National Cancer Institute

Low-Dose Extrapolation of Radiation-Related Risk

Epidemiological Overview and Quantitative Uncertainty Analysis

Charles Land
Division of Cancer Epidemiology & Genetics Radiation Epidemiology Branch
May 16, 2007

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Introduction

- Ionizing radiation (IR) is a known, and well-quantified, human cancer risk factor
- But estimation of radiation-related cancer risk is uncertain
  - Statistical uncertainty
  - Transfer between populations
  - *Extrapolation to low doses*
    - Possibility of a threshold?
- Uncertainty considerations are important
  - Is there really a risk? How strong is the evidence?
  - How high could the risk plausibly be?

2

We know as much as we do about radiation-related risks mainly because we can (often) estimate organ-specific doses with some precision

Even in human populations

Even when the doses are low

3

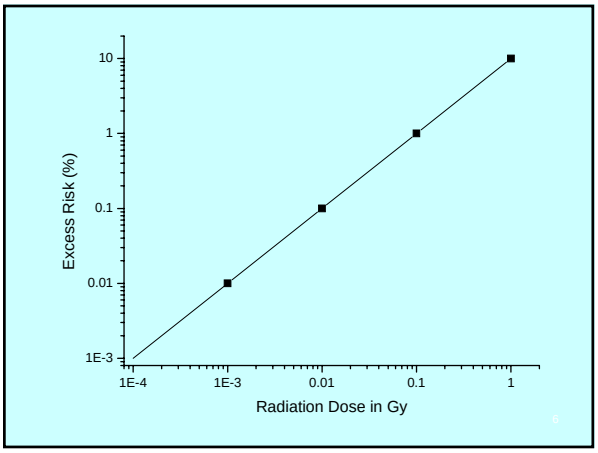
Estimating low-dose cancer risks directly is one of the most difficult tasks there is in epidemiology

4

An overly simple example

- Suppose a *known* population baseline cancer risk of 10% over a 30-year period (i.e., no need to estimate it)
- Suppose a uniform exposure, to dose D
- Suppose also that excess risk is proportional to dose, for $0 \leq D \leq 1$ Gy
- And that risk is doubled for D = 1 Gy

5



6

Statistical power and sample size

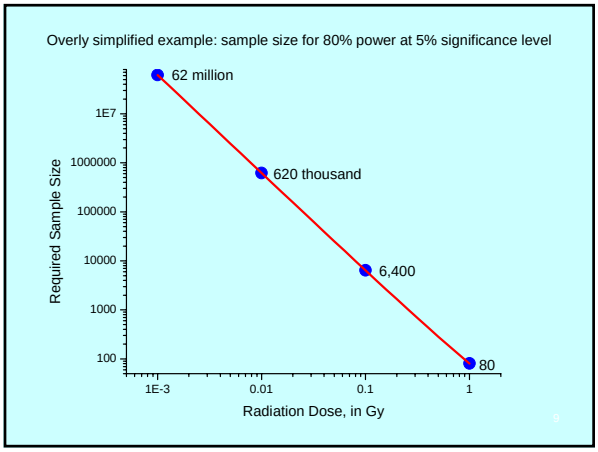
- Consider statistical tests of the null hypothesis of no excess risk at dose D
  - vs. the one-sided alternative that there is an excess
  - for tests at the 5% significance level
- How large a sample size, N, is needed to have an 80% probability of rejecting the null hypothesis when it is false?

7

Example (cont.)

- Number of cancers: binomial (N, p), p = 0.1 H (1+D)
- Est. *excess* risk, ER = (number of cancers) / N - 0.1
  - Approx. normally distributed
  - mean = 0.1 H D
  - variance = 0.1 H (1+D) H [1 - 0.1 H (1+D)] / N
- If no dose response, ER has mean = 0, variance = 0.09/N (standard deviation = 0.3/ $N^{0.5}$)
- We reject the null hypothesis if $N^{0.5}$H ER / 0.3 > 1.645
- *How large must N be for statistical power $ 80%?*

8



9

Suppose N is too small

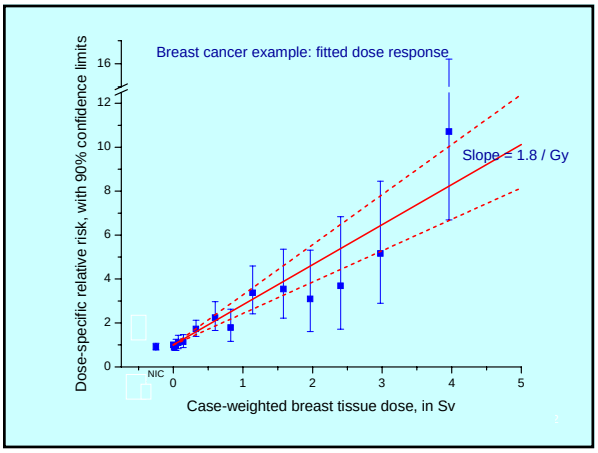
- For D = 0.01 Gy (i.e., excess risk = 0.1%) and N = 50,000, the probability of rejecting the null hypothesis is 19%
  - Under the null hypothesis, it is 5%
  - Failure to reject would be predicted by both null and alternative hypotheses
- Thus, (in the example) even a large study would be very unlikely to yield conclusive results
  - In fact, a significant result would be misleading, because the estimated excess risk would be biased upward:
  - If the lower 95% confidence limit > 0 for N=50,000, the estimate must be > 0.22%, over 2 times the true value of 0.1%

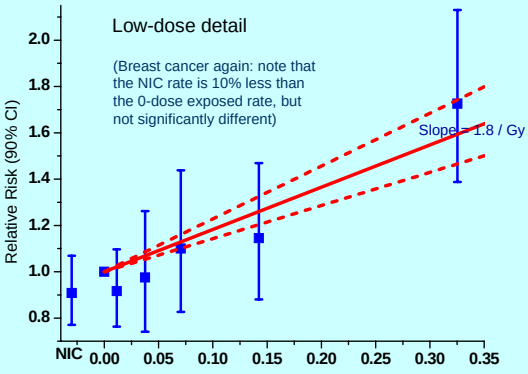
10

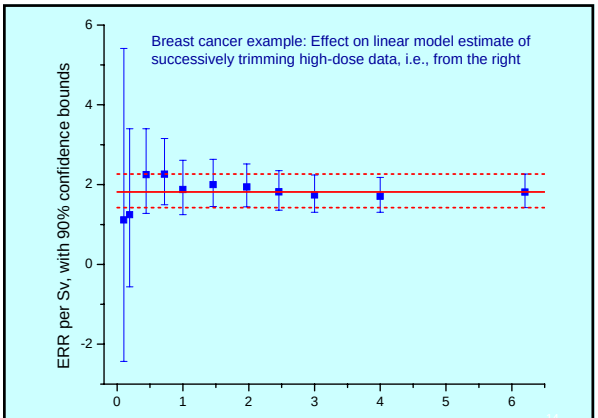
It's actually worse than that:

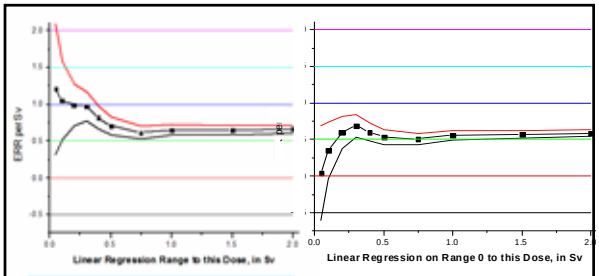
- We don't "know" the baseline; we have to estimate it, which requires about twice as many subjects
- Are we estimating the "right" baseline?
  - How could we possibly control for every non-radiation risk factor that might increase risk from 10% to 10.1%, or decrease it to 9.9%?
  - How many such factors are known?
  - How many are unknown?
- **Low-dose extrapolation of estimates is unavoidable**

11









Regarding the baseline:

Linear regression estimates (" 1 s.d.) after trimming of high-dose data from the right.

Left-hand panel based on proximal (<3000m) survivors only; in right-hand panel the distal (>3000m) survivors also contribute, resulting in a higher zero-dose baseline

Based on data of Pierce & Preston, Radiation Research, 2000; 154:178:86

With all these problems, why do we study populations exposed to low radiation doses?

- Suppose our extrapolated estimates were badly wrong? (especially, way too low?)
- *We would need to know*
- Except for that, we rely on low-dose extrapolation
  - And not on low-dose studies

16

The linear, no-threshold (LNT) theory

- Currently, radiation protection philosophy is based on the LNT model
- The theory states that, at low doses and low dose rates, excess risk is proportional to dose
- That doesn't require linearity of dose response over the entire dose range, just at low doses

17

The LNT theory (continued)

- **For radiation protection, the ICRP posits a "dose and dose rate effectiveness factor" (DDREF) of 2 for low-LET radiation at low doses and dose rates**
  - **(BEIR VII recommends a DDREF of 1.5)**
- **Where the DDREF applies, we divide the linear-model risk based on high-dose data by the DDREF**
  - **In the statistical power example, with a DDREF of 2, excess risk at 10 mGy would be 0.05% instead of 0.1%**
- **A DDREF of 2 is implicit in the linear-quadratic model for leukemia**

18

Implications of the LNT theory: Collective dose

- If the estimated risk from 100 mGy to 10,000 people is 50 excess cancers,
  - The estimated risk from 10 mGy would be 5 excess cancers,
  - But the risk to 100,000 people would be 50 excess cancers
  - And the estimated risk from 1 mGy to 1,000,000 people would also be 50 excess cancers

19

- Of course, you'd never be able to prove it
- It might be expensive to reduce the dose, and the million people might not want to pay for it
- They might feel that someone else should pay for it
- But probably "someone else" would insist on proof

20

The low-dose threshold theory

- If we could agree that there is ***no*** radiation-related cancer risk associated with doses below (say) 2 mGy, the 1 million people exposed to 1 mGy could relax
- Radiation protection might be cheaper and easier than it is today
- It might be even easier with a threshold at 10 mGy
- Unfortunately, a low-dose threshold at 10 mGy or 2 mGy would be difficult to prove, for the same reasons that make it difficult to demonstrate the opposite

21

A long-standing issue*

- Leukemia risk associated with 90-Sr in global fallout from nuclear weapons testing during the 1950s & early 60s
  - Very small doses to very large populations
  - Leukemia risk had been demonstrated from higher-dose exposures:
    - A-bomb survivors, ankylosing spondylitis patients, thymic irradiation patients, **US radiologists (compared to non-radiologist physicians)**

*J Caron, undergraduate thesis
http://resolver.caltech.edu/CaltechETD:etd-03292004-111416

22

- Fruit fly geneticists found linear dose response for drosophila mutations down to 250 mGy
- Moreover, radiation doses to US radiologists were estimated to have accumulated at rate of ~ 1 mGy per day
  - And they had been shown to have a higher cancer risk than non-radiologists
  - Thus, presumably, dose-related risk accumulated daily

23

Edward Lewis and Austin Brues

- Edward Lewis (1957) used available data on leukemia in radiation-exposed populations to fit a linear dose-response model
  - Argued for a mutational factor in radiation leukemogenesis
  - Estimate: 2 excess leukemias per million per cGy per year
  - Argued that there was no experimental or epidemiological basis for radiation threshold

24

- Austin Brues, for AEC: toxicology model argues for radiation threshold – why should radiation be different?
  - Clearly there was a leukemia risk at high doses
  - But no direct proof of excess leukemia risk at very low doses
- Eventually, the LNT model prevailed in radiation protection policy
  - But we are still in the same debate, and using many of the same arguments

25

Quick review of radiobiology

- Unique type of DNA damage by ionizing radiation involves multiple lesions in close proximity (clustered damage)
  - ~ 70% for high-LET, ~30% for low-LET
- Can be induced by single electron track
- Can compromise repair machinery
- Processing and misrepair can lead to chromosome aberrations and mutations
  - Damaged or altered cells can escape cell cycle checkpoint and apoptotic pathways

26

Quick review of radiobiology

- Unique type of DNA damage by ionizing radiation involves multiple lesions in close proximity (clustered damage)
  - ~ 70% for high-LET, ~30% for low-LET
- Can be induced by single electron track
- Can compromise repair machinery
- Processing and misrepair can lead to chromosome aberrations and mutations
  - Damaged or altered cells can escape cell cycle checkpoint and apoptotic pathways

27

Radiobiology Review (cont)

- Roles of radiation-related adaptive response, genomic instability, & bystander effects not well understood; may not be relevant to threshold question
- Critical radiation events in tumorigenic process are mostly early events involving DNA losses and critical genes
- Mechanistic arguments support linear response in low-dose region

28

Evidence differs by tissue

- Stem cells in the intestinal crypt of laboratory mouse: Selective retention of template DNA strands in stem cells, providing protection of the stem cell genome (Cairns 1975; 2002)
- But induction of small intestine cancer by high-dose radiation of exteriorized loop is a well-established experimental procedure
  - Threshold?
- Very different for colon, for which there is clearly a low-dose risk

29

Epidemiological evidence

- For threshold:
  - Shape of dose responses for basal cell skin carcinoma, bone, soft tissue sarcoma, rectum, small intestine
  - Apparent fractionation effect for lung cancer
- Against threshold:
  - X-ray pelvimetry studies (leukemia, solid cancers)
  - TB, scoliosis fluoroscopy studies (female breast)
  - Linear dose responses for female breast, thyroid, all solid cancers combined

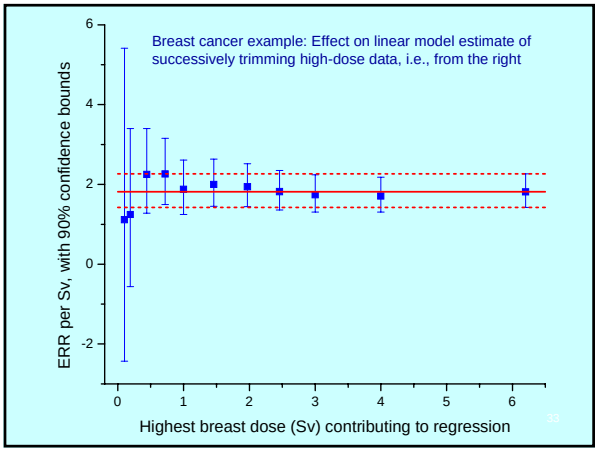
30

- Experimental and epidemiological evidence doesn't preclude tissue-specific thresholds
- But also, it doesn't support existence of a universal threshold, operating in all tissues
- And a threshold has to be universal to have much influence on radiation protection policy

31

But estimates of low-dose risk are uncertain

32



33

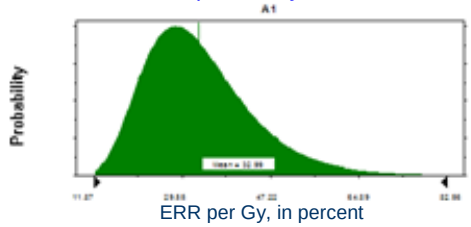
Major uncertain components

- Linear model estimate of ERR at 1Gy
  - Note confidence limits in previous slide
- Correction for transfer from LSS to US population
- DDREF to be applied at low doses and low dose rates
- Possibility of a universal threshold at some dose above that of interest

34

Lognormal statistical uncertainty distribution for all solid cancers, LSS population. Sex-averaged ERR per Gy at age 50 following exposure at age 30.

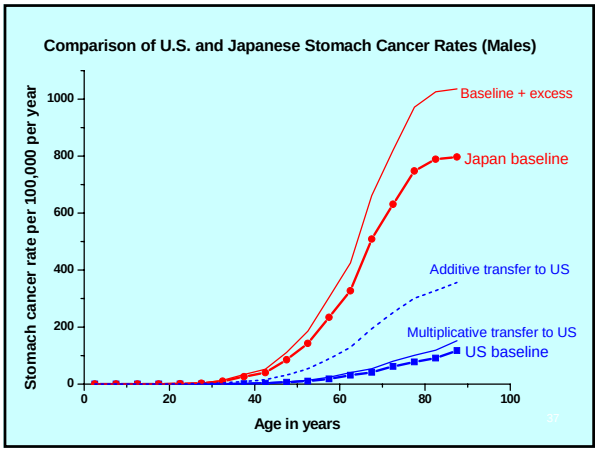
Mean 0.33, 90% probability limits 0.18 - 0.43.



Transfer to the U.S. population

- Baseline cancer rates differ between Japan and the U.S.
- This has uncertain implications for radiation-related risk in the US population
- For a few cancers, choice of a transfer model can really make a difference
- Example: for stomach cancer, Japanese rates are 12 times those in the United States

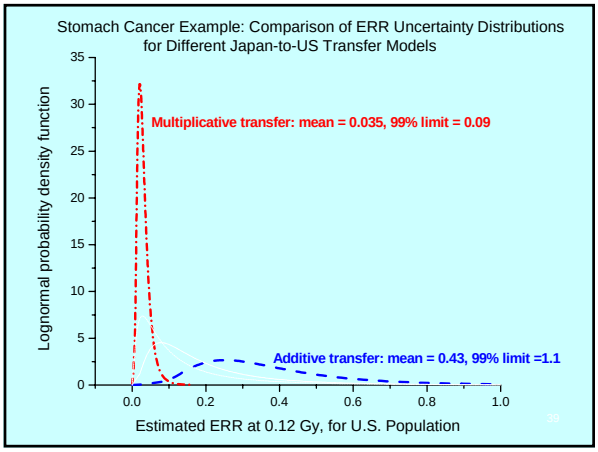
36

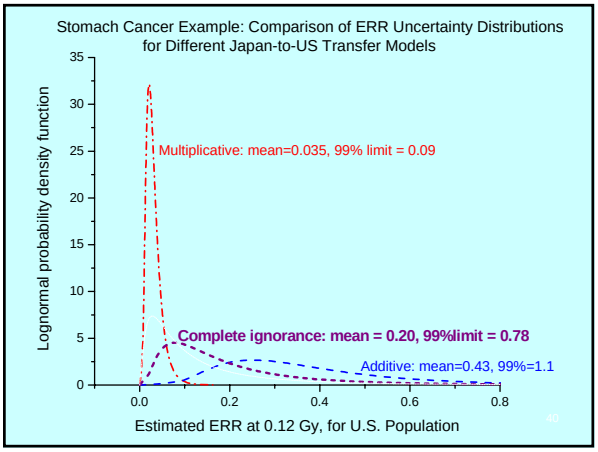


How to transfer ERR estimate from Japan to the US?

- Use the A-bomb survivor ERR
  - **Multiplicative transfer – assume ratio of excess to baseline doesn't change**
  - Biologically plausible if baseline rates differ because of differential exposure to promoters
- **Use the LSS excess rates** (ERR H baseline)
  - **Additive transfer**: **use the Japanese ERR, times 12**
  - Plausible if baseline rates differ because of differential exposure to competing cancer initiators

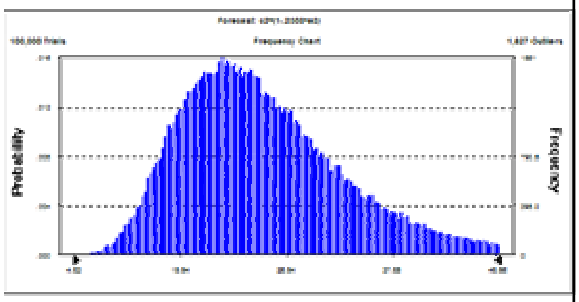
38





- For all cancers combined, the baseline rates are not very different between the US and Japan
  - So the difference between multiplicative and additive transfer is not very great
- In this case, "complete ignorance" about population transfer does not add much uncertainty to the estimate

41

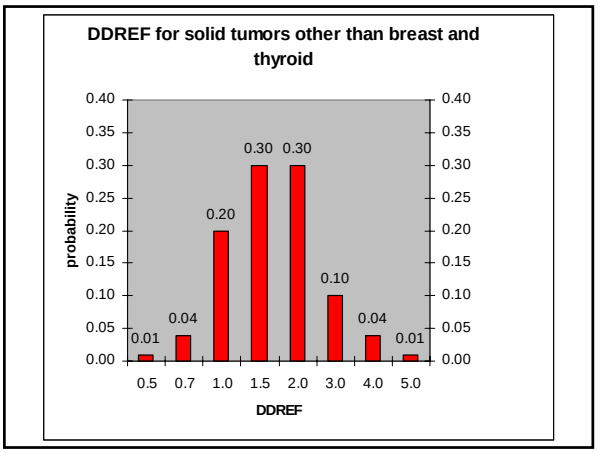


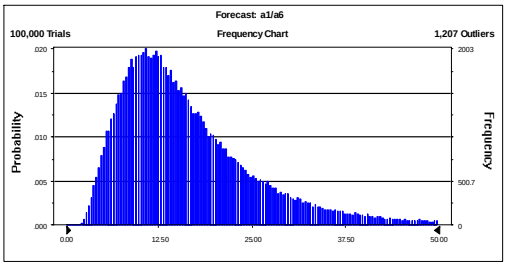
Monte Carlo simulation of the uncertainty distribution for cancer ERR at 1 Sv, after transfer to a U.S. population: the simulated distribution is approximately lognormal, mean 0.25 and 90% probability limits 0.13 – 0.41.

Uncertain DDREF

- Using a DDREF of 2 at low doses and low dose rates means dividing the linear-model estimate by 2
- Using an uncertain DDREF means dividing by an uncertain number
- Which adds uncertainty to the low-dose estimate

43





Monte Carlo simulation of the uncertainty distribution for low-dose cancer ERR per Sv, after division by an uncertain DDREF: the simulated distribution is roughly lognormal with

mean 0.17 and 90% probability limits 0.08 – 0.36.

Point of view:
Implications of an uncertain risk estimate

- It is widely recognized that risk estimation is uncertain
  - Uncertainty distributions like the one in the previous slide aren't a new idea
- Formally, radiation protection today is based on a single, central value, e.g., the mean

46

Point of view (cont.)

- But that ignores important information
- The uncertainty distribution summarizes all the *identified* information about risk
  - (We can't think of everything)
- The exposed population presumably is concerned with upper limits on risk
  - How bad might it be? Is the benefit really worth the risk?

47

Point of view (cont.)

- Those liable for the expense of dose reduction tend to be more concerned with lower limits
  - Is there strong statistical evidence that there is a risk, or that the risk high enough to be of concern? (Can you prove it?)
- Radiation protection is a political process, which depends on the consent of those affected
  - If it is to work, the various points of view must be considered
  - And must be *seen* to be considered

48

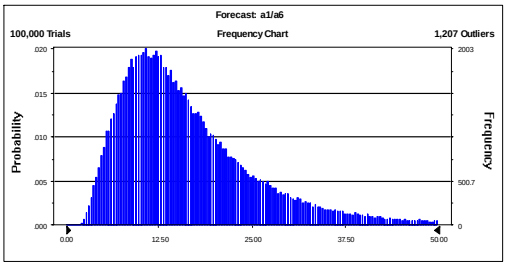
- The process of estimation determines the final uncertainty distribution for excess risk
- That distribution summarizes all we know, think we know, or had to assume in order to get the estimate
  - That includes the uncertainties of the parts

49

Uncertain possibility of a threshold

- Consider a threshold somewhere above (say) 1 mGy as an uncertain possibility, with probability *p*.
- Then, with probability *p*, ERR for radiation-related cancer at 1 mGy would be zero
- And with probability *1-p*, ERR at 1 mGy would be distributed lognormally with
  - mean 0.00017
  - upper 95% probability limit 0.00036

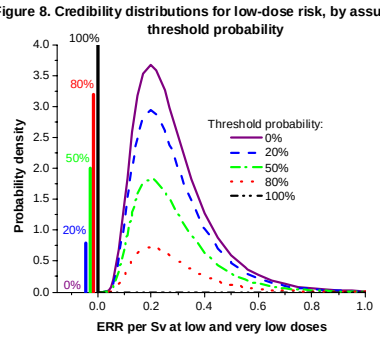
50



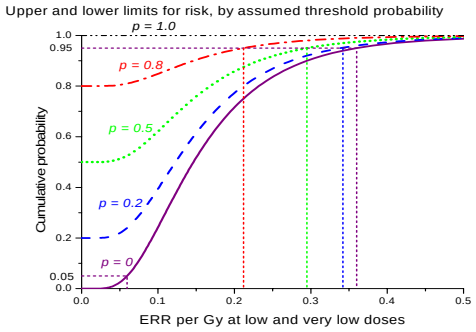
Monte Carlo simulation of the uncertainty distribution for low-dose cancer ERR per Sv, after division by an uncertain DDREF: the simulated distribution is roughly lognormal with

mean 0.17 and 90% probability limits 0.08 – 0.36.

Uncertain possibility of a threshold



Uncertain threshold possibility



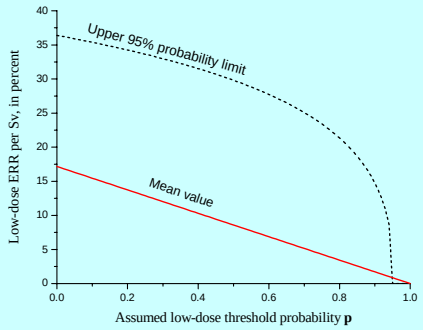
Assume uncertain threshold possibility, with probability *p*

- ERR at 1 mGy is estimated to be
  - zero with probability *p*
  - lognormal (0.00015, 1.73) with probability *1-p*

p	mean	5% limit	95% limit
0	0.00017	0.00006	0.00036
0.2	0.00014	0	0.00034
0.5	0.000085	0	0.00030
0.8	0.000034	0	0.00021
1	0	0	0

54

Effect of uncertain threshold assumption on a lognormal (mean 0.17, upper 95% limit 0.36) uncertainty distribution for ERR per Sv



55

Implications of an uncertain threshold for radiation protection

- For the simple case (threshold probability = *p*)
  - The mean of the uncertainty distribution for excess risk is multiplied by *1-p* and therefore decreases with increasing *p*
  - It doesn't disappear until *p* reaches 1
  - An upper uncertainty limit also decreases with increasing *p*, but the decrease is rather slow until *p* approaches the uncertainty level for the upper limit.
- The epidemiological and radiobiological information available does not suggest a high value for *p* at any dose level high enough to matter.
- Thus, allowing for the *possibility* of a threshold would make very little difference to radiation protection

56

Conclusions

- Unless the benefit of a low-dose exposure clearly outweighs the risks, most people would prefer not to be exposed
- So upper limits on risk are important.
- If a threshold is judged to be very likely, it would make sense to take that into account
- Otherwise, the threshold possibility should make very little difference to radiation protection
- LNT is an appropriate basis for radiation protection

57

The NIH radio-epidemiological tables – a real-life example

- In 1983 Congress passed a law directing the Secretary of the Department of Health and Human Services (DHHS) to compile "probability of causation" tables
- PC = ERR/(1+ERR) estimates the actuarial likelihood that a given cancer diagnosis could be attributed to a given prior history of radiation exposure
- The mandate specified that the tables be updated as new scientific information became available

58

- DHHS Secy directed NIH to respond, and a working group was put together
- WG (NIH, 1985) computed "radio-epidemiological tables" for estimating site-specific ERR as a function of exposure history, age at diagnosis, and other data
  - Uncertainty assessment included
- Tables used by the Dept. of Veterans Affairs (VA) to adjudicate compensation claims by military veterans
- VA asked CIRRPC (another govt. comm.) to help make the tables easier to use

59

- CIRRPC devised "screening" tables to screen out obviously unmeritorious claims
- CIRRPC tables screened out claims for which the 90th, 95th, or 99th percentile of the uncertainty distribution for PC = ERR/(1+ERR) was < 50%
- VA decided to accept claims not screened out at the 99th percentile, i.e., at the least stringent screening level
- In 1998 VA asked NCI to update the tables
- REB replaced tables by "Interactive Radioepidemiological computer Program" (IREP)
- Program computes uncertainty distribution for PC

60

Applications

- IREP easily modified to calculate yearly ERR for site-specific cancer risk for arbitrary exposure history
  - Lifetable-weighted sum estimates lifetime risk
- Example: Fallout and thyroid cancer risk calculator
- Example: Site-specific lifetime risk calculator
- Next version of IREP to reflect new RERF tumor registry data, BEIR VII report, etc.

61

2000 Energy Employee Occupational Injury Compensation Act (EEOICPA)

- Dept of Labor directed to use radioepi tables (& therefore IREP) to adjudicate claims by DOE & DOE contractor employees
- NIOSH to reconstruct doses
- Compensation claims to be awarded under 99th percentile rule
- NIOSH uses modified version of IREP to calculate PC & advises DOL on claims adjudication

62