

SAB Review of “Blue Book”

EPA Radiogenic Cancer Risk Models and Projections for the U.S. Population



J.S. Puskin & D.J. Pawel
Radiation Protection Division
Office of Radiation & Indoor Air
March 23, 2009

Purpose of Review

Consider proposed revisions to EPA's methodology for estimating radiogenic cancer risks.

Briefing Outline

- Background and history
- Specific topics pertaining to risk projections
 - Stationary population
 - Approach to obtaining nominal estimates
 - Risks at low doses and dose rates
- BEIR VII models and modifications
- Risk projections
- Bone and skin cancer models, prenatal exposures
- Uncertainty analysis
- RBE for higher LET radiations

Risk Characterization

- Provides EPA managers with critical information upon which to base decisions
 - Estimated magnitude of risks
 - Scientific basis of risk estimates
 - Uncertainties: sources and magnitudes

Current EPA Radiation Cancer Risk Estimates

- Methodology described in 1994 “Blue Book” and 1999 *Addendum on Uncertainty*
- For many sites, employed GMC constant ERR model adapted from an ICRP report, which relied on 1985 LSS mortality data (Land & Sinclair 1991)
- DDREF=2 for sites other than breast
- α -particle RBE=20 (except for bone marrow)
- Used to calculate radionuclide specific risk coefficients (FGR-13)

Process Envisioned for Revising EPA Cancer Risk Coefficients

- Revise “Blue Book,” *Estimating Radiogenic Cancer Risks* (1994)
 - Publication of BEIR VII (2006)
 - White Paper Advisory (Fall 2006)
 - Advisory received (January, 2008)
 - **SAB review of draft revised Blue Book (March, 2009)**
 - Publish final version
- Revise FGR-13
 - New ICRP dosimetry, EPA risk coefficients
 - Review

BEIR VII Report

- Sponsored by EPA and other Federal agencies (DOE, NRC, DoD, DHS)
- Updated risk models and projections of risk to U.S. population from low dose, low-LET radiation in light of new data, especially LSS incidence data and revised A-bomb dosimetry
- Quantified uncertainties
- Reconsidered low dose (dose rate) extrapolation in light of new radiobiological findings (adaptive response, bystander effect, etc.)

White Paper Advisory

- *Draft White Paper* submitted August, 2006
- Presented to SAB September, 2006
- EPA advocated adherence to BEIR VII recommendations with certain extensions and modifications
- “The RAC endorse[d] EPA’s proposal to base its approach...on BEIR VII” and accepted most of its specific recommendations

Elements of SAB Advisory (I)

Mostly follow BEIR VII recommendations:

- Models for most sites based on LSS incidence data
- Form of site-specific models
- LNT
- DDREF=1.5 for solid cancers
- Weighted GM of EAR and ERR projections

Elements of SAB Advisory (II)

- Four conditions for modifying BEIR VII
 - Not treated in BEIR VII (skin, bone, high-LET)
 - More recent or relevant data (vital stats.)
 - Compelling evidence for more appropriate method (breast cancer mortality, uncertainty)
 - Implementation requirements necessitate adaptation or alternative (stationary popul.)

Elements of SAB Advisory (III)

Modifications, extensions:

- Updated vital statistics
- Stationary population (distribution of ages in the population is invariant)
- Method for combining EAR and ERR projections
- Refined estimate of breast cancer mortality
- Add risk estimates for sites not covered in BEIR VII: bone, skin (kidney)
- Risks from α 's and lower energy β/γ
- Add risk estimate for prenatal irradiation
- Modify/expand uncertainty analysis

Elements of SAB Advisory (IV)

- Alternative weighting for lung cancer
- Thyroid cancer risk model
 - NCRP vs. BEIR VII approach
 - Effectiveness of I-131

Additional Elements Since SAB Advisory

- Geometric mean (BEIR VII) vs. arithmetic mean (ICRP) for risk transfer
- Expanded uncertainty analysis, including Bayesian approach to account for sampling errors
- Biophysical approach to RBE for low energy photons and electrons
- Consideration of new analysis of LSS data on skin cancer

Why the stationary population?

- Stationary population: $N(a)=N_0 S(a)$
- Risk/dose to stationary population = Risk/dose for constant lifetime exposure
 - Chronic exposure risk used throughout EPA
 - Traditionally used by ORIA
- Calculational advantage – estimated risk/dose independent of temporal pattern of exposure (same for acute and chronic exposures)
- Used by BEIR III-VI, UNSCEAR 2000
- Chronic lifetime exposure risks also included in BEIR VII

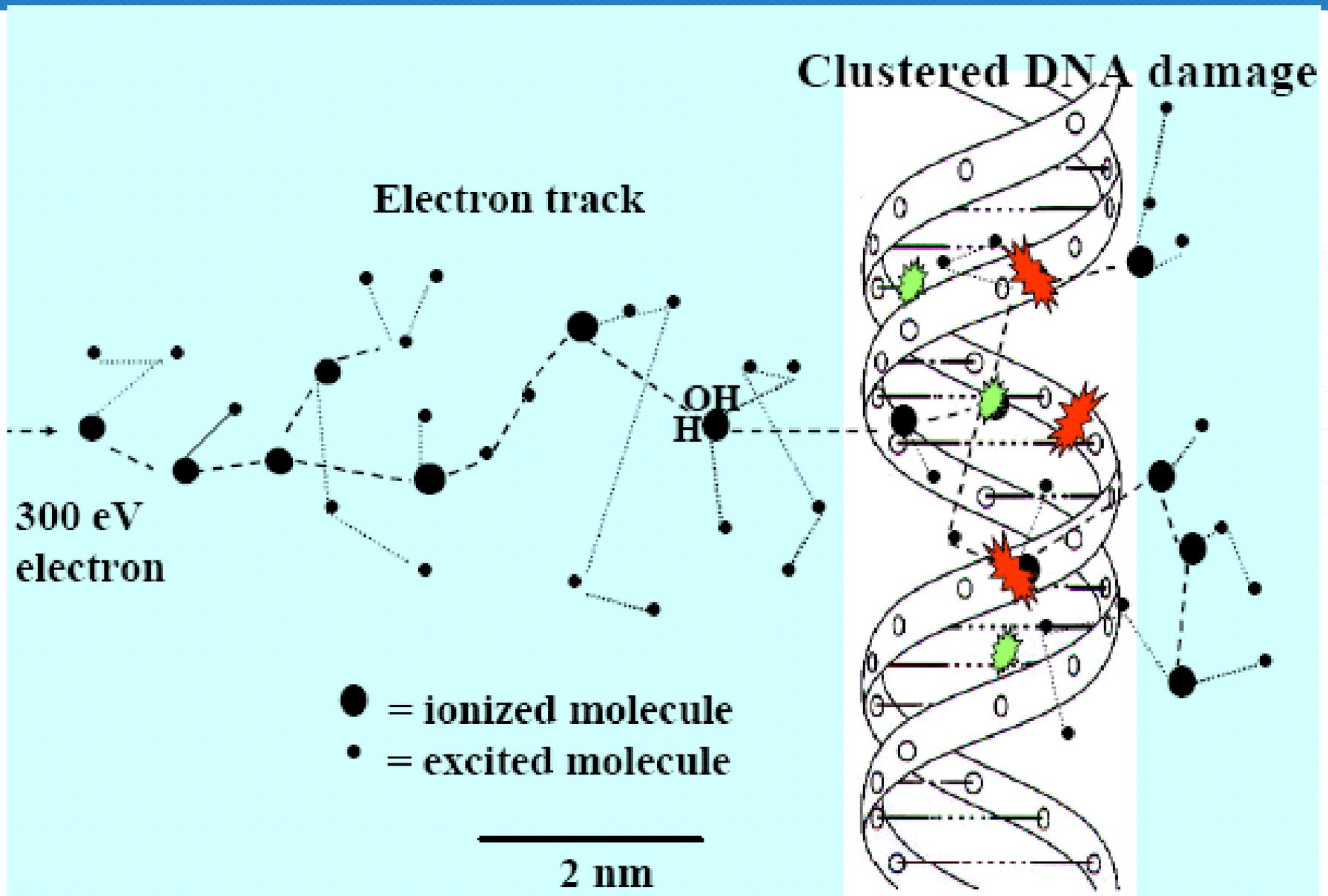
Why not use uncertainty distribution to derive central estimates?

- Not recommended in BEIR VII
- Too much (EPA) subjectivity and too little transparency
- Uncertainty analysis not designed for that purpose, but rather to provide (90%) uncertainty bounds

Linear No-Threshold (LNT) Hypothesis

- Risk at low doses proportional to dose with no (effective) threshold
 - Clustered damage → single tracks dominate damage; incomplete repair
 - Single mutation can ↑ risk of cancer
 - Animal and human data on carcinogenesis
 - Not indicative of a threshold
 - Consistent with linearity as low as we can look
 - Supporting data on epidemiological studies involving chronic and fractionated exposures

Generation of clustered damage



Epidemiological Studies at $<100 \text{ mGy d}^{-1}$ (0.1 Gy/d)

- Medical exposures
 - Prenatal X-rays
 - Fluoroscopy patients
 - Scoliosis patients
- Chronic exposures
 - Techa River cohort
 - Nuclear power and defense workers
 - Medical workers
 - Taiwanese building residents
 - Semipalatinsk area residents
 - Chernobyl cleanup workers

Leukemia Risk in Recent Studies (Schubauer-Berigan)

Leukemia excluding CLL	Excess relative risk % at 0.1 Sv (95% CI), n
Mayak workers ¹	10 (90% CI: 5, 20), 66
IARC 15-country study ²	19 (<0, 85), 196
NIOSH multisite leukemia case-control ³	26 (<-10, 100), 184
Chernobyl (Ukraine), includes CLL ⁴	34 (4.7, 98), 71
Chernobyl (Belarus/Russia) ⁵	50 (90% CI: -38, 570), 19
Rocketdyne workers ⁶	34 (-27, 145), 18
Taiwan building study (men) ⁷	19 (1, 31), 6
Techa River ⁸	42 (12, 130), 61
A-bomb survivors (men age 20-60 at exposure), n=83 ²	
Linear-quadratic (linear region) :	15 (-11 to 53)
Linear:	32 (16 to 57)

1 Shilnikova et al. 2003; Rad. Res. 159:787-98

3 Schubauer-Berigan et al. 2007; Rad. Res 167:222-32

5 Kesminiene et al. 2008; Rad. Res. 170:721-35

7Hwang et al. 2008; Rad. Res. 170:143-148

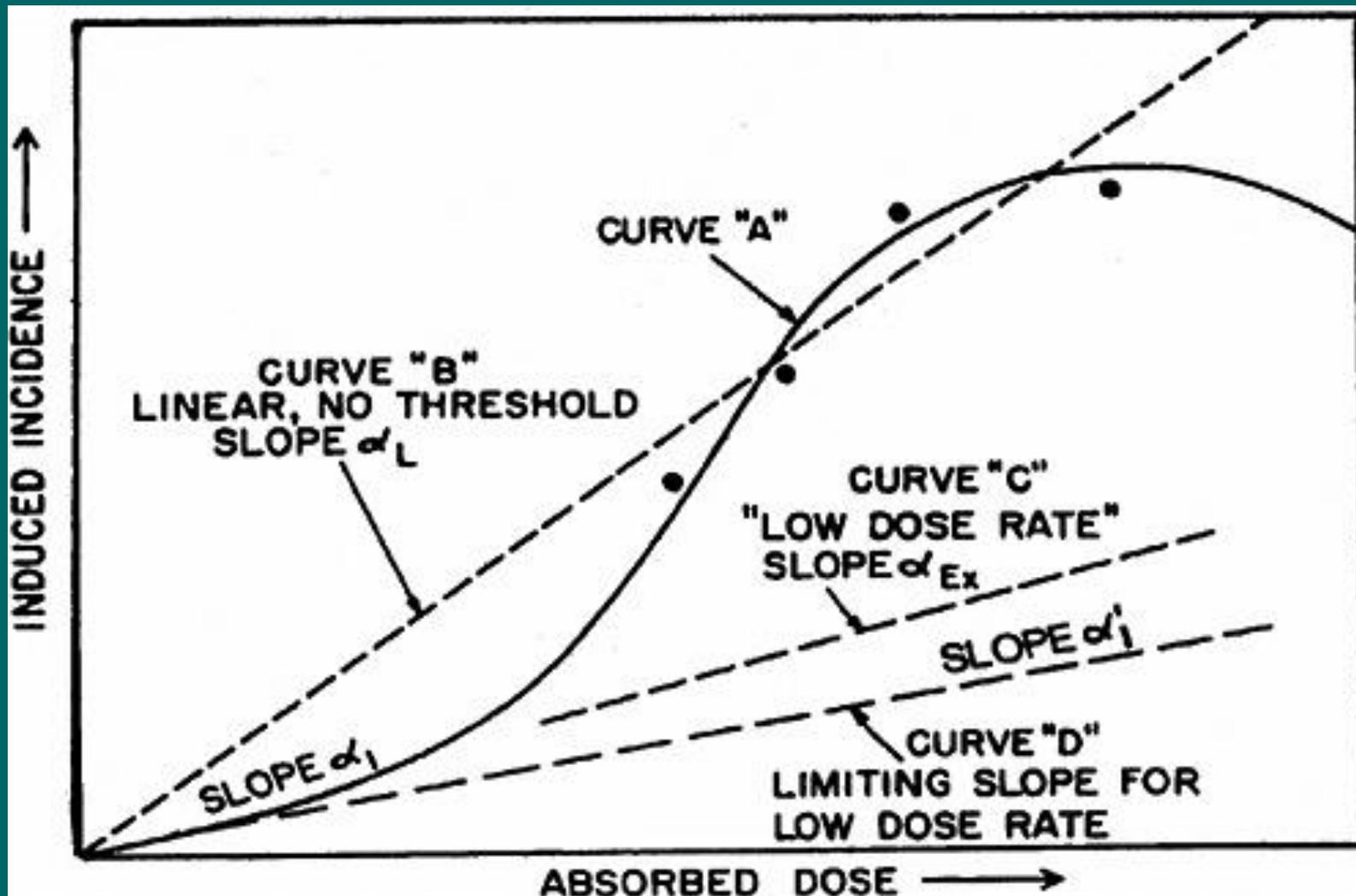
2Cardis et al. 2005; BMJ 331:77-81

4 Romanenka et al. 2008; Rad. Res. 170: 691-720

6Boice et al. 2006; Rad. Res. 166:98-115

8Krestinina et al. 2005; Rad. Res. 164:810-819

Schematic Dose-Response for Cancer Incidence (BEIR VII)



Projecting Risks at Low Doses & Dose Rates (I)

Linear-quadratic (LQ) model:

$$E = \alpha_1 D + \alpha_2 D^2 = \alpha_1 D (1 + \theta D)$$

Tied to 2-hit damage mechanism

Assumes that $\theta \rightarrow 0$ at low dose rates

Low dose risk coefficient = α_1

LQ model \Rightarrow

Low Dose Effectiveness Factor (LDEF)

= Dose Rate Effectiveness Factor (DREF)

= DDREF = $1 + \theta D$

Projecting Risks at Low Doses & Dose Rates (II)

- For *leukemia*, BEIR VII fit to LSS data: $\theta=0.88 \text{ Sv}^{-1}$
- For *solid cancers*, BEIR VII did not explicitly adopt LQ dose-response
 - Fit data to linear model
 - DDREF=1.5, based on LDEFs estimated from LSS and radiobiological data ($\theta=0.5 \text{ Sv}^{-1}$)
 - Other DDREF estimates (e.g., in BEIR V or ICRP Pub. 99) have been higher (2-3), but LDEFs were generally evaluated at higher doses; according to BEIR VII, the extrapolation of the LSS data is effectively from $\approx 1 \text{ Sv}$

Uncertainty at Low Doses (I)

- BEIR VII
 - Quantifies uncertainty bounds on DDREF, but this *presumes* LQ dose-response model
 - Concludes that “weight of evidence” favors LNT
- ICRP Publication 99
 - “no compelling evidence for a threshold,” but “question remains open”
 - Unless possibility of threshold is very likely, it will not drastically affect central or upper bound estimates

Uncertainty at Low Doses (II)

- Assigning a probability distribution to fully characterize the uncertainty in risk at low doses and dose rates must rely heavily on subjective judgment
- EPA proposes to follow BEIR VII in not assigning a numerical probability to a threshold – or an effective threshold – in the dose region inaccessible to epidemiology. A qualitative discussion of the issue is included, and it is noted that this is a source of uncertainty not accounted for in the quantitative uncertainty bounds.

EPA Risk Models and Projections for low-LET radiation

Chapter 3

Some Key Points

- EPA projections for low-LET radiation for almost all sites based on the BEIR VII ERR and EAR models
- BEIR VII used a weighted GM to combine results from the ERR and EAR projections. So does EPA, but we applied the WGM to age-specific values
- BEIR VII (Table 12D-3) and EPA used essentially the same life table methods to calculate risks for a constant lifetime dose
 - Exception: Breast cancer mortality
- ***Followed White Paper & Advisory recommendations***

EPA Risk Projections (Ch. 3)

- Models for most sites based on LSS incidence data
- ***Form of site-specific models***
- Updated vital statistics, ***stationary population***
- ***Weighted GM of EAR and ERR projections***
- ***GM or arithmetic mean?***
- ***Refined LAR projection for breast cancer mortality***
- Add risk estimates for kidney, bone and skin
- DDREF=1.5 for solid cancers

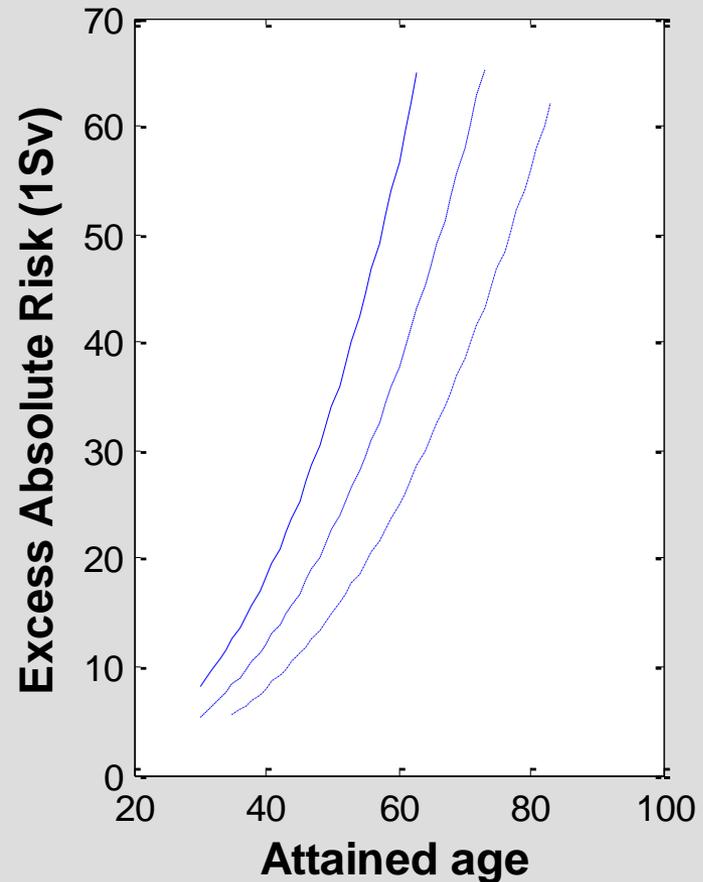
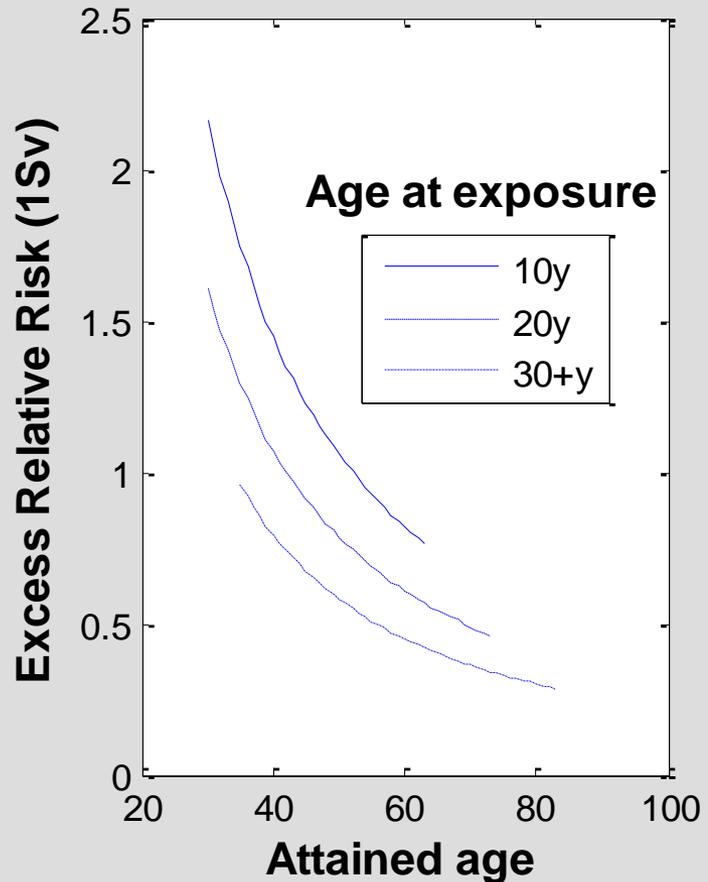
Form of Site-Specific Models

Followed White Paper & Advisory

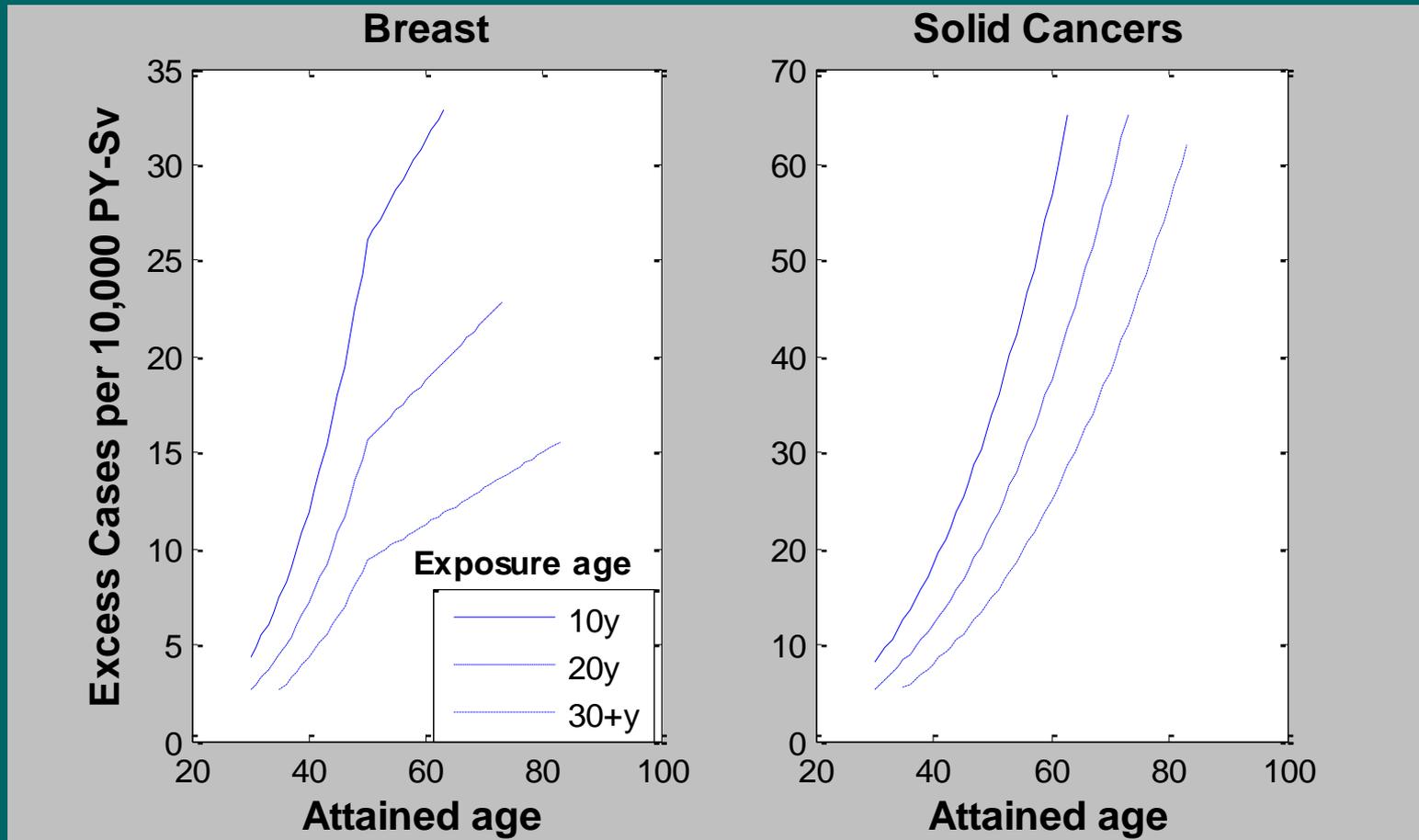
BEIR VII Solid Cancer Models

- Model for ERR and EAR (same form)
- $ERR(c,s,d,e,a) = \beta(c,s) d \exp(\gamma e^*) a^n$
 - Linear in dose
 - Depends on sex
 - Decreases with age at exposure to age 30 y
 - ERR decreases with attained age
 - EAR increases with attained age
 - Minimum latency of 5 years

Age-time patterns in ERR and EAR



EAR Model for Breast Cancer



EPA Risk Models for Leukemia

- Same as in BEIR VII
- Excludes CLL
- ERR and EAR incidence models based on LSS *mortality* data
 - LSS leukemia data obtained when leukemia almost always fatal
- Linear-quadratic in dose
 - curvature parameter ~ 0.9 per Sv
- Effect modifiers: sex, age-at-exposure, time-since-exposure

Stationary Populations

Appropriate for calculating LAR?

Followed White Paper & Advisory

Calculating Lifetime Attributable Risk (I)

Single Exposure at age (e)

- $LAR(d,e)$ = Lifetime attributable risk approx. probability that person will get cancer from radiation dose x at exposure age e .

$$LAR(d,e) = \int_{e+L}^{110} M(d,e,a) \cdot S(a) / S(e) da$$

- $M(d,e,a)$ = age-specific EAR per person year at attained age a .
- $S(\cdot)$ = Survival function

Calculating LAR (II)

Constant lifetime dose

$$LAR(d, const) = \frac{\int_0^{\infty} S(e) \cdot LAR(d, e) \cdot de}{\int_0^{\infty} S(e) \cdot de}$$

- $LAR(d, const)$ = Weighted average of age-at-exposure specific $LAR(d, e)$.
- Weight for age 50-51 (for example) = portion of the total lifetime dose one expects to receive between ages 50 & 51.
- Weight is approx. equal to $S(e)$ divided by the life expectancy.

LAR (*cases / 100K males* exposed to 1 mGy/y)

Cancer Site	BEIR VII (Table 12D-3; 95-99 data)	EPA (Table 3-10; avg 74.1 mGy; 98-02 data)
Stomach	24	23
Colon	107	105
Lung	96	93
Leukemia	67	60
All	621	582 , 611*

* BEIR VII method for combining risk models

LAR (*cases/100K females* exposed to 1 mGy/y)

Cancer Site	BEIR VII (Table 12D-3; 95-99 data)	EPA (Table 3-10, avg 79.5 mGy, 98-02 data)
Stomach	32	31
Colon	72	72
Lung	229	216
Leukemia	51	48
All	1019	977 ,1026*

* BEIR VII method for combining risk models

Calculating LAR (III)

Single exposure to population

- $LAR(d, pop) =$ weighted average of $LAR(d, e)$

- $N(e) =$ number at age e

$$LAR(d, pop) = \frac{1}{N^*} \int_0^{110-L} N(e) \cdot LAR(d, e) \cdot de$$

- $N^* =$ total number summed over all ages

- For stationary populations, $N(e)$ is proportional to $S(e)$

Combining Risk Projection Models

Methods for Combining Models for Projecting Risk

- BEIR VII calculates LAR values separately based on preferred ERR and EAR models
- How might results from the two models be combined for purposes of projecting LAR to the U.S?
- What do we know? The “true” population risk for the U.S. is either
 - Equal to $LAR^{(R)}$
 - Equal to $LAR^{(A)}$
 - Somewhere in between $LAR^{(R)}$ and $LAR^{(A)}$
 - Outside the interval bounded by $LAR^{(R)}$ and $LAR^{(A)}$ (Can ignore?)
- Reasonable to choose a value somewhere in between the two “extremes”

BEIR VII Approach: Weighted GM

- LAR projections averaged on the log scale
 - weighted geometric mean:
$$\log (\text{LAR}^{(B7)}) = w^* \log (\text{LAR}^{(R)}) + (1-w^*) \log (\text{LAR}^{(A)})$$
- First integrate to calculate lifetime risk, then use weighted geometric mean to “average” (lifetime) risks from each model.
- BEIR VII used a biologically based modeling approach to justify a nominal weight of 0.7 for most sites, i.e. for these sites there is more support for the ERR model.

Two Questions for Combining Projections

- If the GM is used, should it be applied to LAR, or should the GM be applied to age-specific quantities? (Should the GM be applied before or after risks are integrated for calculating lifetime risks)? *Discussed in detail during Advisory.*
- Should the approach be based on a weighted GM or should an arithmetic mean (AM) be used instead?

GM vs. AM

- AM > GM unless projections are identical
- For many cancer sites, AM ~ GM
 - Exceptions include stomach, liver, prostate, uterus
- Decision inevitably involves subjective judgment
 - Ideally would (somehow) factor in evidence from epidemiological studies, understanding of biological mechanisms, etc.
 - Could it be based on a generic uncertainty distribution?
- Evidence towards ruling out stomach cancer EAR model
 - According to EAR model, most of the stomach cancer risk in Utah can be attributed to ubiquitous background radiation exposures.

Combined Risk Projections for Specific Sites (cases per 10K person-Gy)

Site (sex)	ERR	EAR	AM	GM	Ratio: AM/GM
Stomach(F)	20	204	75	40	1.87
Liver(M)	17	92	40	28	1.40
Prostate	125	4	89	45	1.99
Lung(F)	482	233	308	290	1.06
Total (M)			921	785	1.17
Total (F)			1361	1230	1.11

Projections for Selected Cancer Sites

Breast Cancer Mortality

- Breast cancer projections based on absolute risk model.
- For EAR projections of mortality risks, BEIR VII uses:

$$M_M(d, e, a) = EAR_I(d, e, a) \frac{\lambda_M(a)}{\lambda_I(a)}$$

- This can result in bias because of birth cohort effects and the “lag” between incidence and mortality.
- Reasonable for most cancers, because the time between diagnosis and death is typically short.

EPA's Projection of Breast Cancer Mortality

- Formula based on
 - Age-specific radiogenic breast cancer rates as calculated in BEIR VII
 - Probability of survival from age of exposure to age of cancer incidence
 - Probability of survival from cancer to age when death may occur.
 - Estimate of breast cancer death rate for breast cancer patients.
- LAR Projection = 0.81% per person-Gy
 - About 30% larger than using BEIR VII method

Central Nervous System and Brain

- Small or negligible component of radiogenic risk for ingestion/inhalation of most radionuclides
- BEIR VII and EPA: residual cancer site
- UNSCEAR incidence model for acute exposures
 - Based on LSS incidence data
 - ERR and EAR linear dose models
 - ERR ↓ with age-at-exposure
 - LAR ~ 0.3%/Gy (ERR model); 0.2%/Gy (EAR model)

Thyroid Cancer Risk Estimates

- BEIR VII and draft NCRP report both used combined analysis (Ron et al. 1995) to arrive at the ERR/Gy. For ages < 15, ERR was 7.7 Gy^{-1} (95% CI 2.1, 28.7)
- Females had twice the ERR/Gy as males, but difference was not significant: BEIR VII, but not NCRP, incorporated gender difference
- No recommendation by BEIR VII regarding any adjustment factor for estimating risks from radio-iodines. Expect NCRP to provide this.
- EPA proposes to use BEIR VII model (with adjustments for DDREF and RBE)

Prenatal Exposures

- Not included in current population risk estimates
- LSS data
 - Suggest risk of adult cancers from prenatal exposures may be similar to that from childhood exposures (assumed equal in Draft Blue Book)
 - But no evidence for risk of childhood cancers
- Case-control studies of *in utero* exposures to diagnostic x rays indicate childhood cancer risk of $\sim 6 \times 10^{-2}/\text{Gy}$ (ICRP)
- Based on an estimated RBE of ~ 1.4 for x rays, γ -ray risk coefficient would be $\sim 4 \times 10^{-2}/\text{Gy}$

Skin Cancer

- Current model: constant EAR
- Current mortality estimate assumes:
 - SCC 1% fatal; BCC fatalities negligible
 - Radiogenic skin cancers 5/6 BCC + 1/6 SCC
- Current incidence estimate neglects nonfatal cases (*usually* not serious)
- New assessment by Shore concludes that essentially all radiogenic cases are BCC

BCC Incidence Model

- EPA proposed model based on recent LSS analysis by Preston et al. (2007)
 - Derived from BCC incidence data
 - Applicable to adults (omits age dependence --- ERR falls off at >10% per y in LSS and Tinea Capitis cohorts)
- Extrapolation from Japanese to U.S. population problematic: interaction of IR and UV

Refined Approach to BCC Incidence Model

- Develop BCC incidence model based on:
 - Comparison of risks to children in LSS and other studies
 - Variation of risk with age
 - Further consideration of differences between induction of BCC in U.S. and Japanese populations

BCC Model Projections

- Large uncertainty in low-dose risk to U.S. population projected from LSS
- UNSCEAR assumes quadratic dose-response for NMSC, which include SCC
- Nonfatal cases not included in BCC incidence projections, consistent with SAB WP Advisory

Skin Cancer (BCC) Mortality

- To estimate mortality, need baseline BCC mortality rate vs. age
 - SEER does not provide incidence or mortality rates for BCC
 - Assume, typical of solid cancers, that incidence increases as $(\text{age})^{4.5}$
 - Published lethality estimate of 0.05% for BCC

Comparison with ICRP and UNSCEAR

Risk models and projections

Comparison with ICRP

- Both primarily based on 1958-98 LSS incidence data
- Similar solid cancer risk models with effect modifiers: sex, age-at-exposure, attained age
- Populations
 - BEIR VII: **U.S.**
 - ICRP: Average of Euro-American and Asian
- DDREF = **1.5** (BEIR VII) or 2 (ICRP)
- Transport
 - **Weighted GM** (BEIR VII)
 - Arithmetic Mean (ICRP)

Comparison with ICRP (Risk Models)

BEIR VII	ICRP
Gender effect <i>depends on site</i>	Gender effect same for many sites
ERR, EAR ↓ with exposure age <i>up to age 30</i> . For most sites, 26% or 34% per decade	ERR, EAR ↓ with age-at-exposure. For most sites 17% or 24% per decade.
Attained age exponent = -1.4 (ERR) or 2.8 (EAR) for most sites	Attained age exponent = -1.65 (ERR) or 2.4 (EAR) for most sites

EPA and “ICRP” Projections of LAR to the U.S. Population

- **ICRP** projections *larger* for ***stomach*** (ratio ~1.7) and ***liver*** cancer (ratio ~1.1) despite larger ICRP DDREF
- **EPA** projections *larger* (ratio ~1.3 to 1.6) for many other sites, e.g. colon, lung, ovary, bladder. Much of this difference is *due to larger ICRP DDREF* (ratio = 1.33)

UNSCEAR 2006 Risk Models

- Models for esophagus, brain/CNS, bone, non-melanoma skin, but none for prostate, kidney
- EAR and ERR models linear in dose (pure quadratic for skin & bone)
- Modifiers depend on site, e.g. sex (lung), attained age (most), time-since-exposure (colon EAR, skin), age-at-exposure (CNS)
- Breast cancer model derived from LSS
- Linear-quadratic solid cancer mortality models with effect modifiers: sex (ERR only), time-since-exposure, attained age

EPA and UNSCEAR Lifetime Risk Projections (%/Sv acute)

Cancer Site	ERR model		EAR model	
	EPA	UN	EPA	UN
Stomach	0.3	0.2	2.8	2.5
Colon	2.0	1.7	1.3	1.5
Lung	4.8	4.4	2.6	2.0
Breast		6.4	4.2	1.4

Uncertainties in Projections of LAR for Low-LET Radiation

EPA Approach

Quantifying Uncertainties

- Reasons to follow BEIR VII
 - Important sources of uncertainty relate to
 - Sampling variation, Risk transport and DDREF
 - Discomfort with use of subjective distributions
- Reasons for departing from BEIR VII
 - RAC recommendation to include uncertainties associated with dosimetry, disease detection & classification, and temporal patterns
 - Compelling evidence for a more appropriate method
 - Consistency, e.g. upper limits for prostate vs. all solid

BEIR VII Uncertainty Intervals (from Table 12-5A)

Cancer Site	LAR 95% Subjective CI (Adjusted by DDREF) Cases per person-Gy
Prostate	(<0, 0.186)
Solid cancers (males)	(0.049, 0.192)

BEIR VII Approach

- $\text{Var}[\log(\text{LAR})] = \text{sum of variances of } \log(\text{LAR}) \text{ for}$
 - Sampling variation
 - Assumes linear dose response model
 - For specific sites did not account for variation associated with age-at-exposure, attained age
 - Risk Transport
 - Assumed “correct” model is either EAR or ERR
 - DDREF
 - Variance of $\log(\text{LAR})$ equals 0.09
- Assumed lognormal distribution for LAR for 95% CI

BEIR VII Distributional Assumptions

- No distribution explicitly assigned for any of the three sources of uncertainty
 - Approx. Lognormal distribution for combined uncertainty might be justified as consequence of CLT ... if no one source dominates
 - For sites for which transport uncertainty dominates, the uncertainty associated with risk transport is implicitly approx. lognormal

Are Uncertainty Intervals in BEIR VII too Wide?

- For some sites, probably yes ...
 - Overstated risk transport uncertainty, e.g. for stomach and prostate cancers
 - Bernoulli assumption to calculate variance
 - Lognormal distribution is implicitly assumed
 - Large sampling variability, e.g. prostate
 - Results sensitive to how cancers are categorized
- For all solid cancer, probably no ...

BEIR VII Approach for All Solid Cancers

- Sampling variation based on the fitting of EAR and ERR models to the LSS all solid cancer data
- Transport risk uncertainty based on the ratio of ERR vs. EAR projections of LAR for all solid cancers. With no DDREF adj.:
 - Males: 0.155 vs. 0.125 (% per person-Gy)
 - Females: 0.223 vs. 0.188

Uncertainties in LAR Projections: Low-LET Radiation

In many ways mimics the approach discussed in Ch. 3 for calculating central projections of risk ...

Derivation of Central Risk Projections & Uncertainty Intervals

Central Projection (B7)	Uncertainty (Ch 4, IREP)
ERR & EAR models for describing risks in LSS	Only ERR models. IREP fits models to data; EPA uses Bayes methods
ML (best) estimates are determined for sex, age at exposure, age	Results determine multivariate distributions for same parameters
	Simulate parameter values
EAR and ERR model based projections of LAR	EPA calculates LAR for each set of parameter values.

Central Risk Projections & Uncertainty Intervals (II)

Central Risk Projection	Multiply Simul. LAR by
Multiply by Inverse of Nominal DDREF	Inverse of Nominal DDREF (if appropriate)
Weighted GM to account for Transport from LSS	Random uncertainty factor. Distribution based on ratio of EAR/ERR projections
	Random uncertainty factors for dosimetry, disease detection, etc.

Central Risk Projections & Uncertainty Intervals (III)

Central Risk Projection	Uncertainty Intervals
	Intervals bounded by 5 th and 95 th percentile LAR values for each site
For uniform whole-body dose, sum site-specific risk LAR projections	Sum is done separately for each simulated set of site-specific LAR values.

Sampling Variability (Traditional Approach)

- Based on maximum likelihood estimates (MLE) of the parameters in EAR or ERR risk models
- Distributions for parameter values
 - Based on properties of the MLE
 - Examples: multivariate normal, lognormal
 - Incorporate correlations among MLE for (different) parameters
- Used in IREP

Why not use the traditional
approach?

Insufficient Data Problem for Specific Sites

- Not enough data to adequately derive parameter value distributions for most cancer sites
- Parameters might be assumed to be the same or set to zero for several sites, e.g. same value for sex or age-at-exposure parameters for “digestive” site cancers.
- Data from different cancer sites are often pooled, e.g. residual site cancers BUT note that this can have unintended consequences ...
- BIG difference in uncertainty in ERR parameter for prostate cancer and “residual” site cancers

Sampling Variability (Bayesian)

- Probability distribution of parameter values is proportional to the likelihood function times a prior distribution
- Typically yields similar results as ML approach when “flat”, “non-informative” priors are used

A Bayesian Approach for All Solid Cancer Risk in the LSS

- Use same parametric models for ERR and baseline rates as in Preston et al. (2007)
 - For example, $ERR(c,s,d,e,a) = \beta(c,s) d \exp(\gamma e) a^n$
- Prior distributions for baseline rates and ERR model parameters normal with extremely large variances
- Essentially reproduced results in Preston et al. (2007)

Bayesian Approach for Site-specific Cancer Risks in the LSS

- Non-informative priors for baseline rate parameters
- $ERR(c,s,d,e,a) = \beta(s) d \exp(\gamma e^*) a^\eta$
 - Cancer sites: stomach, colon, liver, lung, bladder, prostate, uterus, ovary, breast and residual
- What prior distributions should be used for the ERR model parameters?

Linear Dose-Response Parameter

- Non-negative
 - Prior distributional assumption: lognormal
- Sex-dependent, perhaps some similarity among sites.
 - Prior distribution for males: $\log(\beta_j) \sim N(\mu_M, \tau^2)$
- Want to assume nothing or little about how much similarity there is among sites or where these distributions are to be centered
 - $\mu_M \sim N(-1, 10)$; Non-informative prior for tau

Age-at-Exposure Parameter

- What is the prior based on?
 - Very little known for specific sites
 - More uncertainty than implied by BEIR VII 90% CI for all solid cancers: $-0.51 < \gamma < 0.10$
 - The ERR can vary an order of magnitude or more for ages 0-30y
- Prior distribution: $\gamma \sim U(-1,1)$
- No age-at-exposure effect for prostate, uterus, ovary

Attained Age Parameter

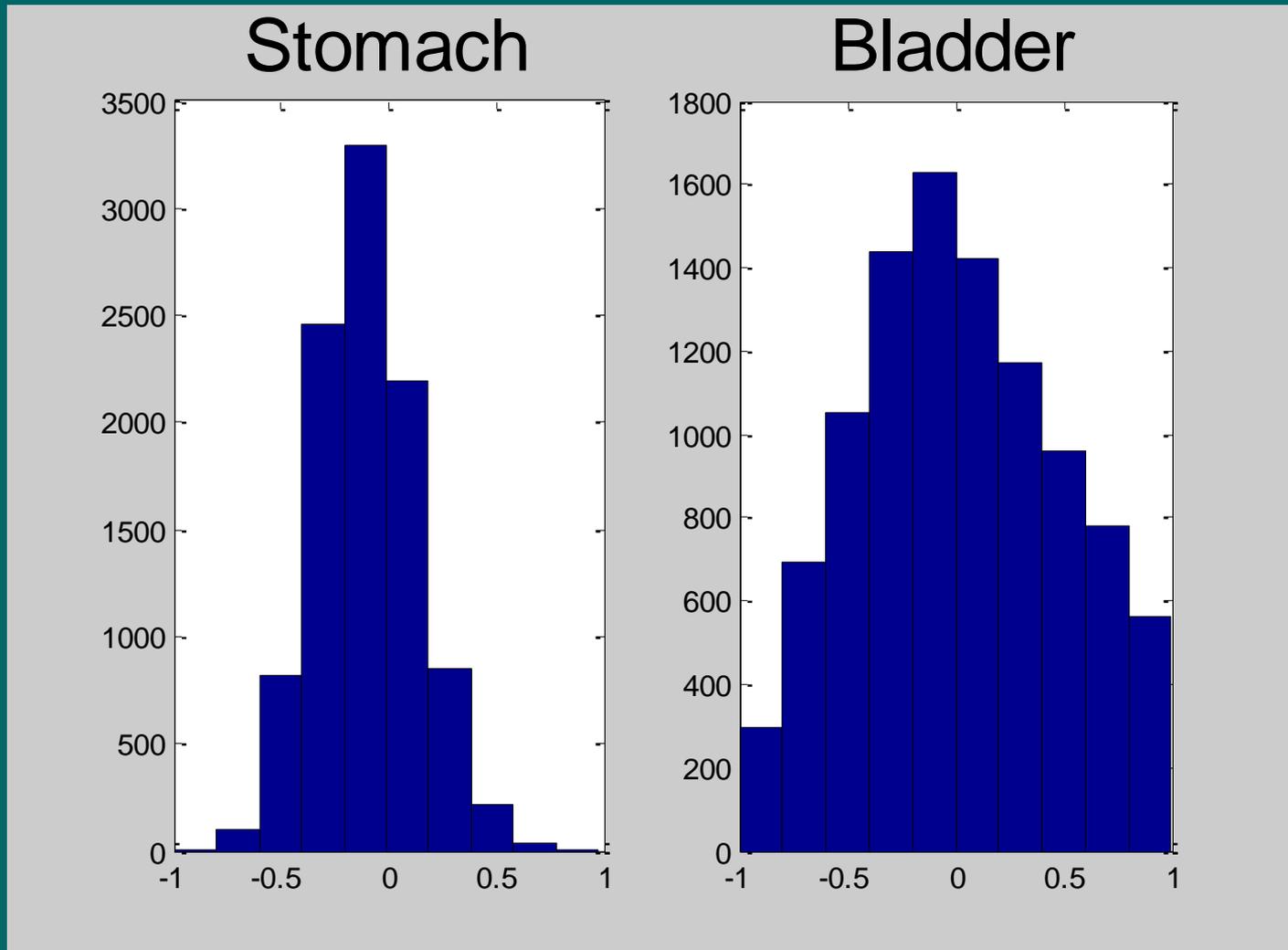
- What properties might the prior distribution for γ have?
 - Center \sim MLE for all solid cancers: -1.4
 - “Smallest” values for attained age parameter should be consistent with model in which EAR does not depend on attained age
- Prior distribution: $\gamma \sim N(-1.4, 2)$
- No attained-age effect for prostate, uterus, ovary

95% Uncertainty Limits for ERR/Sv

(age 30, attained-age 70)

Cancer Site	EPA	BEIR VII
Stomach (F)	(0.24, 0.64)	(0.25, 0.59)
Colon (M)	(0.18, 0.88)	(0.30, 0.89)
Liver (F)	(0.11, 0.69)	(0.08, 0.81)
Prostate (M)	(0.05, 0.56)	(<0, 0.56)
Bladder (F)	(0.24, 2.2)	(0.56, 3.2)

Posterior Distribution for Age-at-Exposure Parameter



Three types of extrapolation

- Risks observed for acute exposures in the LSS to those for lower dose and chronic exposures (DDREF)
- Transport of risks observed in Japanese LSS population to risks in the U.S. (ERR or EAR model)
- Extrapolation of risks observed in the LSS during the follow-up period (1958-98 for solid cancer) to risks for time-since-exposure < 13 or > 53 y

DDREF Uncertainty

- Uncertainty factor: LN(1.0, 1.35)
- GSD same as in BEIR VII

Risk Transport Uncertainty

- Impossible to characterize uncertainty for “true” risk outside interval spanned by EAR & ERR projections
- What matters is how likely the “true” risk is very close to one of the two extremes, i.e. close to either the EAR or ERR projection. We assigned:
 - Probability = 0.5: true risk equals $LAR^{(R)}$ or $LAR^{(A)}$
 - Probability = w^* (0.5): true risk equals $LAR^{(R)}$
- If the “true” risk is well within the interval spanned by the two extremes, then assume the distribution is either uniform or log-uniform. We assigned:
 - Probability of 0.25 to each of these two distributions

Model Uncertainty

(relates to limited follow-up)

- Projected risk associated with the period of follow-up in LSS (time-since-exposure of 13 to 53 y for solid cancer) accounts for about 50% of the projected risk for lifetime exposure
- Extrapolation based on modeling of **age and temporal dependence**
- **Uncertainty factor: LN(1.0, 1.2)**

Uncertainty Associated with Dosimetry

- Systematic (DS02 report): LN(1.0, 1.1)
- Random (Pierce et al. 2008)
 - Assumed independent LN with CV=0.35
 - Linear dose response: probably negligible
 - Curvature
 - effect on DDREF < 20%
 - Uncertainty factor: LN(1, 1.1)
- Nominal Neutron RBE: LN(0.95, 1.05)

Other Sources of Uncertainty

- Errors in disease detection diagnosis
 - Similar uncertainty factor distribution as in NCRP (1997) and EPA (1999)
 - Based on results in Sposto et al. (1992), Pierce et al. (1996)
 - Does not account for misclassification among different cancer types
- Selection bias: LN(1.1, 1.1) based on Pierce et al. (2007)

Uncertainty Limits for LAR for Cancer Incidence

Cancer site	EPA Projection	Lower 5% Limit	Upper 95% Limit
Stomach*	35	11	290
Colon*	116	50	250
Lung*	199	93	490
Prostate	42	0	520
Total*	1010	700	2360*; 2000**

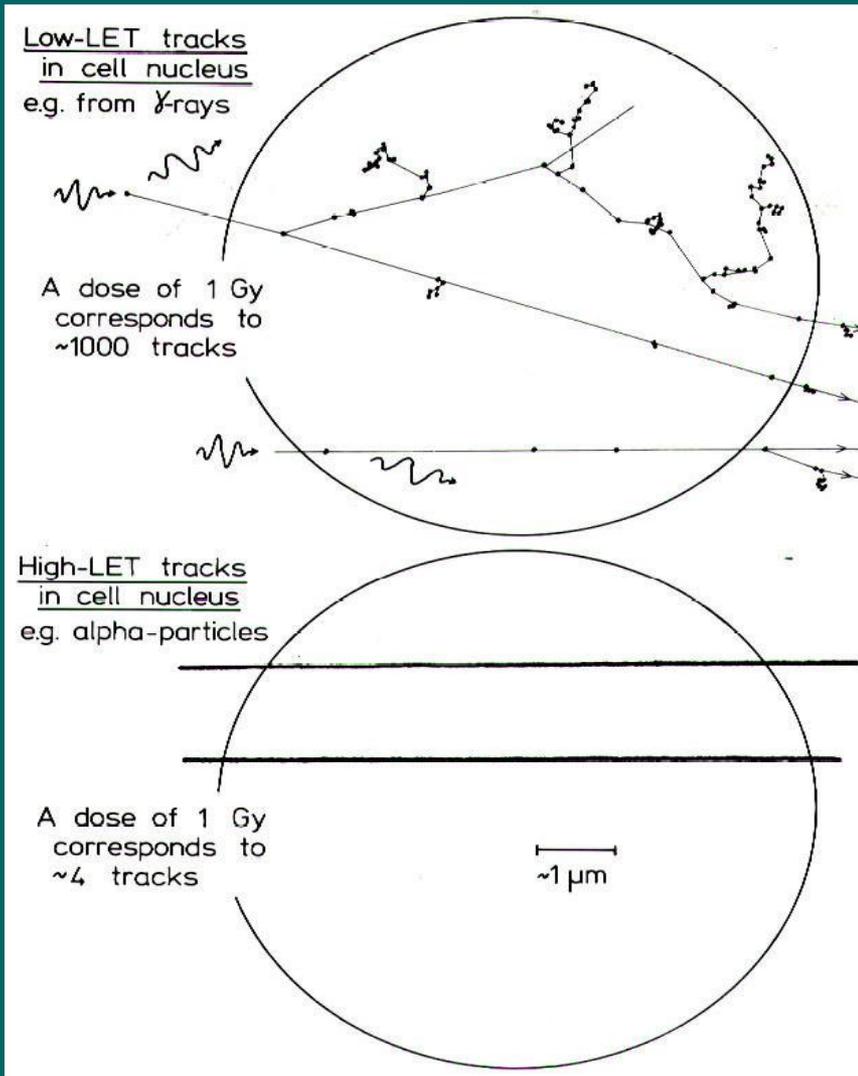
Cases per 10K person-Gy; * Sex-averaged; ** Males

Other Types of Radiation

Moderate LET: X-rays and lower energy γ -rays, some β 's

High LET: alphas

Comparison of High- and Low-LET Tracks Traversing Cell Nucleus



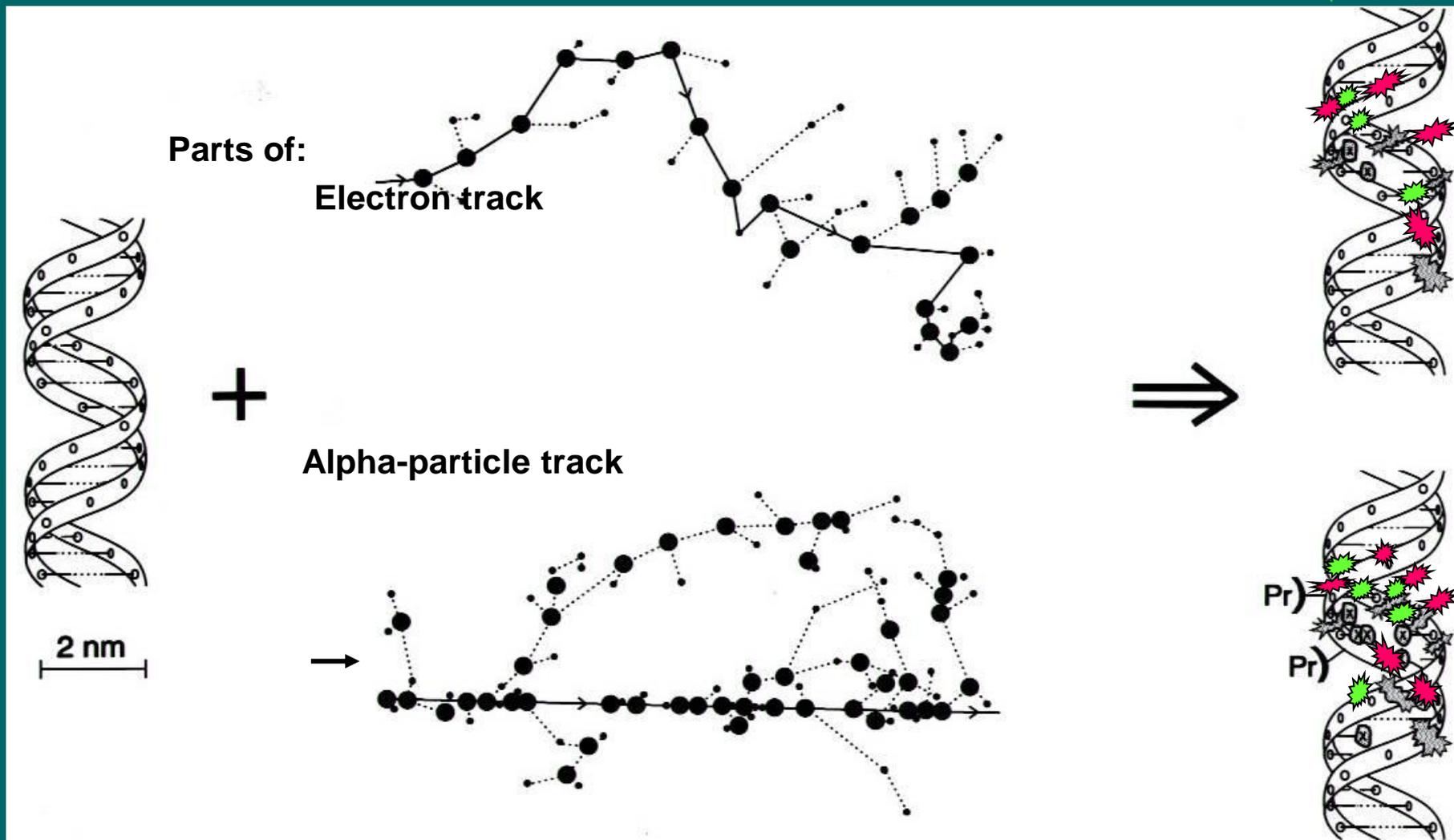
Low-LET reference radiation:
Sparsely ionizing on average,
but $\sim 1/4$ of energy deposited via
denser clusters of ionizations
from low-energy secondary
electrons (on scale of nm)

High-LET radiation:
Densely ionizing on average
(especially for low-velocity ions,
natural alpha-particles, etc)

(D. Goodhead)

Single tracks of 'low'- LET or high- LET radiation can produce Complex Clustered Damage in DNA (Locally Multiple Damaged Sites)

Two examples of Complex Clustered Damage in DNA



Risks from Medical X-Rays

- LET of 200 kVp x-rays about 10x that of ^{60}Co γ -rays
- Laboratory studies indicate an RBE of about 2-3
 - Extensive data on dicentrics, which may not be relevant
 - Lethal mutations
 - Dicentrics may require 2 DSBs
 - Supporting data on tumor induction & life-shortening (see Kocher *et al.* Health Phys **89**:3-32; 2005)
- Epidemiological studies of breast cancer, thyroid cancer, *etc.*, generally have too much uncertainty to test whether $\text{RBE} > 1$

Relative Effectiveness of X-Rays and γ -Rays

BEIR VII (p. 276): *Because of the lack of adequate epidemiological studies, the committee makes no specific recommendation for applying risk estimates in this report to estimate risk from exposure to X-rays. However, it may be desirable to increase risk estimates in this report by a factor of 2 or 3 for the purpose of estimating risks from low-dose X-ray exposure.*

Alternatives for Assessing Risks from “Medical X Rays” (≈ 200 kVp Photons)

- Treat x rays like γ rays: RBE=1
 - Consistent with ICRP
- RBE ≈ 2 , based on laboratory studies
- *Biophysical approach, based on fraction of energy deposited at the end of tracks*

Lower energy x rays (<30 keV) and some low energy betas (e.g., tritium: $E_{av} = 5.7$ keV) might be expected to have an even higher RBE than medical x rays

Report of the Committee Examining Radiation Risks of Internal Emitters (CERRIE)

- Radiobiology theory & RBE experiments
→ ^3H RBE >1
- Observed effects of HTO → RBE values of 1 to 3.5
 - Compared to gamma rays, mostly 1-3
 - Compared to X-rays, mostly 1-2
(predominantly 1-1.5)
 - Values closer to 1, relative to X-rays, for carcinogenesis in animals

Report of the Committee Examining Radiation Risks of Internal Emitters (CERRIE)

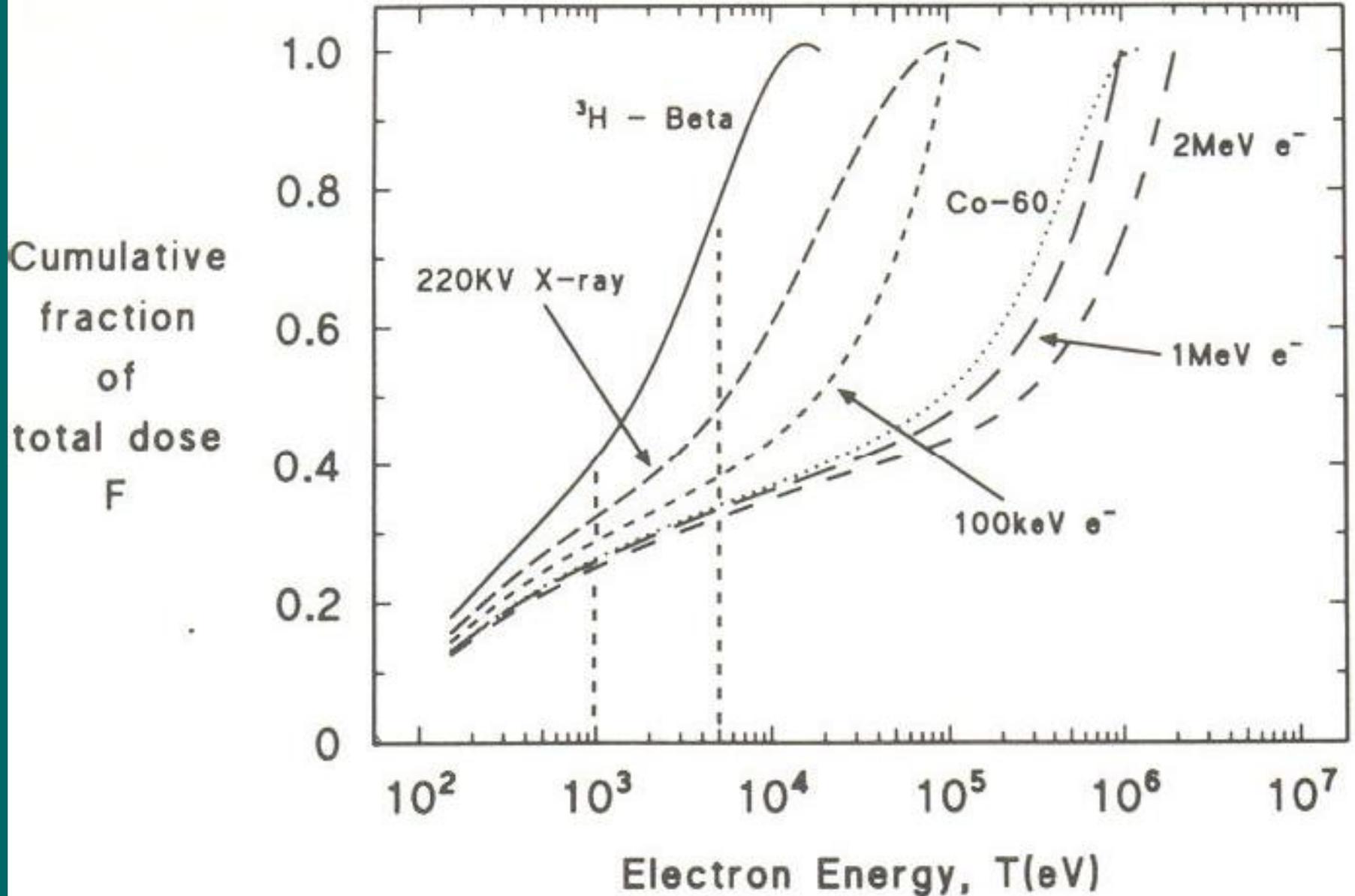
- Low energy beta emissions from ^3H decay have RBE values of up to 2 to 3 (compared to γ rays) for endpoints including cell killing, mutations, chromosome aberrations
- 250 kVp x-rays can be substantially more effective than Co-60 γ rays for producing some effects

Tritium Beta Particle RBE

- *RBE relative to chronic γ radiation (Kocher et al., p. 22)*
 - Carcinogenesis studies: 1-2
 - Genetic: 1.5-3
 - Chromosome aberrations: 1.5-3.5
- Kocher et al. recommended a distribution for ^3H RBE with GM=2.4, and 95% CI (1.2, 5.0) and slightly wider distribution for low energy x-rays.
- *CERRIE Committee recommends an RBE of 2*

*Biophysical approach to estimating
RBE for lower energy photons and
electrons*

F(E): Burch Method

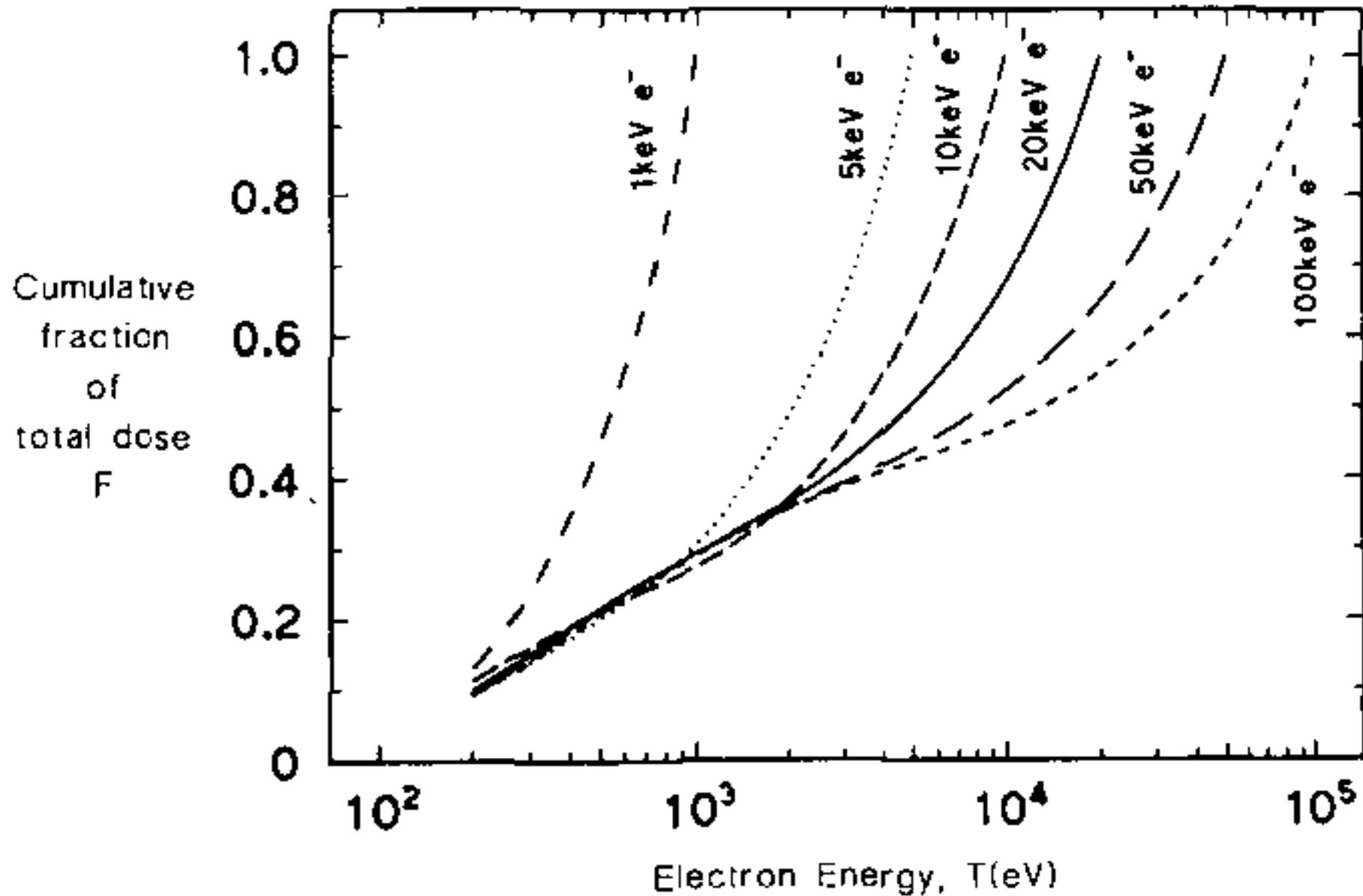


Estimated RBEs

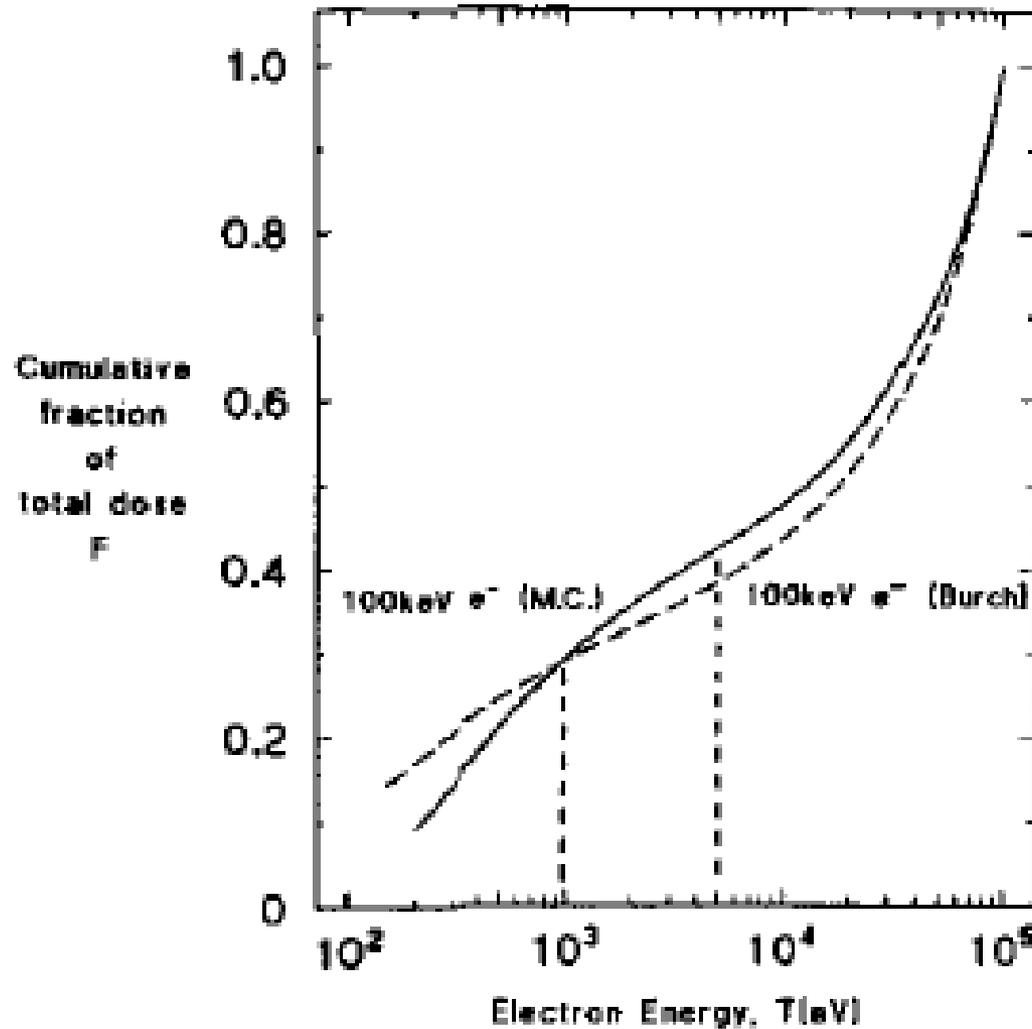
Assuming that the biological effectiveness is proportional to $F(5 \text{ keV})$,

RBE ≈ 2.3 (^3H) and ≈ 1.4 (220 kVp x-rays)
(*relative to ^{60}Co gamma-rays*)

F(E): Monte Carlo



Error in Burch Method (Nikjoo & Goodhead 1991)



RBE for Lower Energy Photons

- For photon of energy E_γ , derive secondary electron spectrum (Compton electrons and photoelectrons)
- Assign an RBE to each secondary electron based on $F(5 \text{ keV})$
- Calculate RBE as weighted average of secondary electron RBEs

Alpha-Particle RBE

- RBE values of 1-80 observed for various end-points, exposure conditions (high values generally refer to a high DDREF for low-LET radiation)
- Default value 20 (recommended by ICRP)
- Deviate from default value where we have relevant data (leukemia, liver, bone)

Sites for Which There Are Human Data on Alpha Particle Risk

- Leukemia
- Bone
- Lung
- Liver

Targets for Alpha-Emitters

- **Colon:** less important with new ICRP GI model
- **Liver:** never dominates α -risk (except for Thorotrast)
- **Bone:** risk estimate directly based on ^{224}Ra
- **Bone marrow:** effective RBE for bone-seekers appears to be low (<3) based on laboratory and epidemiological studies
- **Lung:** α -dose nonuniform; conflicting data
 - Mayak data \rightarrow RBE \sim 20
 - Comparison of LSS & radon data \rightarrow RBE \sim 3
 - Animal studies also conflicting
- **Stomach:** ingested radon

Comparison of LSS and Radon Derived Lung Cancer Risk Estimates

- Exposure different
 - Acute vs. chronic
 - Gamma vs. alpha
 - Uniform vs. non-uniform
- Models differ
 - Age/temporal dependence
 - Gender dependence
 - Interaction with smoking

Leukemia from Alphas

- γ -ray risk estimate from LSS
- For high-LET:
 - Thorotrast data \rightarrow RBE=2
 - Ankylosing spondylitis patients injected with ^{224}Ra \rightarrow RBE=1 or 2, depending on control group
 - Neutron-induced leukemia in mice \rightarrow RBE=2.5
- Propose α -particle RBE=2 (uncertainty range 1-3)

Bone Cancer

- Risk model derived from ^{224}Ra injection data, with updated dosimetry (Nekolla *et al.* 2000)
- Lognormal temporal response: $\text{GM} \approx 12.7\text{y}$, $\text{GSD} \approx 1.8$
- Incidence risk coeff. decreased slightly from 2.7×10^{-3} to 2.0×10^{-3} per Gy (*to bone surface*)
- 35% cases fatal
- Based on beagle ^{226}Ra and ^{90}Sr data, apply RBE of 10 to obtain risk for low-LET
- Low-LET data on medically exposed suggestive of nonlinearity in dose-response

Uncertainties in High-LET Risk Estimates

- Errors in high-LET epidemiological studies (^{224}Ra and Thorotrast patients, Mayak workers)
 - Disease frequency: sampling, misclassification
 - Dosimetry: must consider biokinetics
- Alpha particle RBE
- Errors in low-LET risk estimates