is age-specific
- Differences in baseline risks in different races or ethnic groups in U.S. not accounted for (except skin cancer)

LIMITATIONS OF IREP (5)

[9] Lung cancer in females due to radon

- Modeled ERRs in male miners assumed to apply to females
- In LSS cohort, ERRs in females about factor of 5 higher than in males (RERF)

[10] Effects of smoking

- Interaction with radiation for lung cancer only
- Interaction plausible at other sites (e.g., oral and nasal cavities, stomach); could reduce ERRs due to radiation

LIMITATIONS OF IREP (6)

[11] Probability distributions of DDREF

Data in humans suggest mean DDREF closer to 1.0, substantial probability < 1.0

- Weight given to DDREF < 1 often important in estimating 99th %-tile of ERR and PC/AS

[12] Correlations of uncertain doses from multiple exposures not considered

- (e.g., annual doses from intakes of long-lived radionuclides)

IMPORTANCE OF LIMITATIONS OF IREP

Limitations do not imply that IREP is seriously flawed or claimants are treated unfairly

- Most limitations not addressed in other cancer risk assessments (e.g., BEIR, EPA, NCI, RERF, UNSCEAR, ICRP, NCRP, IARC)
- Need to update modeled ERRs for specific cancers in LSS cohort; other revisions should be considered
  - (e.g., minimum latency periods, DDREF, REFs for lower-energy photons)

Conclusions

- IREP is applicable to the evaluation of cancers in military veterans
  - Including those who formerly worked at McMurdo Station
- Biases in application of IREP mostly due to administrative policies designed to give claimants the “benefit of the doubt”
- IREP needs updating to account for advances in the state of knowledge since 2003
- Consider IREP “user justifiable uncertainty factor” as an interim solution

Personal Suggestion

- Currently award of a claim highly influenced by the presence of uncertainty in estimate of PC/AS.
- Consider alternatives to a threshold value of PC/AS of 0.5 to determine the merit of a claim
  - Arithmetic mean value of ERR to determine a central estimate of PC/AS
  - Threshold value of PC/AS of, say, 0.1 or 0.2 to define "substantial contributing factor"
- Consider a double standard
  - Arithmetic mean estimate of ERR and a lower threshold of PC/AS to define "substantial contributing factor"
  - Upper 99th percentile of PC/AS at a threshold value of 0.5

Supplemental slides

BASIC ASSUMPTIONS IN IREP ABOUT RISKS DUE TO RADIATION

[1] All cancer types, except as noted below

ERR is linear function of absorbed dose –

$$ERR = \alpha D$$

[2] All types of leukemia (excluding CLL), acute exposure to low-LET radiation only

ERR is linear-quadratic function of dose –

$$ERR = \alpha D + \beta D^2$$

In IREP, $\alpha = \beta$ and $ERR = \alpha(D + D^2)$

EXAMPLES OF ERRs IN IREP (1)

Statistical uncertainties in modeled ERRs

[1] Liver cancer – Larger number of cancers in LSS cohort; cancer-specific effects of *e, a*

[2] Colon cancer – Smaller number of cancers in LSS cohort; effects of *e* and *a* based on data for most solid cancers combined

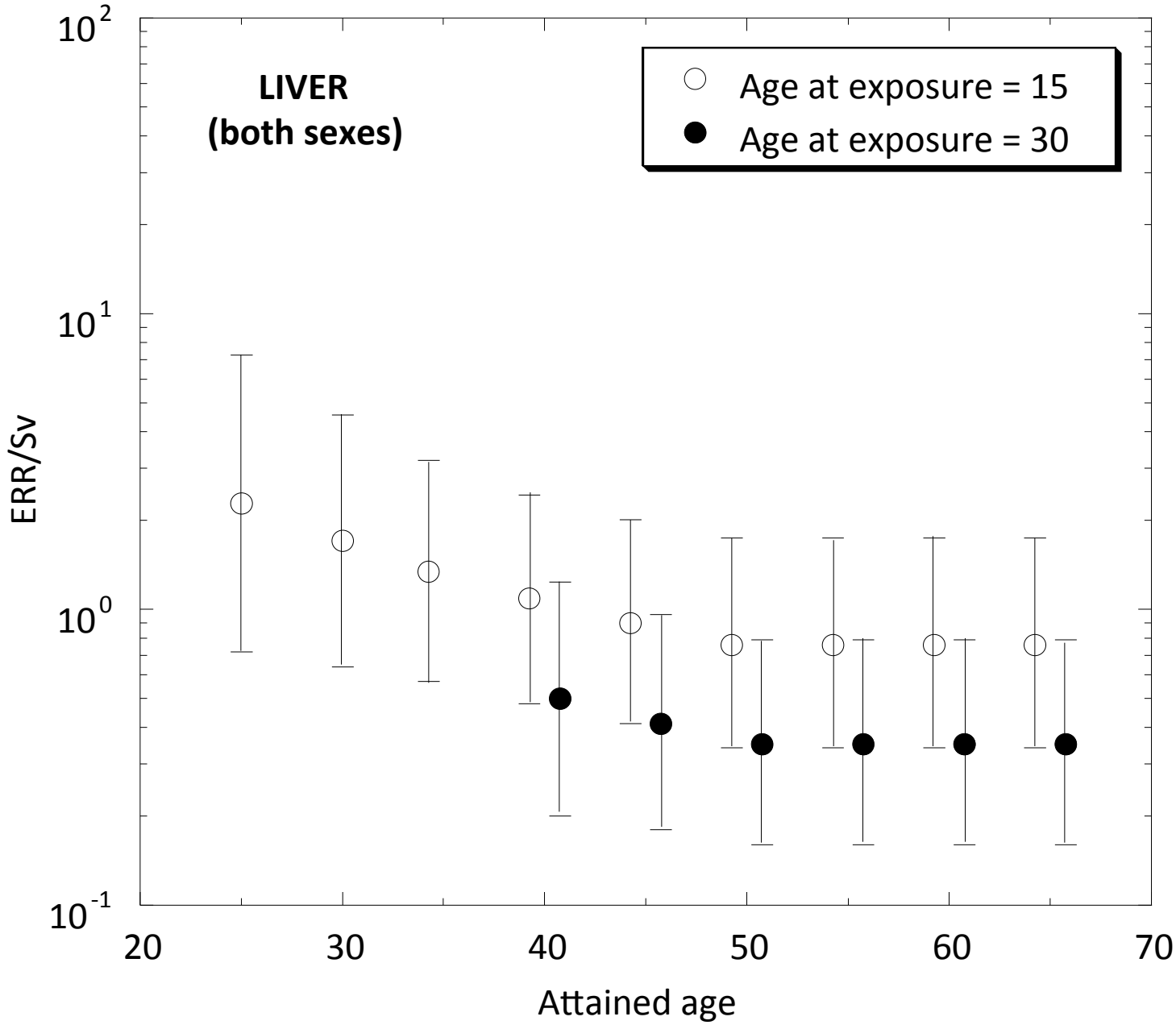
EXAMPLES OF ERRs IN IREP (2)

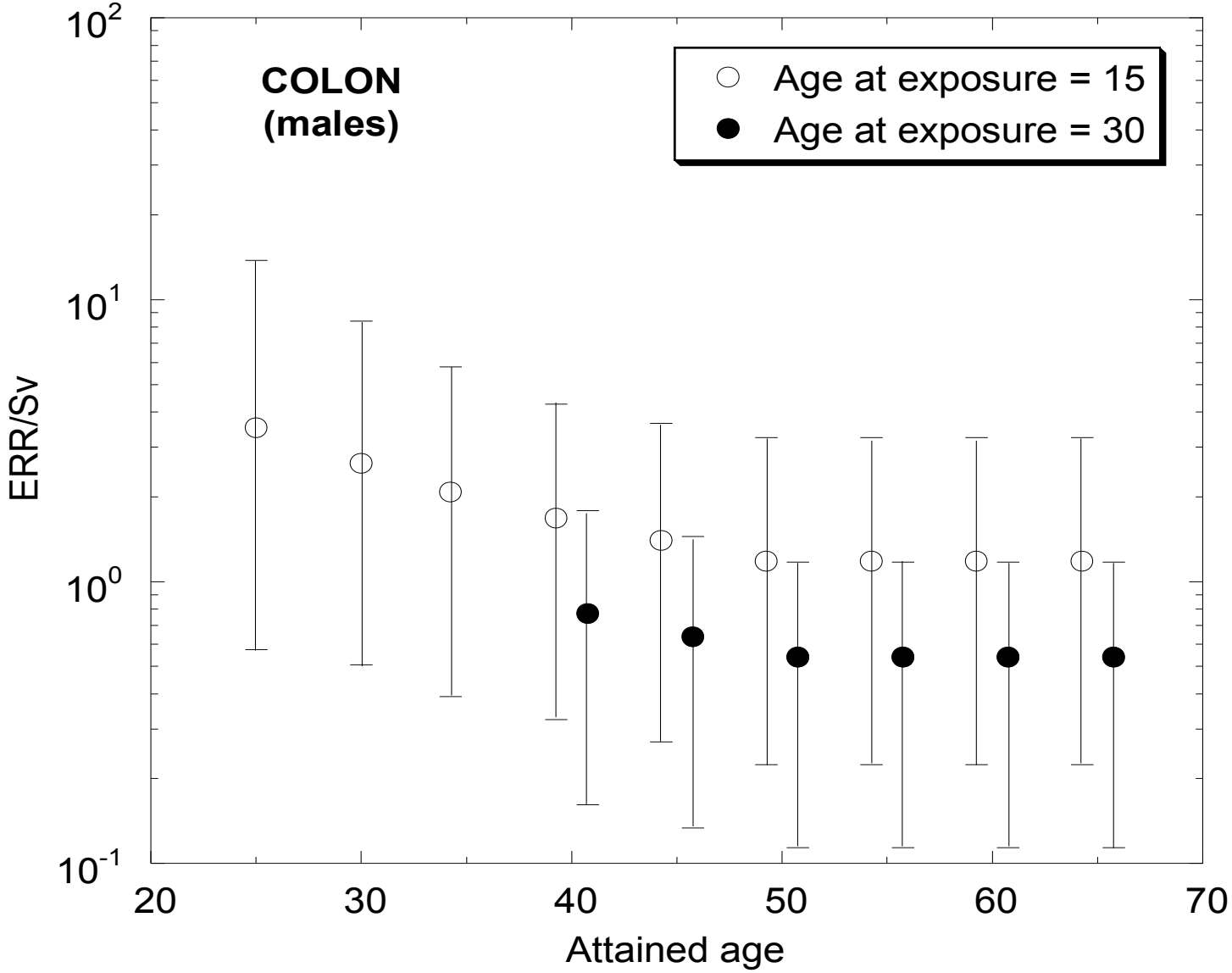
Statistical uncertainties (con't)

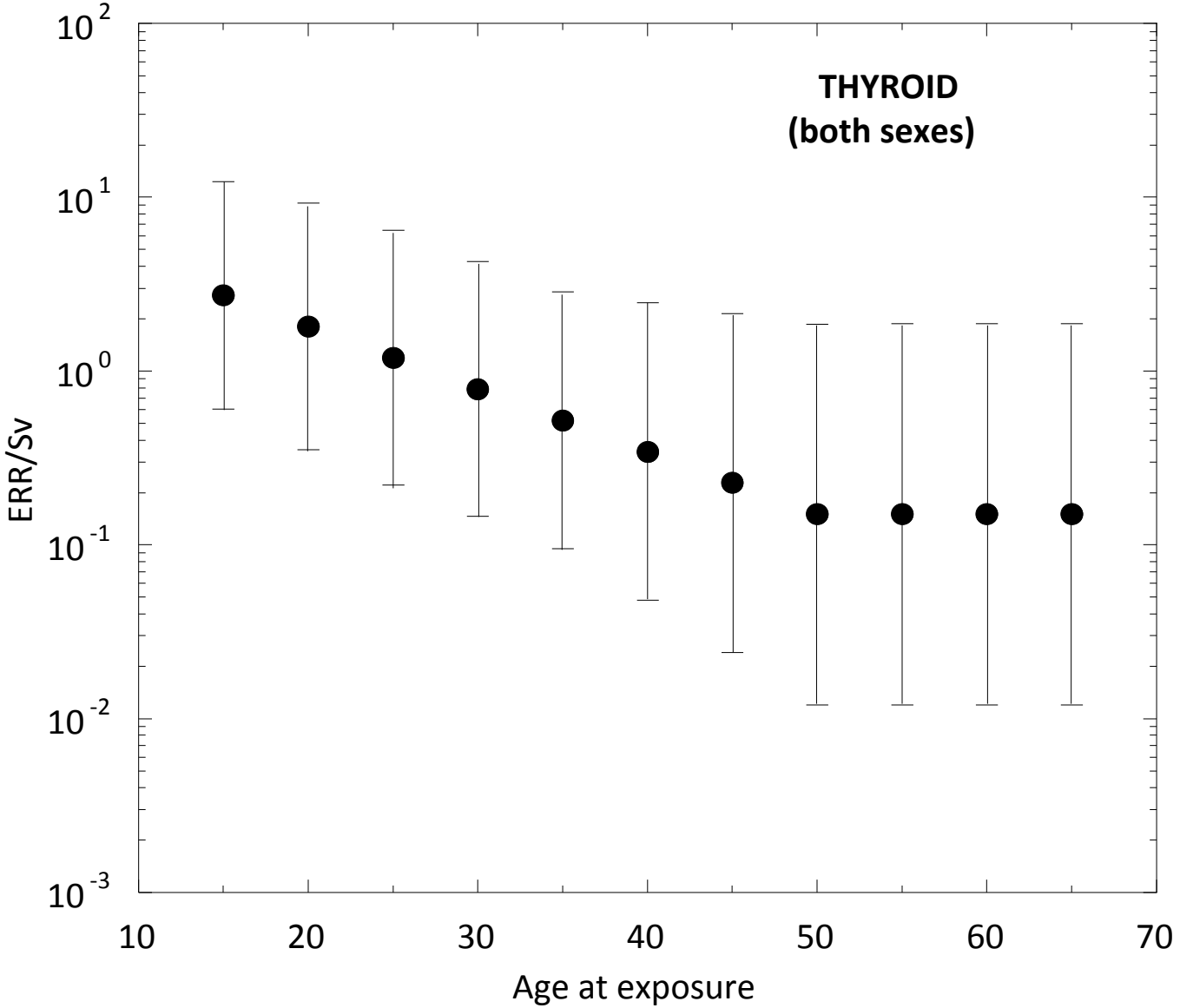
[3] Prostate cancer – Based on data for all male genitalia (few cancers other than prostate); other assumptions same as for colon cancer

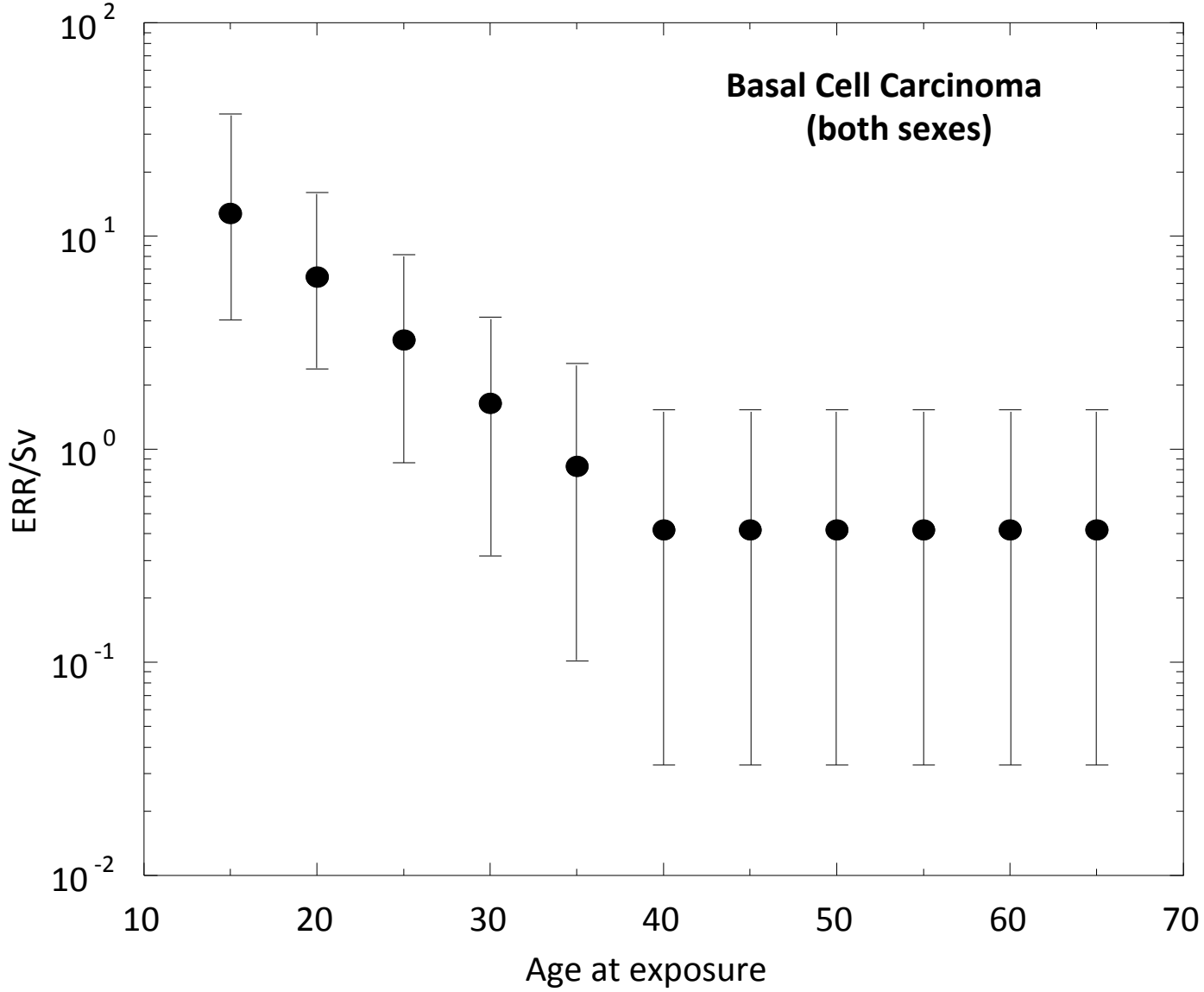
[4] Thyroid cancer, basal cell carcinoma – Unique risk models; dependence on *e* only

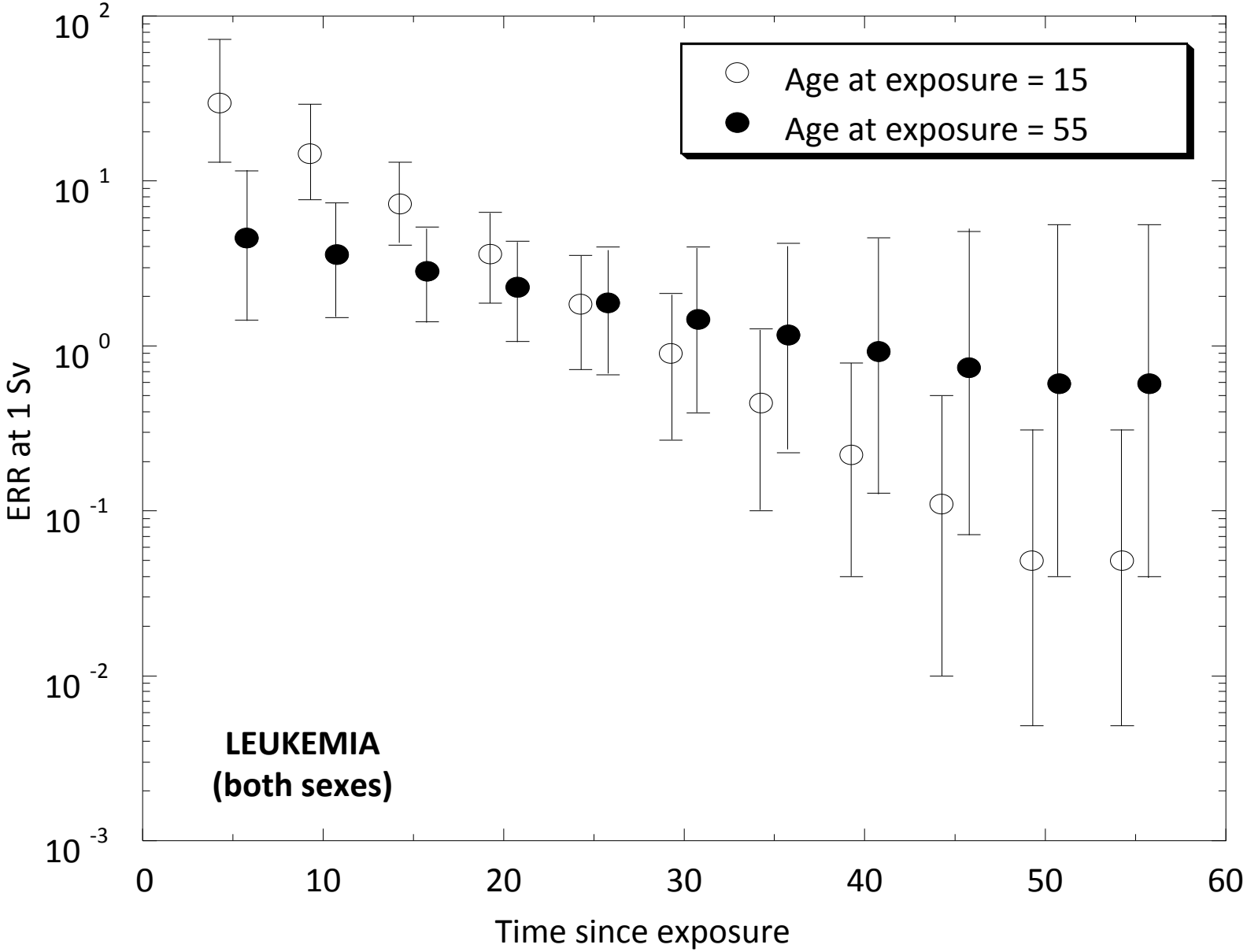
[5] All leukemias combined (except CLL) – Unique risk model; dependence on *e* and *t* (including dependence on $e \times t$)


LIVER
(both sexes)
Age at exposure = 15
Age at exposure = 30
ERR/Sv
10^2
10^1
10^0
10^{-1}
20
30
40
50
60
70
Attained age


COLON
(males)
Age at exposure = 15
Age at exposure = 30
ERR/Sv
10^2
10^1
10^0
10^{-1}
20
30
40
50
60
70
Attained age


THYROID
(both sexes)
ERR/Sv
10 2
10 1
10 0
10 -1
10 -2
10 -3
10
20
30
40
50
60
70
Age at exposure


Basal Cell Carcinoma
(both sexes)
ERR/Sv
10^{2}
10^{1}
10^{0}
10^{-1}
10^{-2}
10
20
30
40
50
60
70
Age at exposure


Age at exposure = 15
Age at exposure = 55
ERR at 1 Sv
10 2
10 1
10 0
10 -1
10 -2
10 -3
0
10
20
30
40
50
60
Time since exposure
LEUKEMIA
(both sexes)

INPUTS TO IREP FOR SKIN OR LUNG CANCER

[1] Skin cancer – race or ethnic group

Baseline rates for specific groups in U.S. used in modeling transfer of ERRs in LSS cohort to U.S. population

[2] Lung cancer – smoking category

Category based on history and intensity of cigarette use

Different categories for lung cancer due to radon and all other exposures

MINIMUM LATENCY PERIOD

Time delay between exposure and earliest observed increase in risk

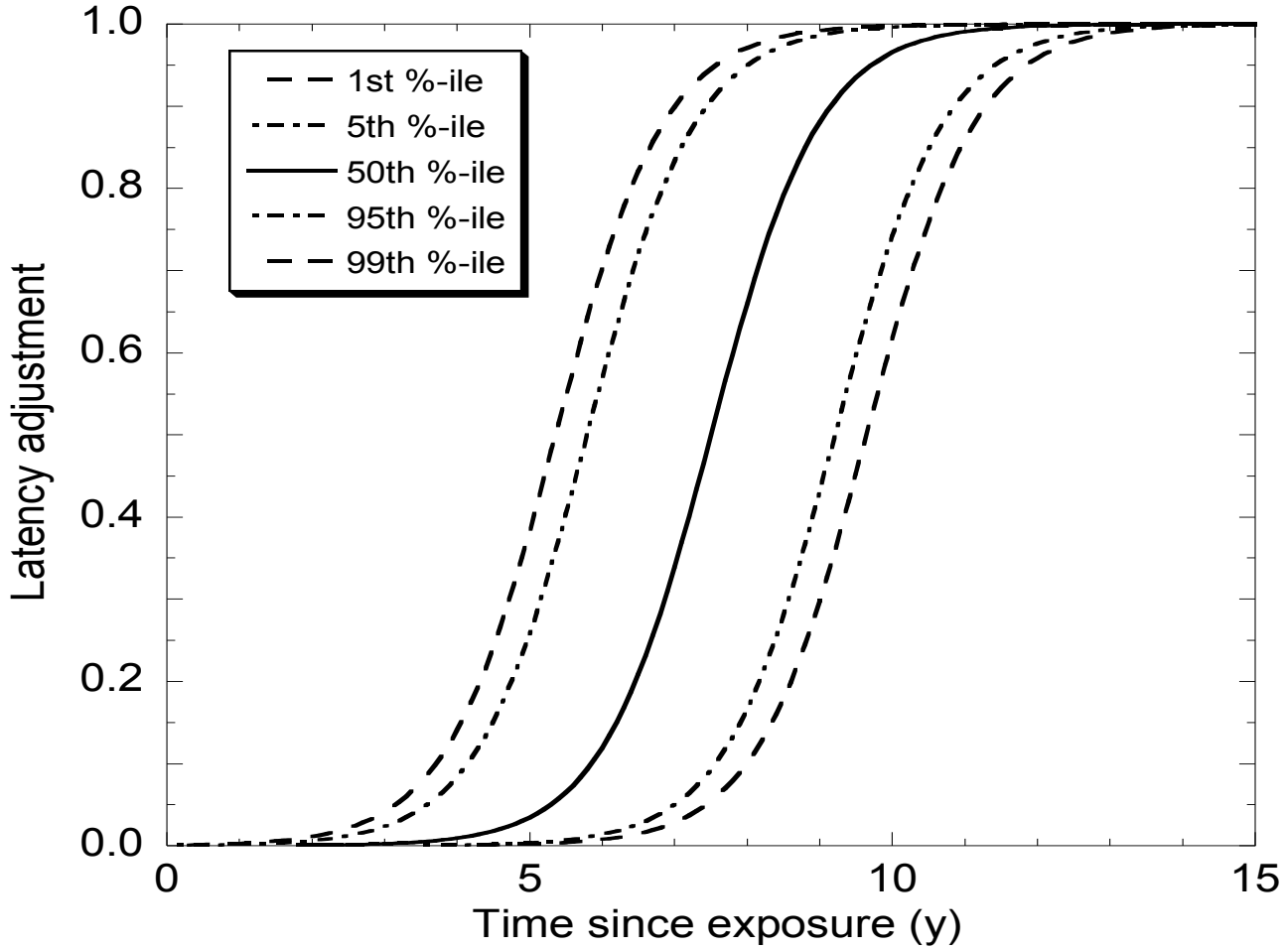
Nominal minimum latency periods in IREP

- leukemias, 2.25 y;
- thyroid and bone cancer, 4.5 y;
- all other cancers, 7.5 y

IREP assumes a gradual increase in ERRs during minimum latency period and accounts for uncertainty

Uncertainty in minimal latency period not considered in other risk assessment models

LATENCY ADJUSTMENT FOR MOST SOLID CANCERS IN IREP



TRANSFER OF ERRs TO U.S. POPULATION

To apply to U.S. population, ERRs in LSS cohort must be adjusted to account for differences in baseline risks (B)

- Issue – Biological relationship between risk due to radiation (EAR) and B not known
- Relationship studied using data on radiation and baseline risks of specific cancers in populations with different baseline risks

TRANSFER OF ERRs TO U.S. POPULATION

- $(ERR)_{US}$ is weighted average assuming multiplicative or additive risk transfer from LSS cohort; assuming uncertain degrees of linear mixing
- BEIR VII risk transfer model –
  - $(ERR)_{US}$ is weighted geometric mean of ERRs from additive and multiplicative models (uncertain degrees of mixing not included)
- IREP, EPA, NCI risk transfer models give higher $(ERR)_{US}$ than BEIR VII model

UNCERTAINTY IN RISK TRANSFER

Uncertainty increases with increasing departure of (B_{LSS}/B_{US}) from 1.0

- B_{LSS} and B_{US} can differ by factor of 10 or more (e.g., stomach, liver, prostate, female breast)
- Similar effect on 99th %-tile of $(ERR)_{US}$ relative to 99th %-tile of $(ERR)_{LSS}$ when $B_{LSS}/B_{US} > 1$

No uncertainty in risk transfer for thyroid cancer (incorporated in pooled ERRs) – also for breast cancer in BEIR VII, EPA, NCI; bone cancer in EPA

Extrapolation from Acute High-dose Exposures to Exposures at Low Doses and Low Dose Rates

ERR per unit dose at low doses and low dose rates of photons and electrons assumed to be lower than at higher acute doses in LSS cohort

For all cancers except leukemia – effect represented by dose and dose-rate effectiveness factor (DDREF)

$$(\mathrm{ERR/Sv})_{\mathrm{low}} = \frac{(\mathrm{ERR/Sv})_{\mathrm{high,acute}}}{\mathrm{DDREF}}$$

DDREF FOR LOW-LET RADIATIONS

DDREF for leukemias –

- For acute exposure, DDREF implicit in assumed linear-quadratic dose-response
  - Dose-dependent DDREF (= 2 at 1 Sv in IREP)
- For chronic exposure, only linear term in linear-quadratic dose-response for acute exposure assumed to apply

DDREFs for Solid Cancers in IREP

- Uncertain DDREFs of 0.5–4.0 (breast and thyroid) or 0.5–5.0 for all other cancers; mean of 1.6 or 1.8
- Small weight (5%) to assumption of higher ERR/Sv at low doses and low dose rates
- Full DDREF applied to all chronic exposures
- Acute exposure – DDREF phased in as dose decreases below uncertain "low dose" value between 0.03 and 0.2 Gy
  - same assumption in NCI RadRAT;
  - full DDREF below 0.1 Gy in BEIR VII

BIOLOGICAL EFFECTIVENESS OF DIFFERENT RADIATION TYPES

IREP accounts for effectiveness of different radiation types in inducing cancer compared with high-energy photons (> 250 keV) using uncertain radiation effectiveness factors (REFs) –

- lower-energy photons (30–250 and < 30 keV)
- low-energy electrons (< 15 keV)
- neutrons (five energy groups in ICRP Pub. 60)
- alpha particles (all energies)

EPA includes uncertain “RBEs” for alpha particles

BIOLOGICAL EFFECTIVENESS OF DIFFERENT RADIATION TYPES

Uncertainties in REFs in IREP

95% CI ($97.5^{th}/2.5^{th}$) spans factors of –

- 4 to 6 for lower-energy photons and electrons
- 10 to 40 for neutrons and alpha particles (REFs for leukemias lower than for solid cancers)

REFs for lower-energy photons now doubtful (based mainly on questionable RBEs for dicentric chromosome aberrations)

DOCUMENTATION OF IREP

Version of NIOSH-IREP used in compensation programs available at –

- http:ww2.niosh-irep.com/irep%5Fniosh/

Information about models in "View Model Details" and several "help" files

Models also documented in –

- Land et al., NIH Publication No. 03-5387 (2003)
- Kocher et al., Health Phys. 95, 119–147 (2008)