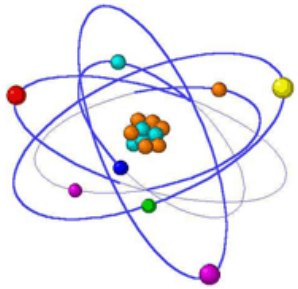
Radioisotope and Radiation Applications (FS2013)



Health Effects of Low Dose Radiation (Week 3c, Seminar)

Pavel Frajtag

01.10. 2013

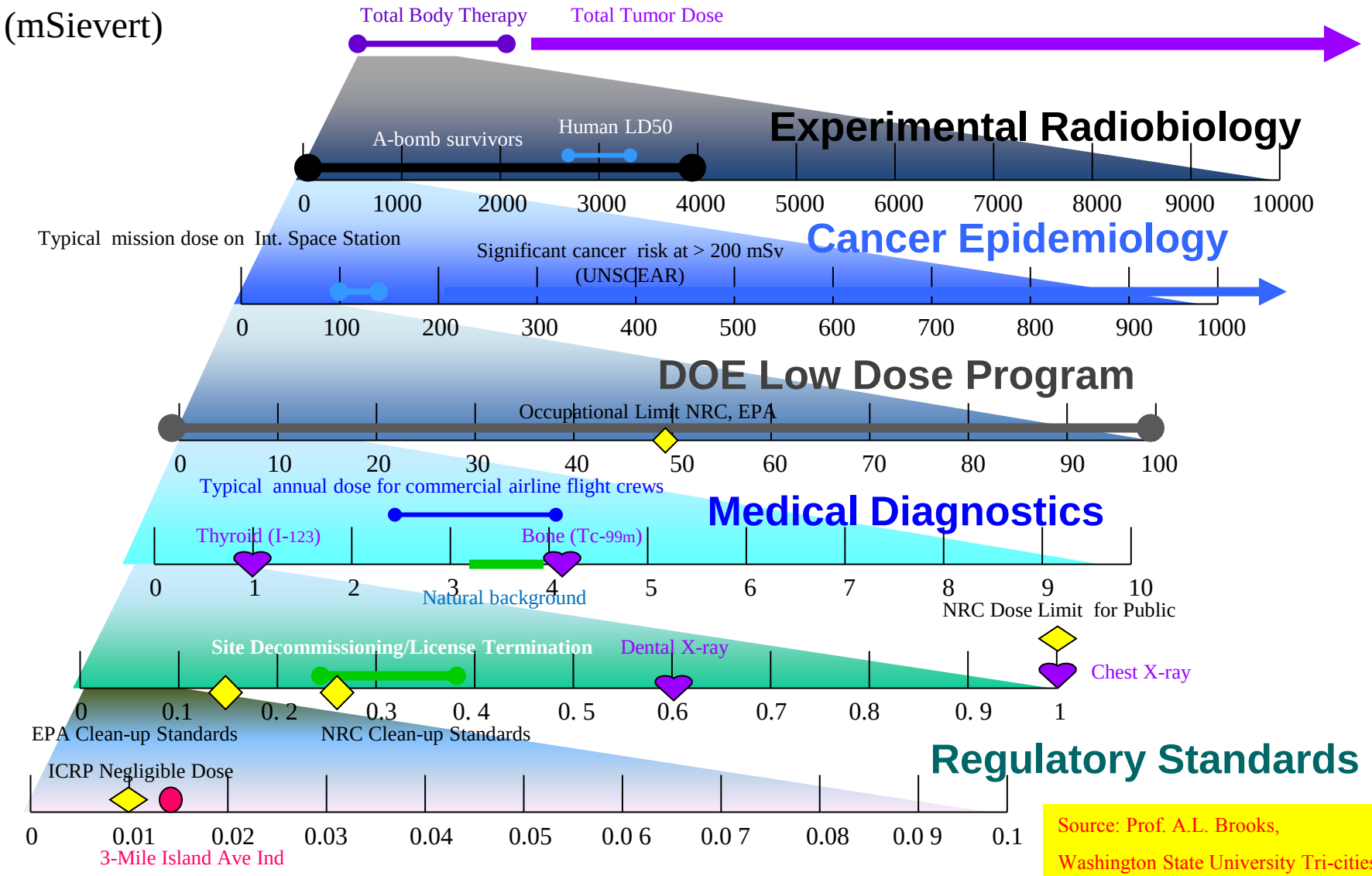
Health Effects of Low Dose Radiation: Outline

- Dose Ranges
- Low Dose Radiation and its Effects
- Radiation Risk and Models for it
- Linear No Threshold (LNT) Hypothesis (LNTH)
  - Features
  - Radioepidemiological facts, problems with (no) data at low doses
  - Controversy, hormesis
  - Economic impact
  - Research needs
- Literature/References

Dose Ranges (1)

- Categorization of dose (approximately):
  - Low doses: < 1 Gy (or < 100mSv)
  - Moderate doses: between 1Gy and 10 Gy (or between 100mSv and 1Sv)
  - High doses: > 10 Gy (or > 1Sv)
- The harmful effects of radiation may be classified into (repetition from last week):
  - ***Stochastic***: the probability of the effect increases with dose. There is no threshold, but it may be assumed that there is always a small probability for the event occurring even at small doses.
  - ***Deterministic***: there is a threshold for the effect, above which the severity increases with dose.
- Thresholds for deterministic effects:
  - Cataracts of eye lens: 2-10 Gy
  - Permanent sterility:
    - males 3.5-5 Gy
    - females 2.5-6 Gy
  - Temporary sterility:
    - males ~0.15 Gy
    - females ~0.6 Gy

Dose Ranges (2)



Source: Prof. A.L. Brooks, Washington State University Tri-cities

Low Dose Radiation: Basics

- Low dose radiation is delivered in doses that are small enough **not** to produce acute damage and fast cell and body responses.
- It can be delivered by any type of radiation.
- People are usually exposed to low doses through:
  - Background radiation sources.
  - Occupational exposure.
- Low dose radiation effects may be categorized as:
  - **Genetic (or hereditary):** transmitted to the offspring.
  - **Somatic:** suffered by the individual exposed, e.g., carcinogenesis.
  - **In utero:** fetal malformations.

Genetic Effects

Mutation of the reproductive cells passed on to the offspring of the exposed individual.

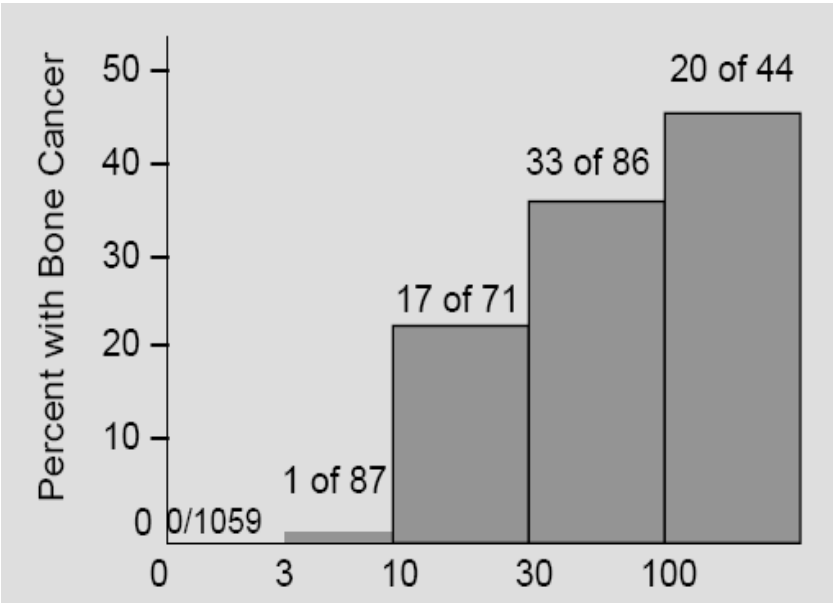
- Facts about genetic mutations induced by radiation:
  - Mutations take place in the sperm or egg cells.
  - Radiation is a **mutagenic** agent (chemicals, certain drugs, viruses also).
  - Radiation **increases** the **spontaneous rate** of **mutations**.
  - Radiation **does not** produce any **new mutations**.
  - Intensive studies of 70,000 offspring of the atomic bomb survivors have **failed to identify** an **increase in congenital anomalies**, cancer, chromosome aberrations in circulating lymphocytes or mutational blood protein changes.
    (Neel et al. Am. J. Hum. Genet. 1990, 46:1053-1072)

Somatic Effects

Related to Cancer

(Carcinogenesis)

- Carcinogens are:
  - Physical: radiation.
  - Chemical: tobacco smoke.
  - Biological: viruses.
- Radiation induced cancer is well documented:
  - Early scientists working with radiation sources: leukemia, skin and bone cancers.
  - Early radium dial painters: bone cancer
  - Uranium miners.
  - Japanese bomb survivors.
  - Patients treated with X-rays to cure spondylarthritis: leukemia.



FOLLOW-UP
OF BOMB SURVIVORS

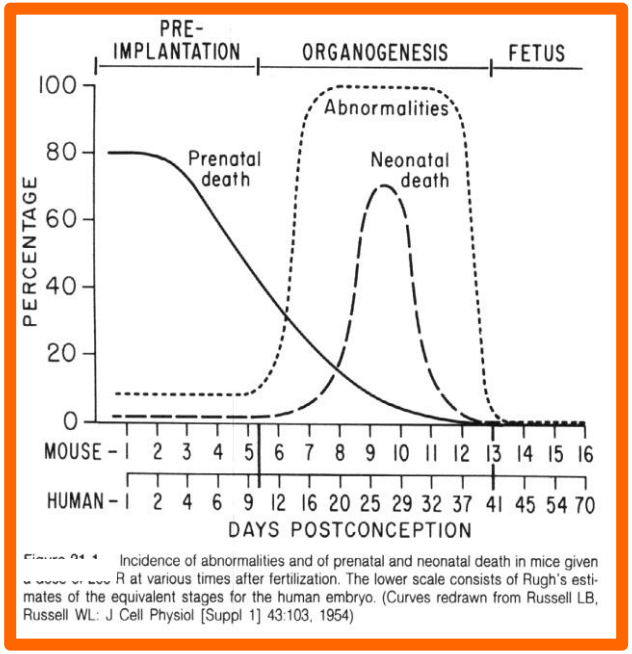
Number exposed	41,719
Number not exposed	34,272
Total Deaths in both groups	28,737
Total cancer deaths In exposed group	3,435
Extra cancer deaths in exposed group due to radiation exposure in 1945	340

In Utero Effects

Production of malformations in developing embryos.

Weeks post conception	Effect
0-1 (pre-implantation)	Intrauterine death.
2-7 (organogenesis)	Developmental abnormalities, growth retardation, cancer.
8-14 (growth stage)	Same as above with lower risk plus possible functional abnormalities.

- Teratogenic agents:
  - Physical: Radiation.
  - Chemicals: thalidomide.
  - Biological: viruses.
- The observed effects depend on the **stage of fetal development**.



Incidence of abnormalities and of prenatal and neonatal death in mice given R at various times after fertilization. The lower scale consists of Rugh's estimates of the equivalent stages for the human embryo. (Curves redrawn from Russell LB, Russell WL: J Cell Physiol [Suppl 1] 43:103, 1954)

Radiation Risk (1)

Risk relates exposure to probability of biological effects

Effect	Excess cases per 10000 exposed per rad (10000 man-rad)
Genetic	2 to 4
Somatic (cancer)	4 to 20
In utero (cancer)	4 to 12
In utero (all effects)	20 to 200

Genetic: 1 rem to reproductive organs 50 to 1000 times **less** than spontaneous risk.

Somatic: Small risk compared to 1 in 4 for normal cancer risk.

In Utero: 5 to 30 times greater than normal exposure to 1 rem.

Medical practice largest source.

Limit for pregnant women is 0.5 rem for entire pregnancy.

Radiation Risk (2): Example, Terms

The Committee's Preferred Estimates of the Lifetime Attributable Risk of Incidence and Mortality for All Solid Cancers and for Leukemia

	All Solid Cancers		Leukemia	
	Males	Females	Males	Females
Excess cases (including nonfatal cases) from exposure to 0.1 Gy	800 (400, 1600)	1300 (690, 2500)	100 (30, 300)	70 (20, 250)
Number of cases in the absence of exposure	45,500	36,900	830	590
Excess deaths from exposure to 0.1 Gy	410 (200, 830)	610 (300, 1200)	70 (20, 220)	50 (10, 190)
Number of deaths in the absence of exposure	22,100	17,500	710	530

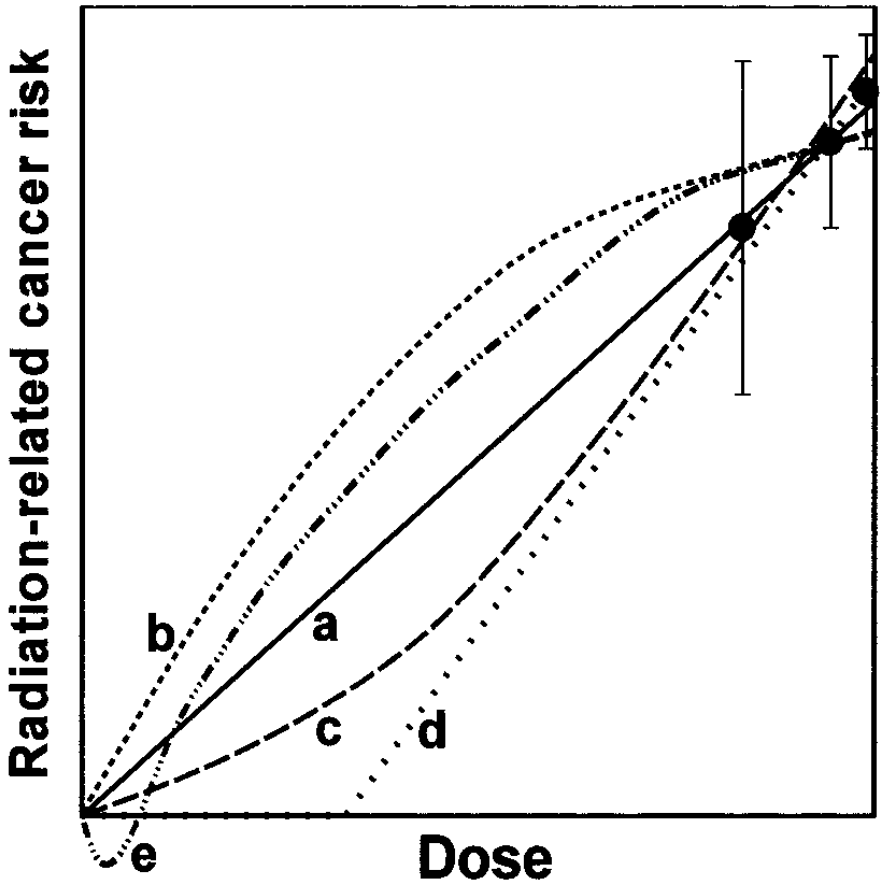
NOTE: Number of cases or deaths per 100,000 exposed persons.

[a]95% subjective confidence intervals.

- The **doubling dose (DD)** is defined as the amount of radiation that is required to produce as many mutations as those occurring spontaneously **in one generation** (~1Sv).
- The **excess relative risk (ERR)** is the rate of disease in an exposed population minus the rate of disease in an unexposed population.

Models For Radiation Risk

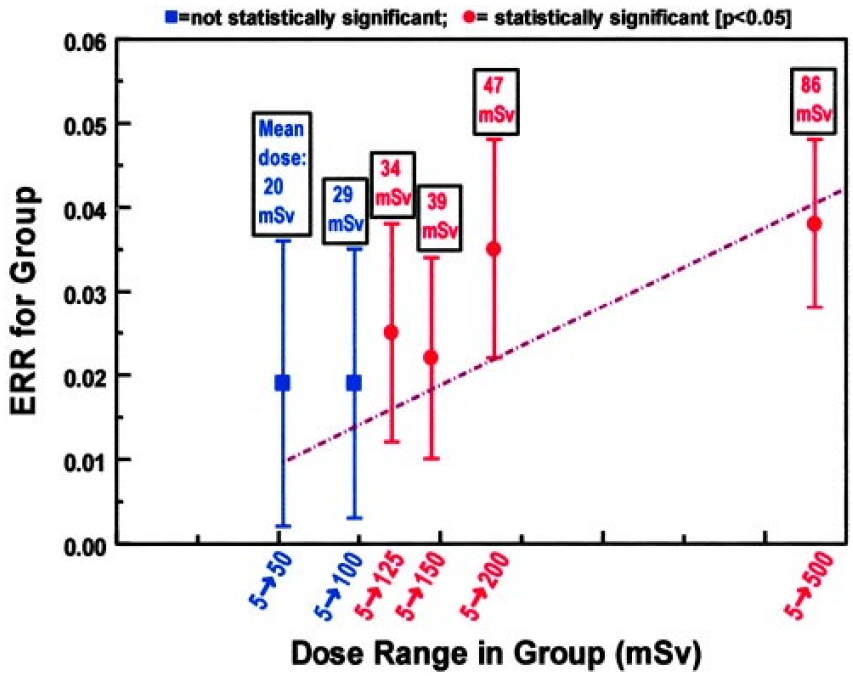
- Based on extrapolation of high dose effects to low doses.
- Models:
  a) **Linear No Threshold model** (LNT).
  b) **Supra-linear model**: risks at lower doses are higher per unit dose than if one extrapolated linearly.
  c) **Sub-linear model**: the end point for biological effect is zero rem. The number of projected cancers grows at a much lower rate than in the LNT model.
  d) **Threshold model**: radiation has no effect up to a certain dose (5 to 20 rem). After this, excess cancers may be observed.
  e) **Hormesis model**: Assumes that high doses of radiation increase the incidence of cancer, but below a value of about 10 rem may be beneficial to the person.



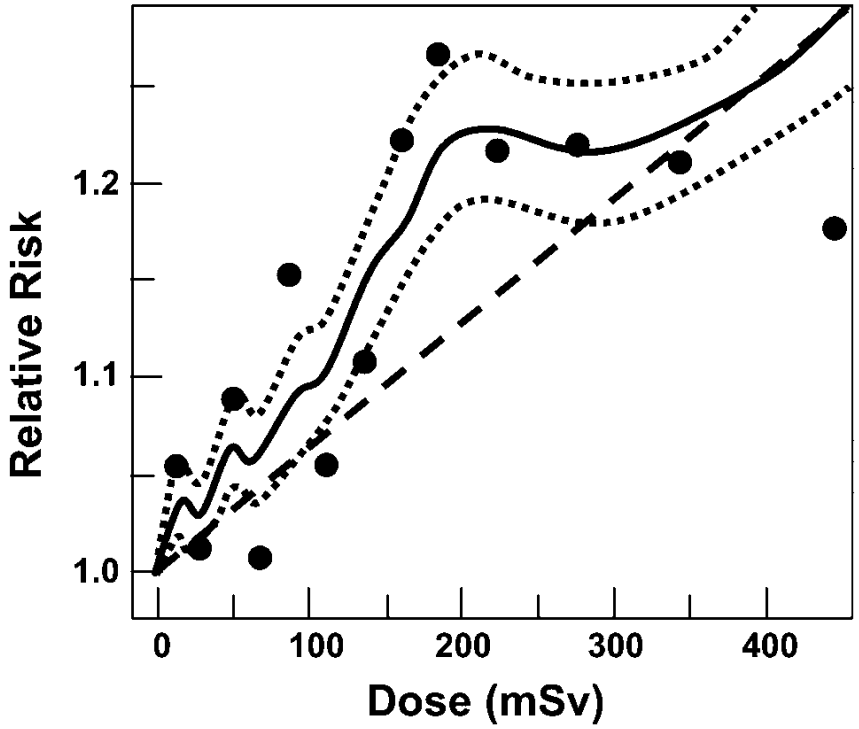
Linear No Threshold Hypothesis: Features

- Based on the assumption that the **damage** caused by ionizing radiation **is linear** (i.e., directly proportional to the dose) **at all dose levels**.
- LNT asserts that there is **no threshold** of exposure below which the response ceases to be linear.
- **The model's virtue is its simplicity:** a quantity of radiation can be translated into a number of deaths without any adjustment for the distribution:
  - If a particular dose of radiation is found to produce 1 extra case of a type of cancer in every 1'000 people exposed,
  - LNT predicts that one thousandth of this dose will produce 1 extra case in every 1'000'000 people so exposed,
  - and that one 10^{-6} of this dose will produce 1 extra case in every 10^{9} people exposed.
- **This means that any given quantity of radiation will produce the same number of cancers, no matter how thinly it is spread.**
- LNT is often claimed to allow for a **simple but conservative** assessment of risk.
- LNT has a great impact on public policy, because it immediately translates:
  - radiation release into number of lives lost,
  - reduction in radiation exposure into number of lives saved.

Radioepidemiological Facts (1): What do we really know?



Estimated excess relative risk (±1 SE) of mortality (1950–1997) from solid cancers among groups of survivors in the LSS cohort of atomic bomb survivors, who were exposed to low doses (<500 mSv) of radiation (2). The groups correspond to progressively larger maximum doses, with the mean doses in each group indicated above each data point. The first two data points (in blue) are not statistically significant ($P = 0.15$ and 0.3, respectively) compared with the comparison population who were exposed to <5 mSv, whereas the remaining four higher-dose points (in red) are statistically significant ($P < 0.05$). The dashed straight line represents the results of a linear fit (2) to all the data from 5 to 4,000 mSv (higher dose points are not shown).



Estimated risks (relative to an unexposed individual) of solid cancer in atomic bomb survivors exposed to low radiation doses (12). Data points are placed at the mean of each dose category. The solid curve represents a weighted moving average of the points shown (dotted curves: ±1 SE), and the dashed straight line is a linear risk estimate computed from all the data in the dose range from 0 to 2,000 mSv. Age-specific cancer rates from 1958 to 1994 are used, averaged over follow-up and gender.

Risk versus radiation exposure levels. Large uncertainty as the curve approaches zero.

Radioepidemiological Facts (2) / Detectability Limits

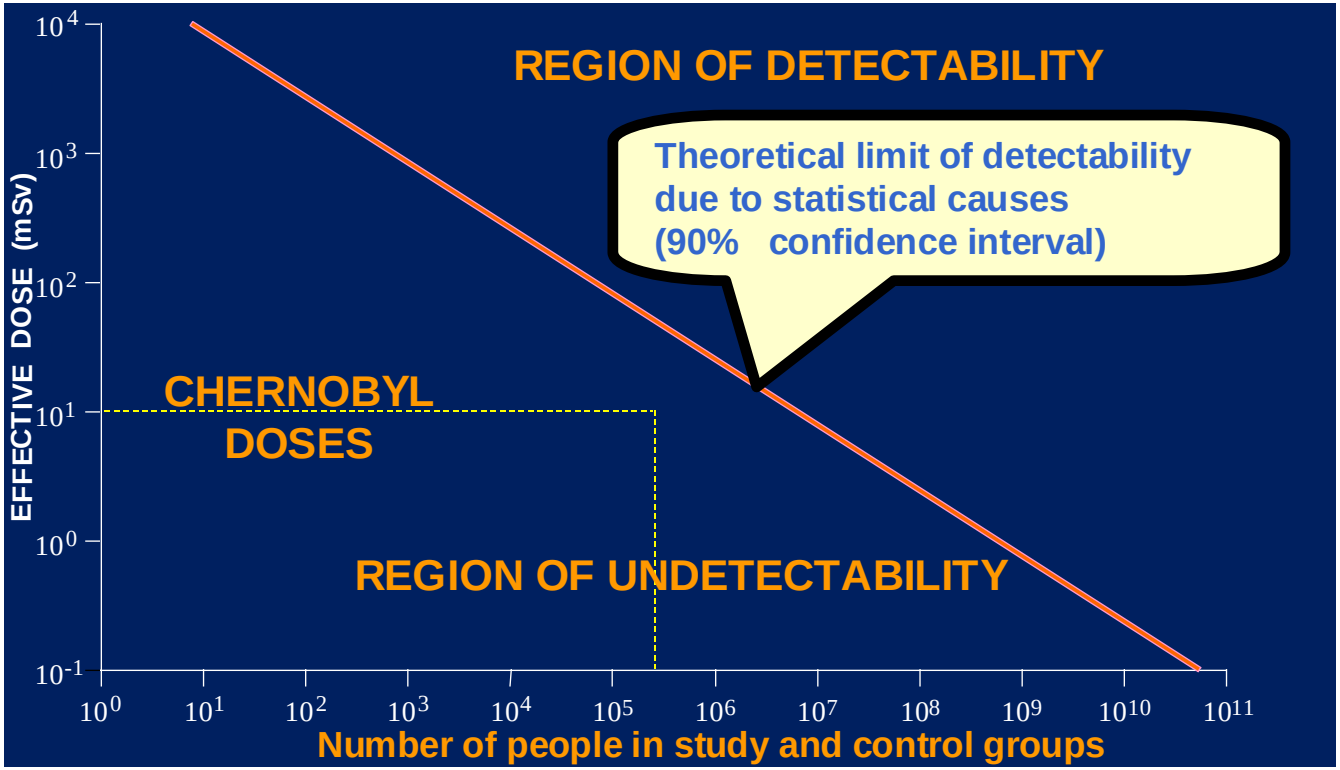
❑ Response to low doses of radiation is different than to high doses:

- The lowest doses of X-ray and gamma-radiation for which good evidence for cancer risk exists: ~10−50mSv for acute exposure, ~50−100mSv for protracted exposure.
- High dose studies are used to estimate risks from cancer.
- These high dose risks are then extrapolated to estimate risk following low dose.

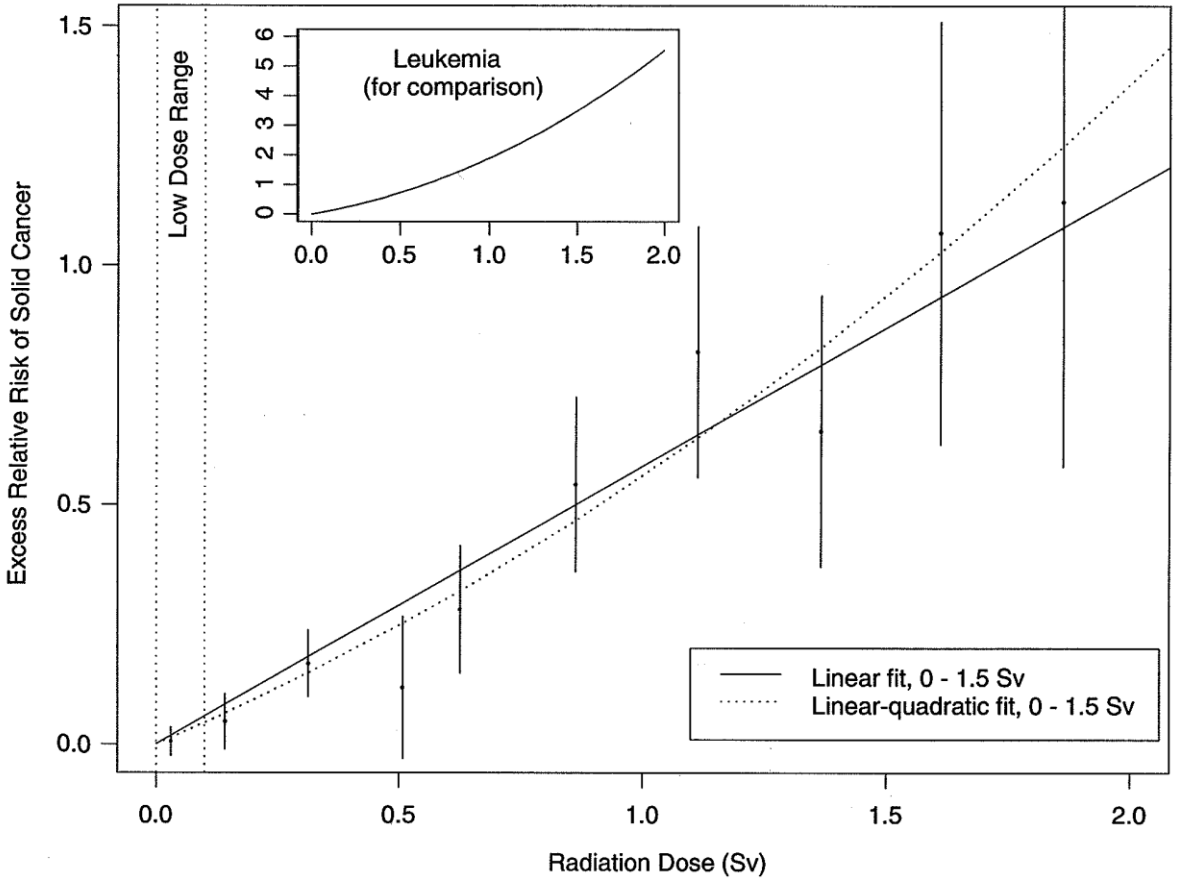
❑ Detectability limits are high (see diagram) because:

- Background radiation is often higher than the level of added radiation exposure.
- There is a high and variable rate of cancer in the human population.
- There is no way to tell a radiation-induced cancer from a spontaneous cancer.

Radiation is a poor mutagen/carcinogen, but a very good cell killer.



Cancer Risk Picture



Excess relative risks of solid cancer for Japanese atomic bomb survivors. Plotted points are estimated excess relative risks of solid cancer incidence (averaged over sex and standardized to represent individuals exposed at age 30 who have attained age 60) for atomic bomb survivors, with doses in each of 10 dose intervals, plotted above the midpoints of the dose intervals. If R(d) is the age-specific instantaneous risk at some dose d, then the *excess relative risk* at dose d is [R(d) – R(0)]/R(0) (which is necessarily zero when the dose is zero). Vertical lines represent approximate 95% confidence intervals. Solid and dotted lines are estimated linear and linear-quadratic models for excess relative risk, estimated from all subjects with doses in the range 0 to 1.5 Sv (not estimated from the points, but from the lifetimes and doses of individual survivors, using statistical methods discussed in Chapter 6). A linear-quadratic model will always fit the data better than a linear model, since the linear model is a restricted special case with the quadratic coefficient equal to zero. For solid cancer incidence however, there is no *statistically significant* improvement in fit due to the quadratic term. It should also be noted that in the low-dose range of interest, the difference between the estimated linear and linear-quadratic models is small relative to the 95% confidence intervals. The insert shows the fit of a linear-quadratic model for leukemia to illustrate the greater degree of curvature observed for that cancer.

Problems with Data at Low Doses (1)

- Cell culture and animal data difficult to extrapolate to humans.
- With respect to human experience:
  - Not randomized controlled.
    - Would be highly unethical.
  - Many assumptions in life time study.
    - Poor dose information (to part or whole body).
    - Often unknown co-existing conditions.
    - Poor statistics (small numbers), e.g.:
      - if a sample size of 500 persons were needed to quantify a dose effect of a 1Sv dose,
      - then a sample size of 50'000 persons is needed for a 100mSv dose,
      - and a sample size of 5 million persons is needed for a 10mSv dose.
  - The natural incidence of cancer is much greater than any contribution from ionizing radiation:
    - 10000 people, 2000 natural cancers, 4 to 8 more from 1 rem exposures.

Problems with Data at Low Doses (2)

- Irradiated populations are:
  - people exposed from the atomic bomb explosions.
  - people exposed during nuclear and other radiation accidents.
  - patients exposed for medical reasons.
  - people exposed to natural radiation.
  - workers in radiation industries.
- Information is scanty (not much, less than needed) on:
  - Consequences of low doses delivered at low dose rates.
    - To detect an increase from a 20% spontaneous cancer incidence to 25% (corresponding to an exposure to ~1 Sv) > 1300 persons must be studied.
  - Consequences of external high LET radiation.
    - (neutrons) and several radionuclides.
  - Presence and influence of confounding factors.
    - especially if different populations are to be compared.

Controversy (pro): Current Practice

- A linear model has long been used in health physics to set maximum acceptable radiation exposures.
- The United States based National Council on Radiation Protection and measurements (NCRP):

  "Radiation's effects should be considered to be proportional to the dose an individual receives, regardless of how small that dose is".

  (Report to Congress on the effects of radiation)

- Regulations (USNRC 10CFR Part 20):
  - Requires that exposure shall be held to the **ALARA** principle.
  - Risk assumed as **directly proportional** to dose, **without any threshold.**

Controversy (con): Criticism

- Some regard the **LNTM** as **conservative or even completely wrong** for predicting the effect of low doses of radiation.

  They claim that there is no evidence supporting the assumption that there is no threshold, and that recent studies suggest changes in this assumption.

- The **European Committee on Radiation Risk (ECRR)** is a committee set up in 1997:
  - It sets out the basic standards regarding radiation protection in the European Union.
  - It includes several prominent critics of the dominant view of radiation risk such as articulated by the International Commission on Radiological Protection (**ICRP**) and the United Nations Scientific Committee on the Effects of Atomic Radiation (**UNSCEAR**).

- French Academy of Sciences and the National Academy of Medicine: *"…in conclusion, this report raises doubts on the validity of using LNT for evaluating the carcinogenic risk of low doses (< 100 mSv) and even more for very low doses (< 10 mSv) …"*

- The American Nuclear Society position statement regarding the health effects of low-level radiation released in June 2001, states: *"It is the position of the American Nuclear Society that there is insufficient scientific evidence to support the use of the Linear No Threshold Hypothesis (LNTH) in the projection of the health effects of low-level radiation."*

- Several scientist also disagree with LNT: It ignores the well known repair mechanism…

Evidence for and against Hormesis

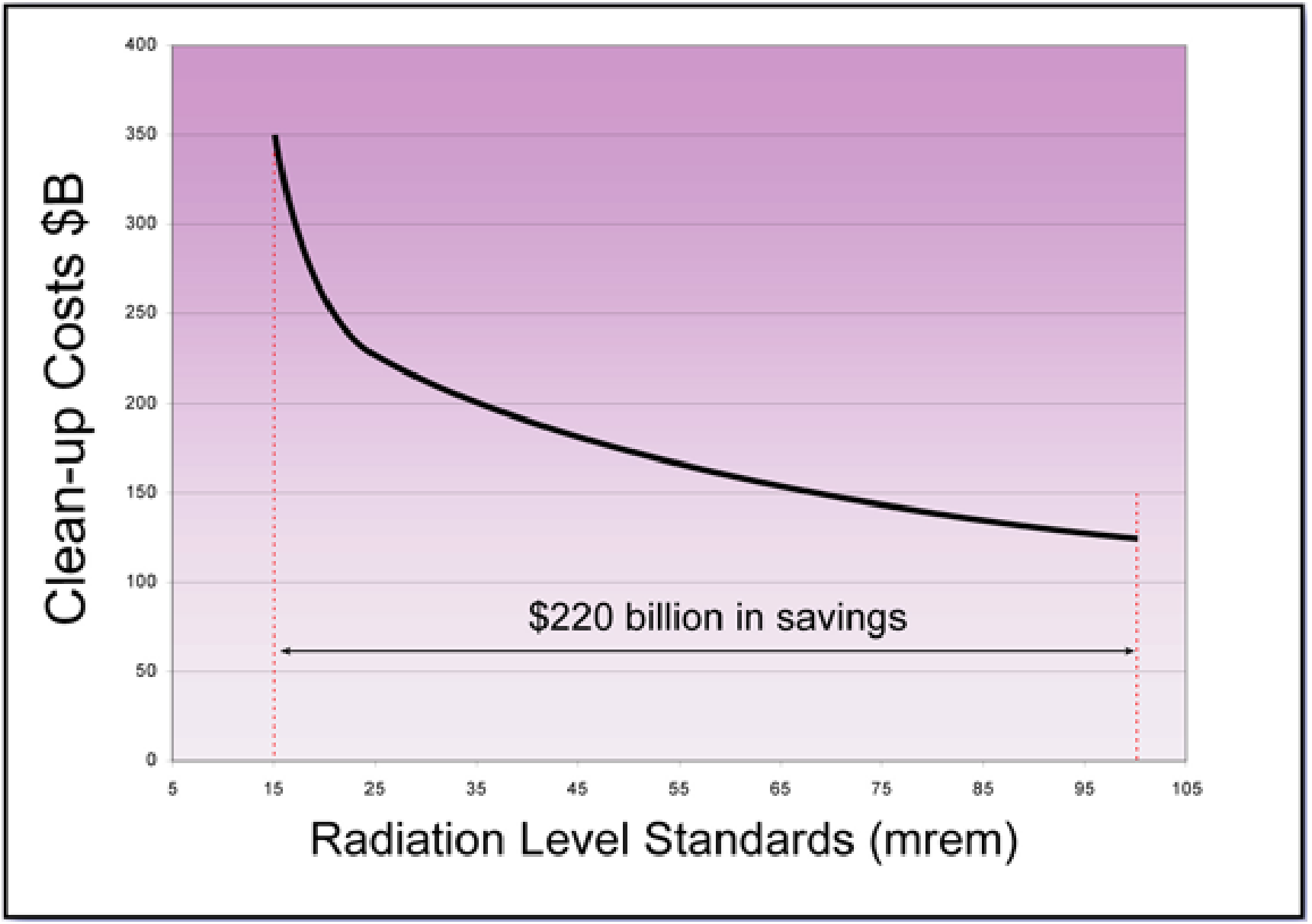
Some evidence for it:

- **Studies of airline crews** are exposed to higher levels of cosmic radiation due to altitude, but show no overall increase in cancer in spite of higher exposure.
- **Incidence of cancer** is found to be low in high-lying areas which are less protected by the atmosphere against cosmic radiation.
- **Genes that protect against radiation** damage have been found to be activated in people exposed to radiation in these areas.
- **Ramsar** has naturally very high radiation (260 mSv) due to its geology, but is found to have no increased cancer risk.
- **No chromosomal damage** was detectable in animals with high radiation counts living around Chernobyl.
- **Lower than expected** increases in cancers have been found from Chernobyl.
- **In Taiwan**, apartments built with radioactive rebar contaminated with cobalt 60 gave doses of an average of 400 mSv/year to the occupants. Mortality and cancers were considerably lower than in reference populations.

Some evidence against it:

- **Pilots** are more prone to brain, rectal and prostate cancers whilst flight crews are twice as susceptible to breast cancer, but are healthier overall than the general public (possibly because they are healthier when selected for the job due to health screening). However there is a contrary suggestion and evidence that breast cancer in flight crews may be caused by jet lag.
- **High-lying areas** have reduced oxygen levels (oxygen is slightly carcinogenic); once this and other effects are accounted for there is actually an increase in cancer incidence with altitude which seems to be attributable to radiation.

Economic Impact of LNTH



Scientific Basis for Challenge

(Prof. A.L. Brooks, Washington State University)

- Hit theory shift to bystander paradigm.
  - A cell does not have to be hit in order to be biologically altered.
- Mutation theory shifts to gene expression paradigm.
  - Radiation induces changes in gene expression that may alter subsequent responses in a large fraction of the cell population.
- Single mutation cancer theory shifts to tissue paradigm.
  - Tissues respond as whole and not as individual cell.
- LNTH challenged by adaptive response & genomic instability.
  - Adaptive response may result in protective, nonlinear dose-responses.
  - Genomic instability or bystander effects could result in either super-linear or sub-linear dose-responses.

BEIR-VII: Recommended Research Needs

1. Determination of the level of various molecular markers of DNA damage as a function of low dose ionizing radiation.
2. Determination of DNA repair fidelity especially with regard to double and multiple strand breaks at low doses, and whether repair capacity is independent of dose.
3. Evaluation of the relevance of adaptation, low-dose hypersensitivity, bystander effect, hormesis, and genomic instability for radiation carcinogenesis.
4. Identification of molecular mechanisms for postulated hormetic effects at low doses.
5. Tumorigenic mechanisms.
6. Genetic factors in radiation cancer risk.
7. Heritable genetic effects of radiation.
8. Future medical radiation studies.
9. Future occupational radiation studies.
10. Future environmental radiation studies.
11. Japanese atomic bomb survivor studies.
12. Epidemiologic studies in general.

Summary

- Both early and late effects and risks from high doses of radiation are well defined and understood.
- The **radiation risks associated with exposure to low doses** of radiation are:
  - **difficult to measure** and
  - **still have major uncertainties** associated with them.
- Rapid advances in technology, techniques in cell and molecular biology are now making it possible to detect and understand biological changes after low doses of radiation.
- More research in the area of health effects of low dose radiation is needed.

Literature / References

- Health Risks from Exposure to Low Levels of Ionizing Radiation: BEIR VII – Phase 2, Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation, National Research Council, ISBN: 978-0-309-09156-5, 424 pages, 8 1/2 x 11, paperback (2006), http://www.nap.edu/catalog/11340.html
- Brenner, David J. *et al.*, "Cancer risks attributable to low doses of ionizing radiation: Assessing what we really know", PNAS **100**, 13761-13766 (2003).
- T. Luckey, "Nurture with ionizing radiation: a provocative hypothesis", *Nutr. Cancer* **34** (1): 1-11 (1999), PMID 10453435.
- R.H. Nussbaum, W. Köhnlein, "Radiation Hormesis & Zero-Risk Threshold Dose: Two Scientific Refuted, but Stubborn Myths", http://www.gfstrahlenschutz.de/docs/hormeng2.pdf
- Position Statement 41 of the American Nuclear Society (ANS), "Health Effects of Low-Level Radiation", http://www.ans.org/pi/ps/docs/ps41.pdf
- Talk of Antone L. Brooks, Washington State University Tri-Cities, at the CEMP Meeting in Charleston, Nevada, July 25, 2006 with the title: "Radiation Risk A Realistic View: Impact of Cellular and Molecular Research".