OVERVIEW OF INTERACTIVE RADIOEPIDEMIOLOGICAL PROGRAM (IREP)

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WHAT IS IREP?

[1] Web-based, interactive computer program

[2] Estimates probability (chance) that diagnosed cancer in an individual was induced by given doses of ionizing radiation.

IREP considers all cancers except chronic lymphocytic leukemia (CLL).

WHAT DOES IREP CALCULATE?

IREP calculates “probability of causation” (PC), defined as –

$$PC = \frac{R}{R + B}$$

R = risk of given cancer due to radiation

B = baseline risk of given cancer due to all other causes (generally depends on age)

PC, R, and B are probabilities (between 0 and 1).

EQUATION TO CALCULATE PC

PC is calculated from estimate of excess relative risk (ERR) due to given radiation doses to organ in which individual's cancer was induced.

$$ERR = R/B$$

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

ERR is not a probability (can be greater than 1).

WHAT DOES IREP DO?

[1] IREP is state-of-the-art tool for estimating cancer risks (ERRs) due to exposure to ionizing radiation.

[2] IREP accounts for many uncertainties in estimating ERR for any exposure situation (acute or chronic exposure, different radiation types).

IREP calculates probability distributions of ERR and PC to represent their uncertainty.

USE OF PC IN COMPENSATION PROGRAMS (1)

When estimate of PC is required, claim normally is granted when –

- 99^{th} percentile of probability distribution of PC is at least 0.5 (usually expressed as 50%).

PC of at least 50% means –

- risk due to radiation (R) is equal to or greater than baseline risk (B) for individual's cancer; or
- ERR is equal to or greater than 1.0.

USE OF PC IN COMPENSATION PROGRAMS (2)

[1] PC of at least 50% represents requirement that it should be “at least as likely as not” that individual’s cancer was caused by radiation.

[2] Use of 99th percentile of PC gives claimants “benefit of the doubt” in presence of uncertainty.

Claim normally is granted when chance that PC is at least 50% is as little as 1%.

BASIC ASSUMPTIONS ABOUT RISKS DUE TO RADIATION

[1] Solid cancers

ERR is linear function of dose:

$$\mathrm{ERR} = \alpha D$$

[2] Leukemia (excluding CLL)

ERR is linear-quadratic function of dose, with equal coefficients of linear and quadratic terms:

$$\mathrm{ERR} = \alpha(D + D^2)$$

SOURCES OF DATA TO ESTIMATE ERRs (1)

[1] ERRs for most cancers estimated based on data in Japanese atomic-bomb survivors.

Data on cancer incidence through 1987.

Dose estimates based on Dosimetry System 1986 (DS86).

Survivors received acute doses from high-energy gamma rays (small contributions from neutrons).

SOURCES OF DATA TO ESTIMATE ERRs (2)

[2] ERRs for thyroid cancer estimated based on data in atomic-bomb survivors and several groups of children exposed to medical x rays.

[3] ERRs for lung cancer due to exposure to radon estimated based on data in U.S. uranium miners (not important for atomic veterans).

FORMULATION OF MODELS TO ESTIMATE ERRs

ERRs for most cancers in study populations assumed to depend on –

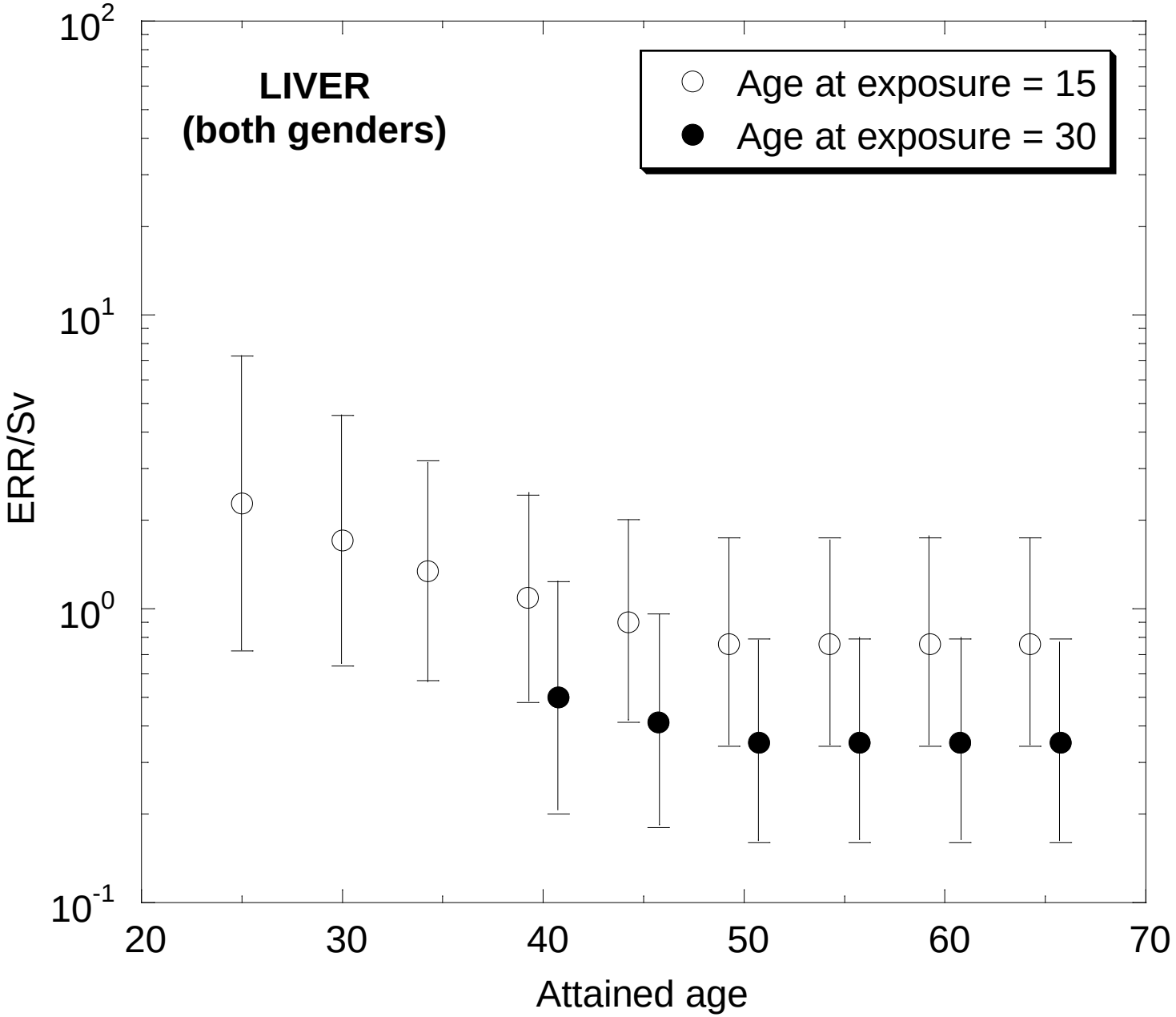
- gender,
- age at time of exposure,
- attained age (all cancers except leukemia) or time since exposure (leukemia only).

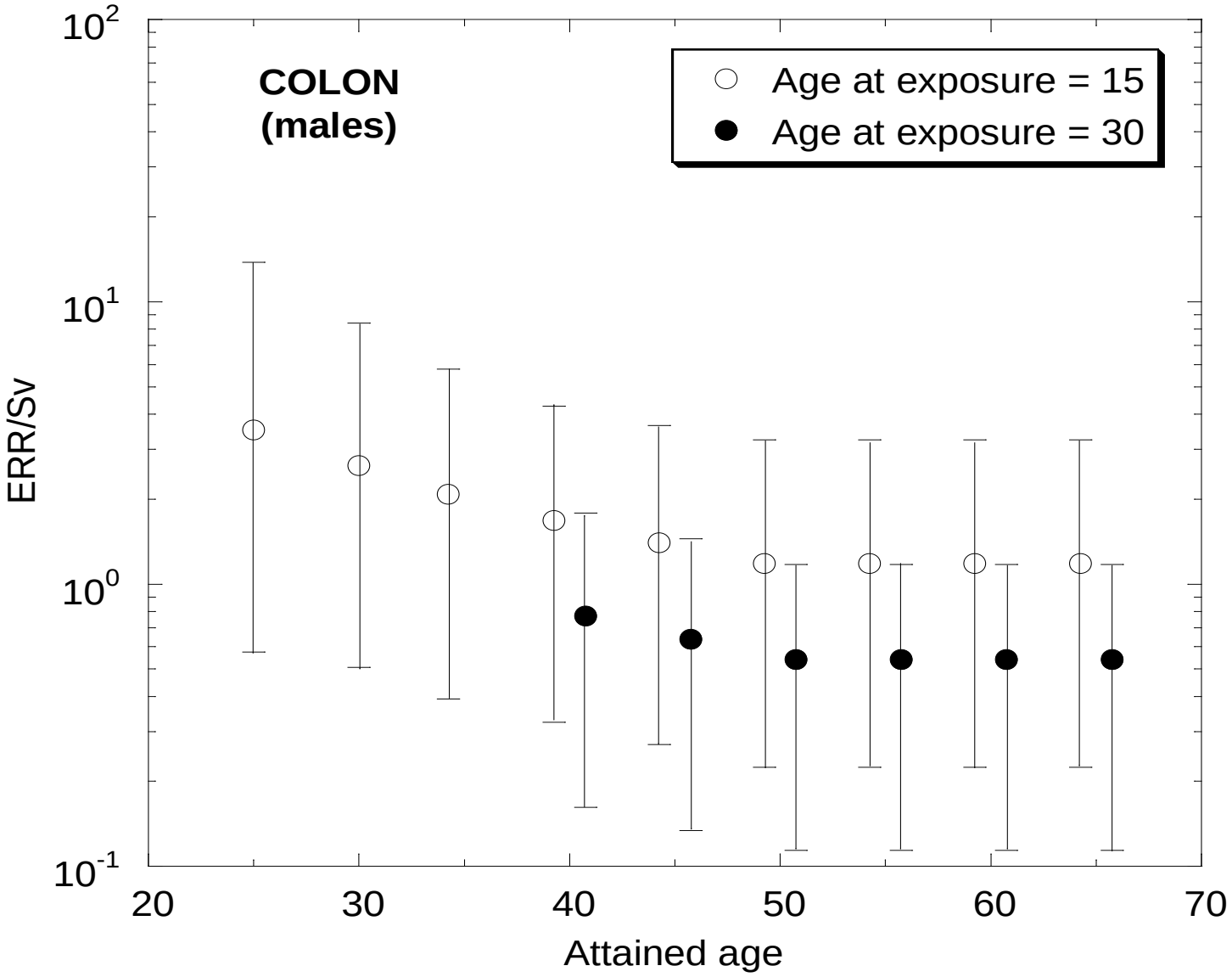
Simple functions used to represent effect of age and time on ERRs.

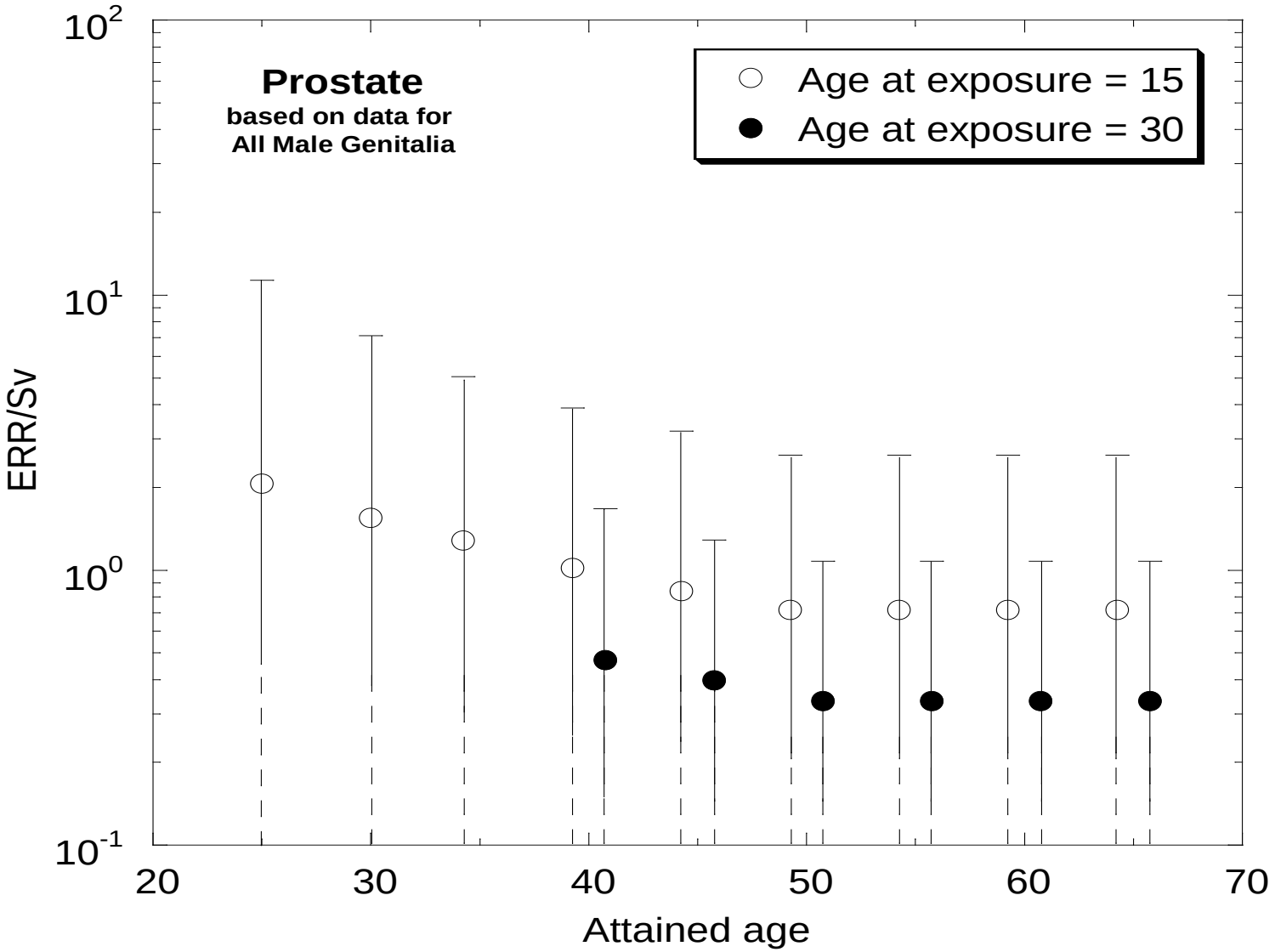
EXAMPLES OF STATISTICAL UNCERTAINTIES IN ERRs

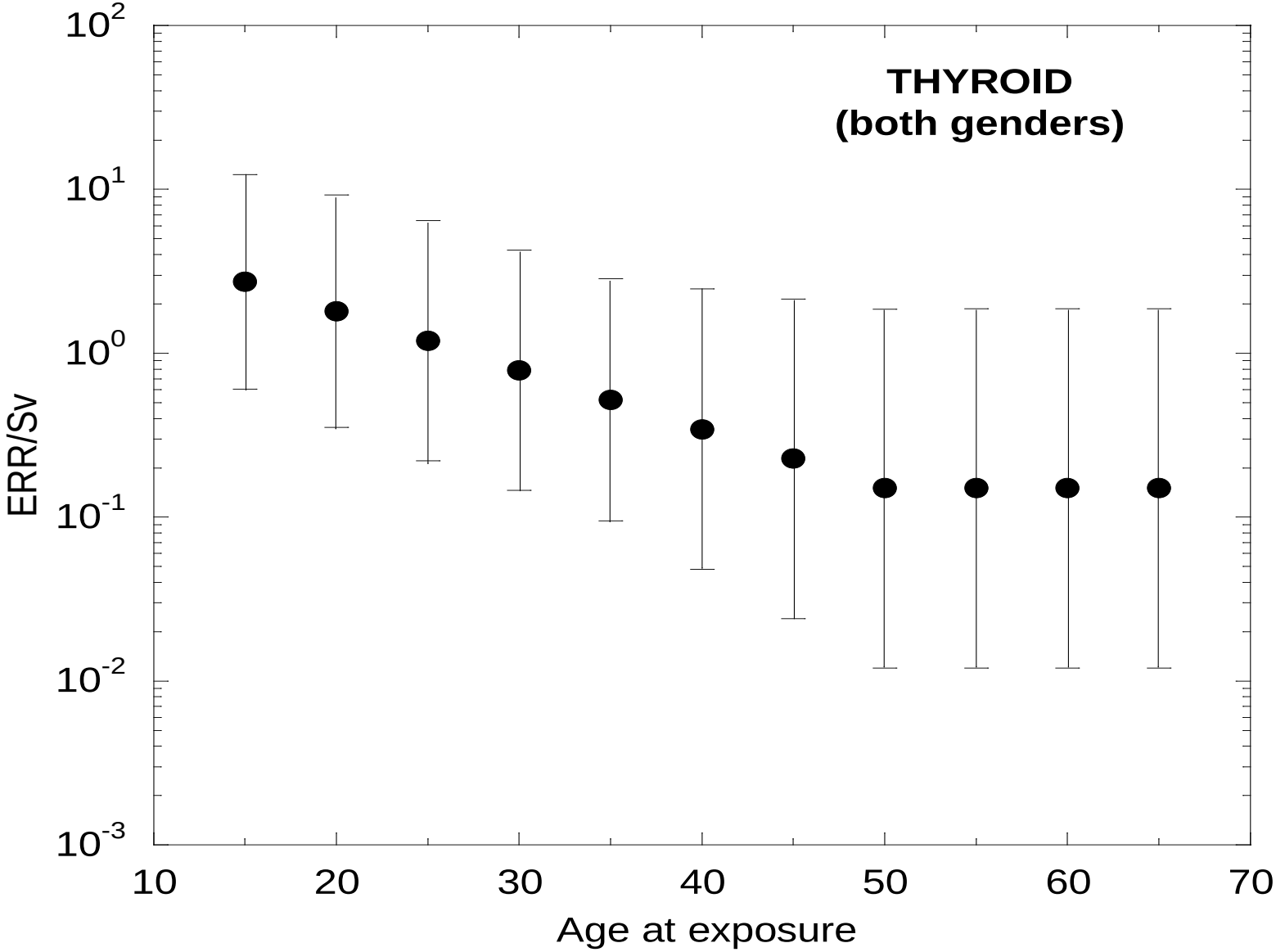
Statistical uncertainties in modeled ERRs obtained from best fits to data in study populations.

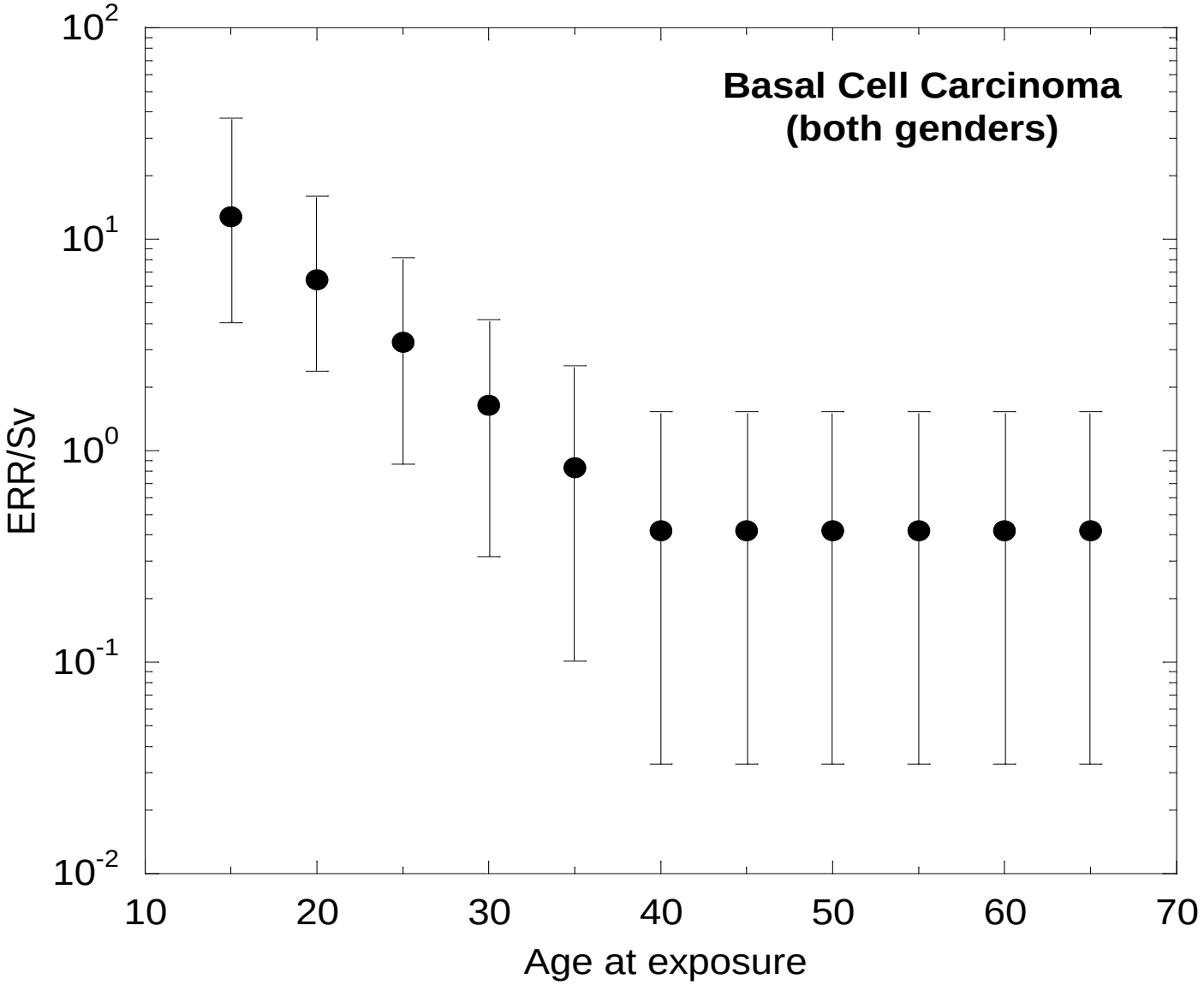
- Estimates are ERRs at dose of 1 Sv (= 100 rem).
- Uncertainties are 95% confidence intervals (2.5^{th} to 97.5^{th} percentiles).
- Uncertainties vary greatly depending on cancer type; can be large when there are few excess cancers in exposed populations.

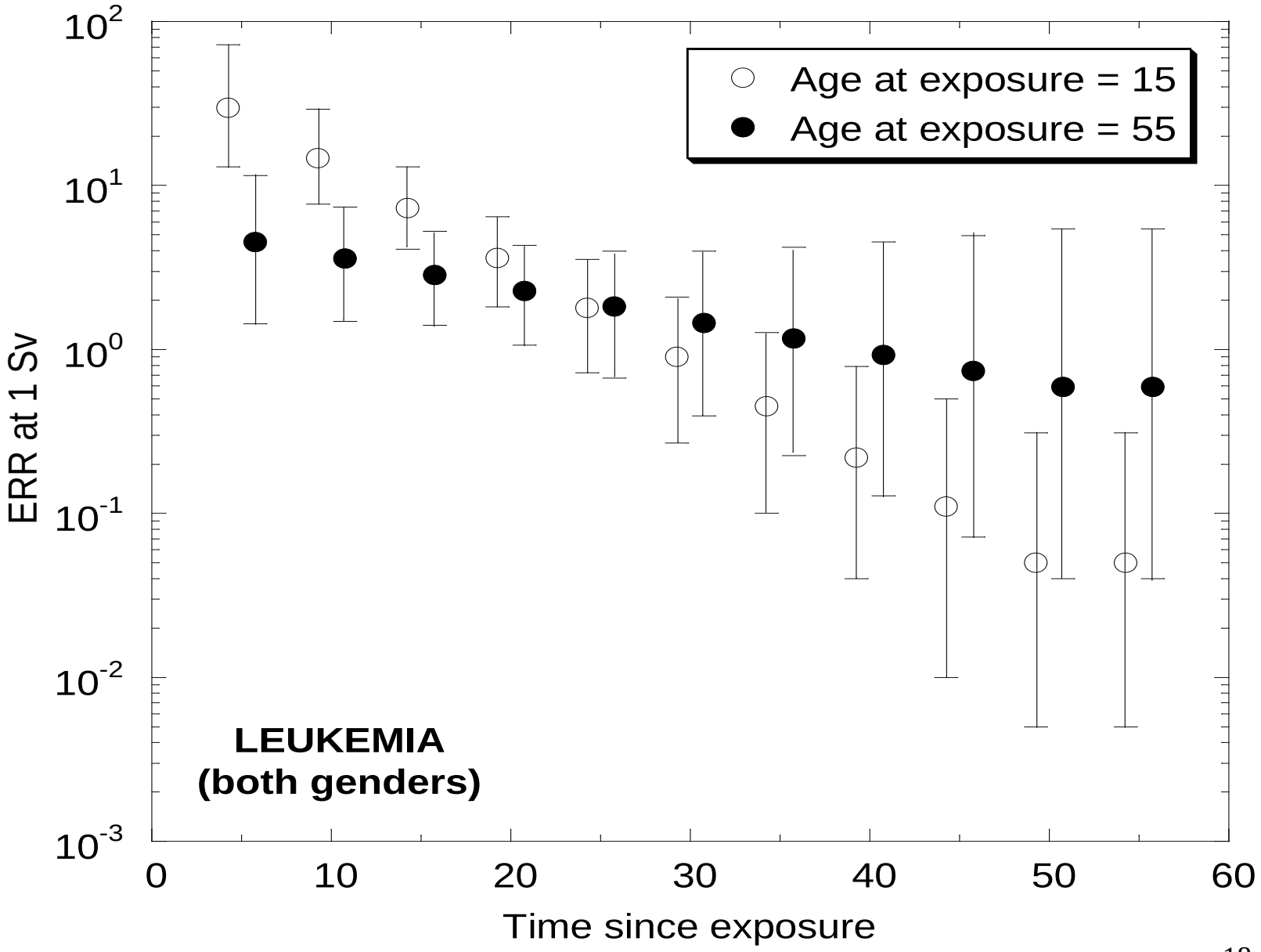

LIVER
(both genders)
Age at exposure = 15
Age at exposure = 30
ERR/Sv
10^2
10^1
10^0
10^{-1}
20
30
40
50
60
70
Attained age


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


Prostate
based on data for
All Male Genitalia
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 genders)
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 genders)
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}
LEUKEMIA
(both genders)
0
10
20
30
40
50
60
Time since exposure

ADJUSTMENTS TO MODELED ERRs

Adjustments to modeled ERRs in study populations take into account –

- random and systematic errors in dosimetry;
- latency period for specific cancers;
- transfer of ERRs in Japanese atomic-bomb survivors to U.S. population;
- dependence of ERR per unit dose for photons and electrons on dose and dose rate;
- differences in biological effectiveness of different radiation types.

ERRORS IN DOSIMETRY

Corrections to ERRs in atomic-bomb survivors to account for random and systematic errors in dosimetry (gamma rays and neutrons).

Overall correction is small:

- ERRs reduced by less than 20%;
- standard deviation is about 10% of mean.

LATENCY PERIOD FOR SPECIFIC CANCERS

Accounts for time delay between exposure and earliest diagnosis of cancer induced by radiation.

Nominal (average) latency period –

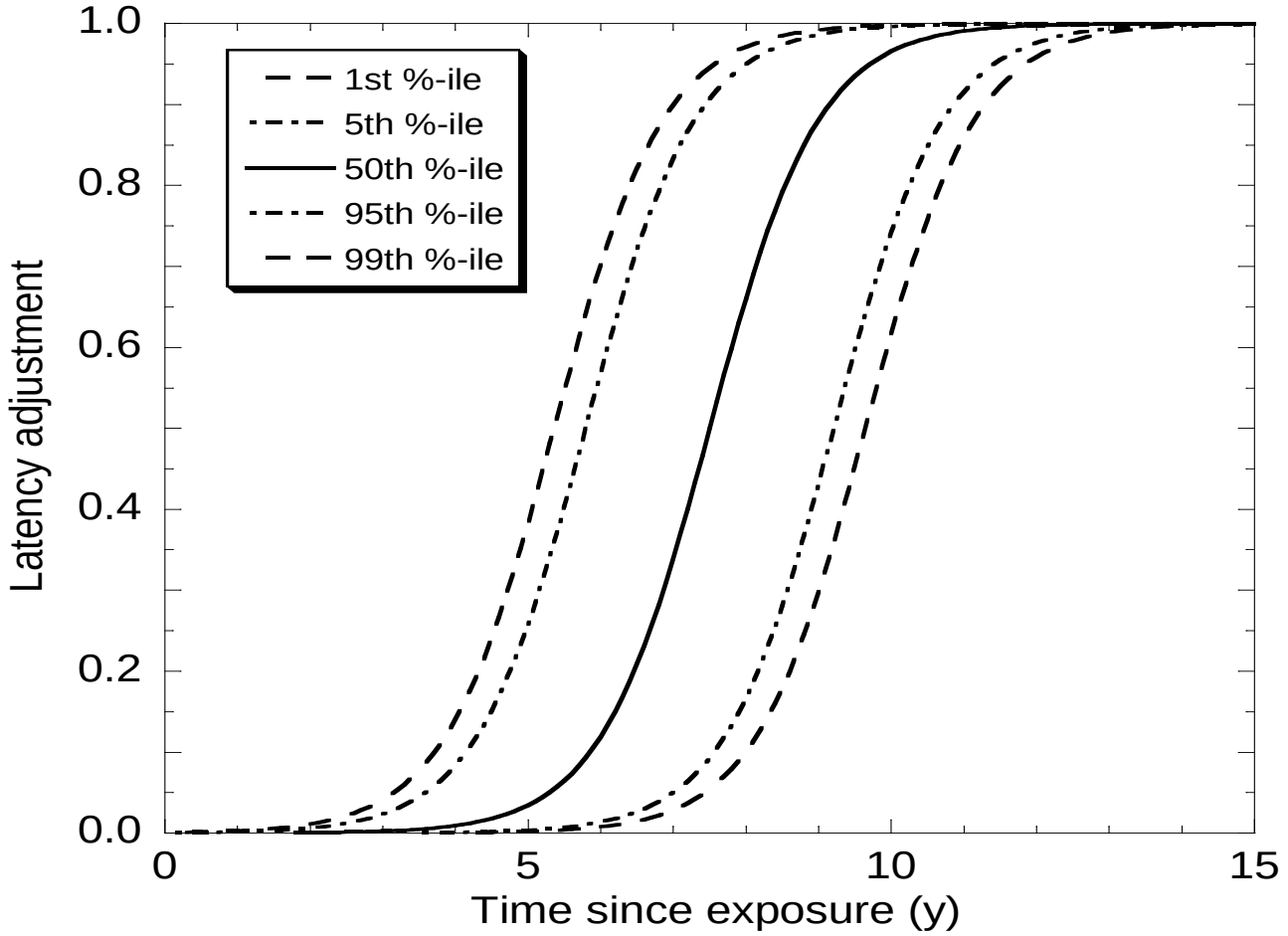
– 2.25 years for leukemia;

– 4.5 years for thyroid and bone cancer;

– 7.5 years for all other cancers.

IREP assumes gradual increase in ERR during latency period and uncertainty in nominal value.

LATENCY ADJUSTMENT FOR MOST CANCERS



TRANSFER OF ERRs TO U.S. POPULATION (1)

To apply to U.S. population, ERRs in Japanese atomic-bomb survivors must be adjusted to account for differences in baseline risks (B).

Basic issue –

Biological relationship between risk due to radiation (R) and baseline risk (B) is not known.

TRANSFER OF ERRs TO U.S. POPULATION (2)

Two options to model risk transfer:

[1] R = constant × B (multiplicative model)

ERR = R/B transfers directly

[2] R independent of B (additive model)

R (not ERR) transfers directly

For most cancers, IREP represents uncertainty by assuming random linear combination of two models.

Uncertainty in risk transfer increases with increasing departure of ($B_{Japan}/B_{U.S.}$) from 1.0.

TRANSFER OF ERRs TO U.S. POPULATION (3)

[1] ERRs for skin cancers are assumed to depend on race or ethnic group.

Accounts for higher baseline risks in lighter-skinned populations; represents interaction of radiation and UV in causing skin cancer.

[2] ERRs for lung cancer are assumed to depend on smoking history.

ERRs due to radiation exposure decrease with increasing use of cigarettes.

DDREF FOR PHOTONS AND ELECTRONS

ERR per unit dose at low doses and low dose rates of photons and electrons is assumed to be lower than at higher acute doses in atomic-bomb survivors.

Effect represented by dose and dose-rate effectiveness factor (DDREF).

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

DDREFs IN IREP

Probability distribution ranges from 0.5–4.0 or 0.5–5.0 (mean of 1.6 or 1.8).

Small weight (5%) given to assumption that ERR per unit dose is higher at low doses and dose rates.

Full DDREF is applied to all chronic exposures to photons and electrons at any dose.

For acute exposure, DDREF for chronic exposure is phased in gradually as dose decreases below uncertain reference dose, D_L, of 3–20 rem.

BIOLOGICAL EFFECTIVENESS OF DIFFERENT RADIATION TYPES

IREP accounts for greater effectiveness in inducing cancer compared with high-energy photons using uncertain radiation effectiveness factors (REFs) –

- lower-energy photons (< 250 keV);
- low-energy electrons (< 15 keV);
- neutrons;
- alpha particles.

95% C.I. of REF spans factor of 4–6 for photons and electrons, 10–40 for neutrons and alpha particles.

CLAIMANT-FAVORABLE ASSUMPTIONS IN IREP (1)

[1] Use of two models for lung cancer and selection of higher 99th percentile of PC.

[2] Likely overestimation of ERRs and PC for thyroid cancer in adults.

[3] In cases of multiple exposures, uncertain ERRs from each exposure are added by assuming they are perfectly correlated.

Multiple exposures are exposures to more than one radiation type at same time, exposures to same radiation type at different times, or both.

CLAIMANT-FAVORABLE ASSUMPTIONS IN IREP (2)

[4] Applying model for basal cell carcinoma to malignant melanoma (usually gives higher PC than alternative model).

[5] In cases of multiple cancers, calculation of 99th percentile of PC by assuming that uncertain PCs for each cancer are perfectly correlated.

OTHER ASSUMPTIONS USED BY NIOSH AND VA

[1] In cases of leukemia, IREP is run for diagnosed type of leukemia and all leukemia as a group (except CLL), and higher PC is used.

[2] NIOSH and VA usually make favorable assumptions about external exposures:

- acute exposure to photons and electrons;
- chronic exposure to neutrons.

SUMMARY OF UNCERTAINTIES IN IREP (1)

[1] Statistical uncertainties in estimating ERRs in study populations are always important.

[2] Uncertainties in corrections to ERRs to account for errors in dosimetry are unimportant.

[3] Uncertainty in latency period is important mainly when time between exposure and diagnosis is less than nominal latency period.

SUMMARY OF UNCERTAINTIES IN IREP (2)

[4] Uncertainty in transfer of ERRs in atomic-bomb survivors to U.S. population is important when baseline risks in two populations differ greatly (e.g., stomach, liver, and prostate cancer).

[5] Uncertainty in DDREF is important mainly when dose from chronic exposure to photons or electrons is important.

[6] Uncertainty in REF is important when dose from lower-energy photons, low-energy electrons, neutrons, or alpha particles is important.

WHERE CAN IREP BE FOUND?

NIOSH-IREP is available to public at –

– www.niosh-irep.com/irep_niosh/

To learn more about models in IREP, click on “View Model Details” on first screen of program.

Information also is given in several “help” files.