The Linear No-Threshold Model (LNT): Made to Be Tested, Made to Be Questioned

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Regulatory Organizations

- NCRP (Nat'l Council on Radiation Protection and Measurements)
- ICRP (Int'l Commission on Radiologic Protection)
- ICRU (Int'l Commission on Radiation Units and Measurements)
- DOE (Department of Energy)
- NRC (Nuclear Regulatory Commission)
- NAS (National Academy of Sciences)
- UNSCEAR (UN Scientific Committee on the Effects of Atomic Radiation)
- EPA (Environmental Protection Agency)

The Public's Fear of Radiation

"Fear vs. Radiation: The Mismatch (NYT 2013)"

Hiroshima/Nagasaki results:

- 112K survivors studied (80% exposed/20% control)
- Nearly 11K died of cancer, 500 estimated to have died from the radiation exposure
- That's less than 1% deaths from radiation (all doses)
- <100 mSv cause no detectable elevation of illness/disease

Fukushima results:

- 0 deaths attributed to radiation but relocation of individuals from nearby communities to distant locations resulted in >400 deaths.

The Precautionary Principle

- If an agent has a suspected risk of causing harm to the public, the burden of proof that it is not harmful falls on those overseeing the agent. Therefore, use of the linear no threshold model (LNT) is expected to “safely” address risk when high-dose radiation observable effects are extrapolated downwards to low doses given at low dose rates.

The “Problem” with Studying Radiation

- Large variability of background radiation.
- No radiation signature (cancer or heritable effects).
- Radiation is a poor mutagen/carcinogen.
- Easy to detect compared to chemicals and other toxic agents so public concern may be easily manipulated.

Issues

- Acute vs chronic doses
- Epidemiological data is from high doses
- Low LET

- Important biological endpoints
  - In utero exposures
  - Cancer induction
  - Heritable effects

Data Analysis and Confounding Effects

- Data available in radiation epidemiology studies
- Demographic data

  age, sex, calendar period
- Data on other risk factors

  smoking, diet, family history of cancer
- Radiation exposure data

- Data available in several huge animal studies

Radiation Risk Models

- Function that relates disease risk (relative or absolute) to exposure (dose) and factors that might modify this risk.
- Models are developed by analyzing epidemiologic data.

Direct Estimates of Risk

- Relative risk (RR)
- Excess absolute risk (EAR)
- Excess relative risk (ERR)

Relative Risk (RR)

- RR is the rate of disease in an exposed population divided by the rate of disease in an unexposed population divided by the rate of disease in an unexposed population

  (rate in exposed pop/rate in unexposed pop)

  Relative risk has no units

Easier to evaluate than absolute risk

Can be estimated from either cohort or case-control studies

Useful for Indicating the strength of an association

Contributes to establishing causation

Excess Relative Risk (ERR) Model

- ERR is the rate of disease in an exposed population divided by the rate of disease in an unexposed population divided by the rate of disease in an unexposed population, minus 1.0

  (rate in exposed pop/rate in unexposed pop) – 1.0

  Relative risk has no units

Excess Relative Risk (BEIR VII, page 148)

(rate in exposed pop/rate in unexposed pop) – 1.0

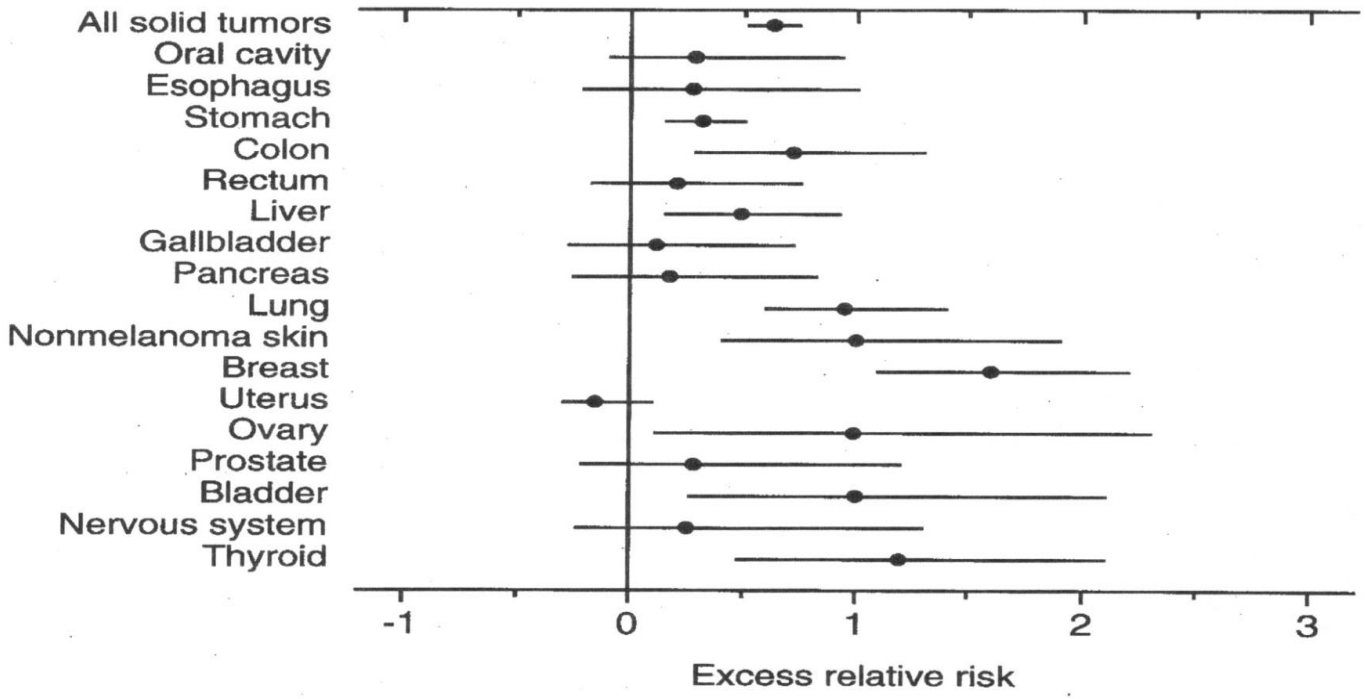


FIGURE 6-4 Excess relative risk at 1.0 Sv (RBE 10) for solid cancer incidence and 95% confidence interval, 1958–1987. SOURCE: Reproduced with permission from Thompson and others (1994).

Excess absolute risk (EAR) model

- EAR = rate of disease in exposed pop – rate of disease in unexposed pop (expressed per population with a time frame)
- More suitable when there are significant differences between the pop under investigation and the pop on which the model was based.

- Useful for estimating burden of disease in a population
- Comparing risks and benefits of interventions/treatments
- Counseling exposed subjects
- More difficult to evaluate than the RR Requires cohort data

Lifetime Risk (All Solid Cancers)

	Males	Females
Excess cases (0.1 Gy)	800	1300
Number of cases (0 dose)	45,500	36,900
Excess deaths (0.1 Gy)	410	610
Number of deaths (0 dose)	22,100	17,500

per 100,000 individuals (typical US age distribution)

Solid cancer risk is based on the linear model

Lifetime Risk (Leukemia)

	Males	Females
Excess cases (0.1 Gy)	100	700
Number of cases (0 dose)	830	590
Excess deaths (0.1 Gy)	70	50
Number of deaths (0 dose)	710	530

per 100,000 individuals (typical US age distribution)

Leukemia risk is based on the linear-quadratic model

Regulatory Issues

Deleterious Effects of Radiation

- In utero exposures (mental retardation) 40%/Sv
- Carcinogenesis (general population) 5%/Sv
- Heritable effects (future generations) 0.2%/Sv

Radiation exposure data

- Varies tremendously from study to study
  - Exposed/unexposed
  - Dose estimates for individuals
- Timing of exposure(s)
- Characteristics of exposure
  - Dose-rate
  - Internal/External
  - Linear Energy Transfer (LET)

Statistical Power

- The probability that under the assumptions and conditions implicit in the model, it will detect a given level of elevated risk with a specific degree of significance.
- Depends on size of cohort, length of follow-up, the baseline rates for the disease, distribution of doses within the cohorts.

Epidemiological Data Sources

- Studies from atomic bomb survivors
- Medical radiation studies
- Occupational radiation studies
- Environmental studies

Atomic Bomb Survivors

- The primary epidemiological source for estimating risk at low doses at low dose rates.
- Life Span Study – 120,000 survivors.
- No radiation induced cancers <100 mGy.
- Data does not exclude a threshold dose.

Medical Radiation Studies

- BEIR VII examined risk for lung, breast cancer, thyroid cancer, leukemia, and stomach cancer.
- For most cancers observed at high doses, a linear model worked well. However, at low doses, cancer risk wasn't detectable until exposures exceeded 100 mSv.

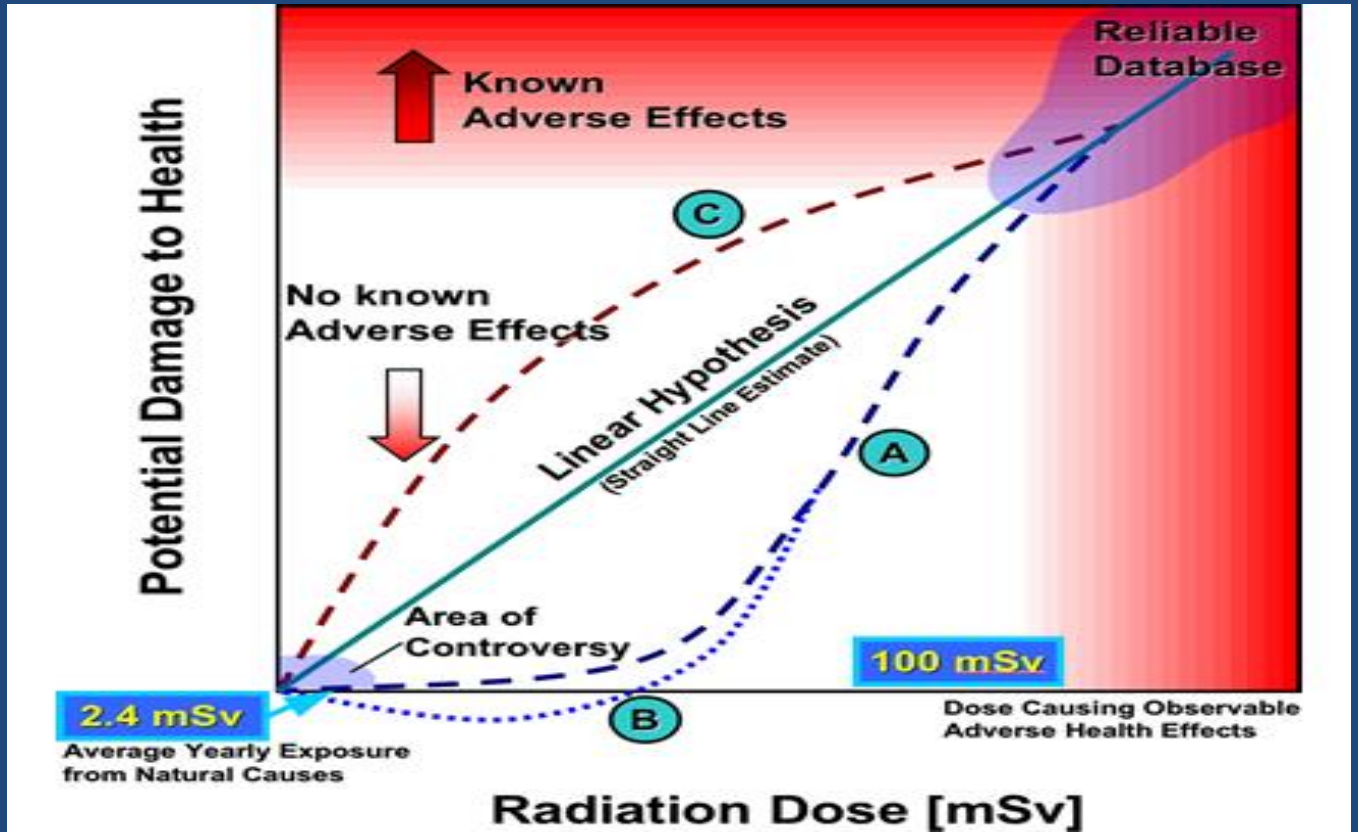
Occupational Radiation

- In the BEIR VII report, radiation workers in the nuclear industry (400K workers world-wide) showed no increased cancer risk (all cancers including leukemia). *Note: The Canadian data initially showed an increase in cancer risk but was re-analyzed and fell in line with the other studies that showed no increase in the cancer risk. Recently, the INWORKS study (BMJ 2015; 351) found a risk of cancer from radiation.*

Environmental Exposures

- Populations living in high natural background radiation.
- Populations exposed to fallout from nuclear accidents.
- Populations living near nuclear facilities.

Extrapolation Models



Risk Models (BEIR VII, page 7)

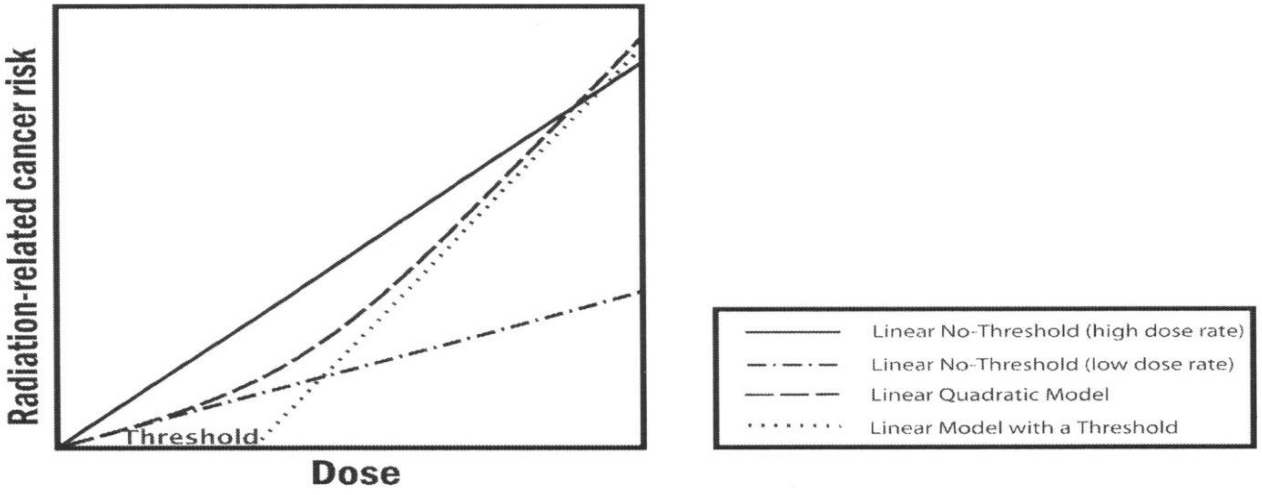


FIGURE PS-3 The committee finds the linear no-threshold (LNT) model to be a computationally convenient starting point. Actual risk estimates improve upon this simplified model by using a dose and dose-rate effectiveness factor (DDREF), which is a multiplicative adjustment that results in downward estimation of risk and is roughly equivalent to using the line labeled "Linear No-Threshold" (low dose rate). The latter is the zero-dose tangent of the linear-quadratic model. While it would be possible to use the linear-quadratic model directly, the DDREF adjustment to the linear model is used to conform with historical precedent dictated in part by simplicity of calculations. In the low-dose range of interest, there is essentially no difference between the two. Source: Modified from Brenner and colleagues.[17]

Factors that Influence Risk Assessments at Low Dose/Low Dose Rate

- Radiation-sensitive subpopulations
- Adaptive response
- Bystander effects
- Hyper-radiosensitivity at low doses
- Genomic instability
- Hormesis
- Extrapolation from acute high doses to low doses received at low dose rates

Table 1. Data selection by inclusion criteria.

Studies	Treatments	Animals	Criteria
302	6,810	452,595	All animal data from ERA and Janus archives
124	2,611	205,758	Individual-level animal data available
35	827	116,542	External radiation exposures
35	457	76,096	Low-LET, whole body exposures
34	230	45,730	Total dose equal to or below 1.5 Sv
32	175	43,043	No other treatments (e.g. no chemical exposures)
26	119	34,439	Digitized data on treatment and lifespan confirmed by primary literature
16	91	28,289[a]	At least three distinct treatment groups per stratum so that a linear-quadratic model could be fitted
9	71	20,325[b]	At least three distinct treatment groups after stratifying by study ID

The number of distinct studies, treatment groups, and individual animals that remained eligible for analysis after application of each of the inclusion criteria. Complete definitions of these criteria are elaborated in the methods section.

[a] dataset used for the "BEIR VII model", "Hormetic correction", and "Heterogeneity correction" models.

[b] a more restricted dataset used in the "Stratification by study" and "Survival analysis" discussed in the results section.

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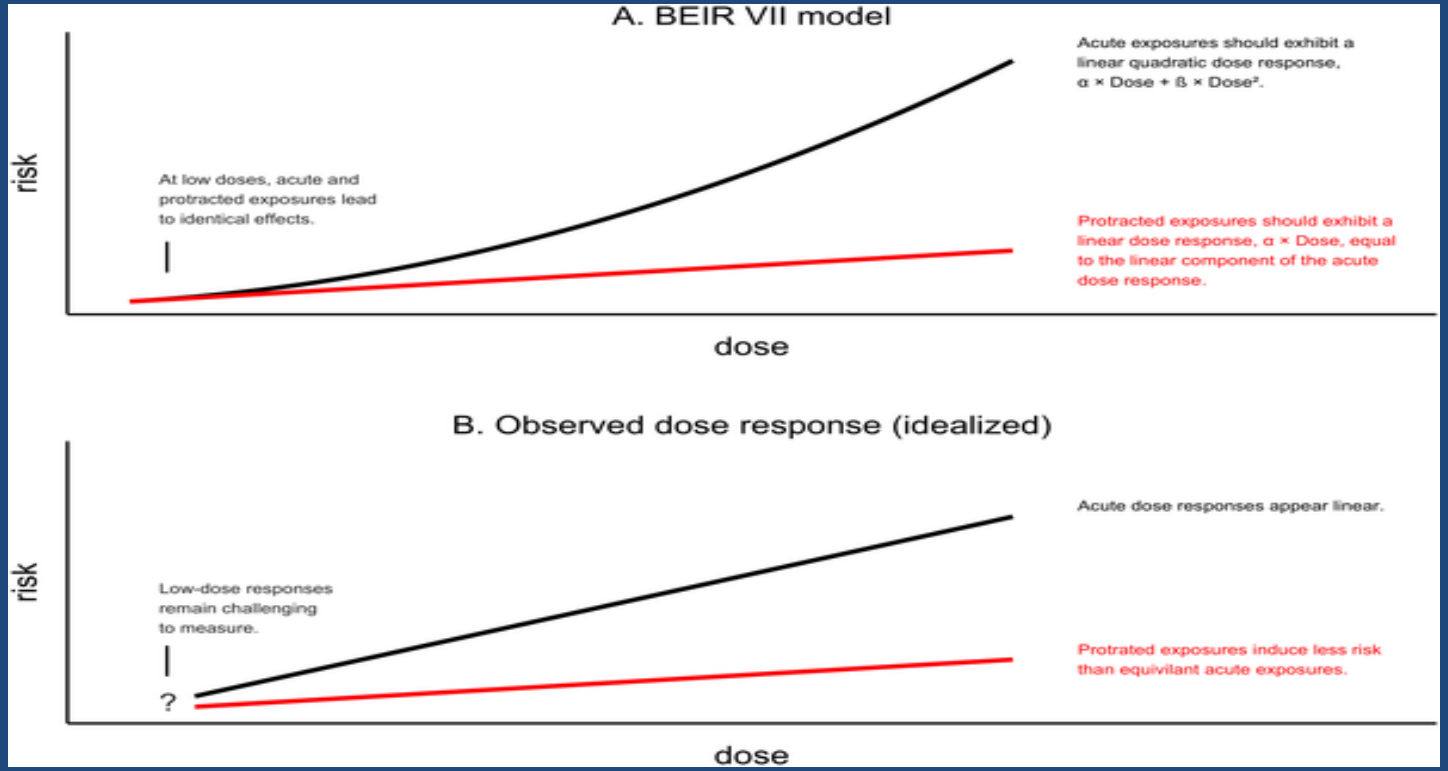
Haley BM, Paunesku T, Grdina DJ, Woloschak GE (2015) The Increase in Animal Mortality Risk following Exposure to Sparsely Ionizing Radiation Is Not Linear Quadratic with Dose. PLoS ONE 10(12): e0140989. doi:10.1371/journal.pone.0140989
http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0140989

PLOS | ONE

Fig 2. Two possible dose response models based on linear-quadratic model (A) and linear/linear model (B).



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http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0140989

Issues Against the LNT

- The adaptive response can substantially modify the effects of radiation.
- The bystander (off target) effect has been amply demonstrated.
- Repair of radiation-induced mutational events is efficient.
- Apoptosis reduces radiation-induced genetic damage.
- Hormesis has been demonstrated in epidemiological and laboratory animal studies.

Stochastic Effects

- Includes genetic effects and cancers (subset of somatic effects)
- Single cell effect and therefore as low as you go with dose, there is still a theoretical possibility of a genetic effect or cancer.
- There is no threshold dose below which no effect will be visible.

Radiation Hormesis

- Low radiation doses activate the **immune system** (improved wound healing, increased lymphocyte production, etc).
- Low doses have been shown to increase the **lifespan** of animal and humans in multiple studies.
- Doses below 100 mSv in the Japanese A-bomb survivors showed no increase in **cancer** incidence.

Active Research

- Molecular markers of DNA damage
- DNA repair fidelity
- Adaptive response, hypersensitivity, bystander effect, hormesis, genomic instability
- Mechanistic effects (hormesis, tumor signaling)
- Genetic factors
- Heritable genetic effects of radiation
- Continued epidemiologic studies
- Review to include additional animal data

Valuable Resources for this Presentation

- David J. Grdina, PhD, Professor, The University of Chicago

- Health Risks From Exposures to Low Levels of Ionizing Radiation: BEIR VII Phase 2. National Research Council, Washington, D.C.: National Academies Press; 2006.
- Calabrese, Edward J. and O'Connor. Estimating Risk of Low Radiation Doses – A Critical Review of the BEIR VII Report and its Use of the Linear No-Threshold (LNT) Hypothesis. Radiation Research 182: 463-474 (2014).
- Haley, Benjamin M., Paunesku, Tatjana, Grdina, David, J., and Woloschak, Gayle, E. The Increase in Animal Mortality Risk Following Exposure to Sparsely Ionizing Radiation Is Not Linear Quadratic with Dose. PLoS ONE 10(12): (2015).