# Radiation Risk A Realistic View: Impact of Cellular and Molecular Research

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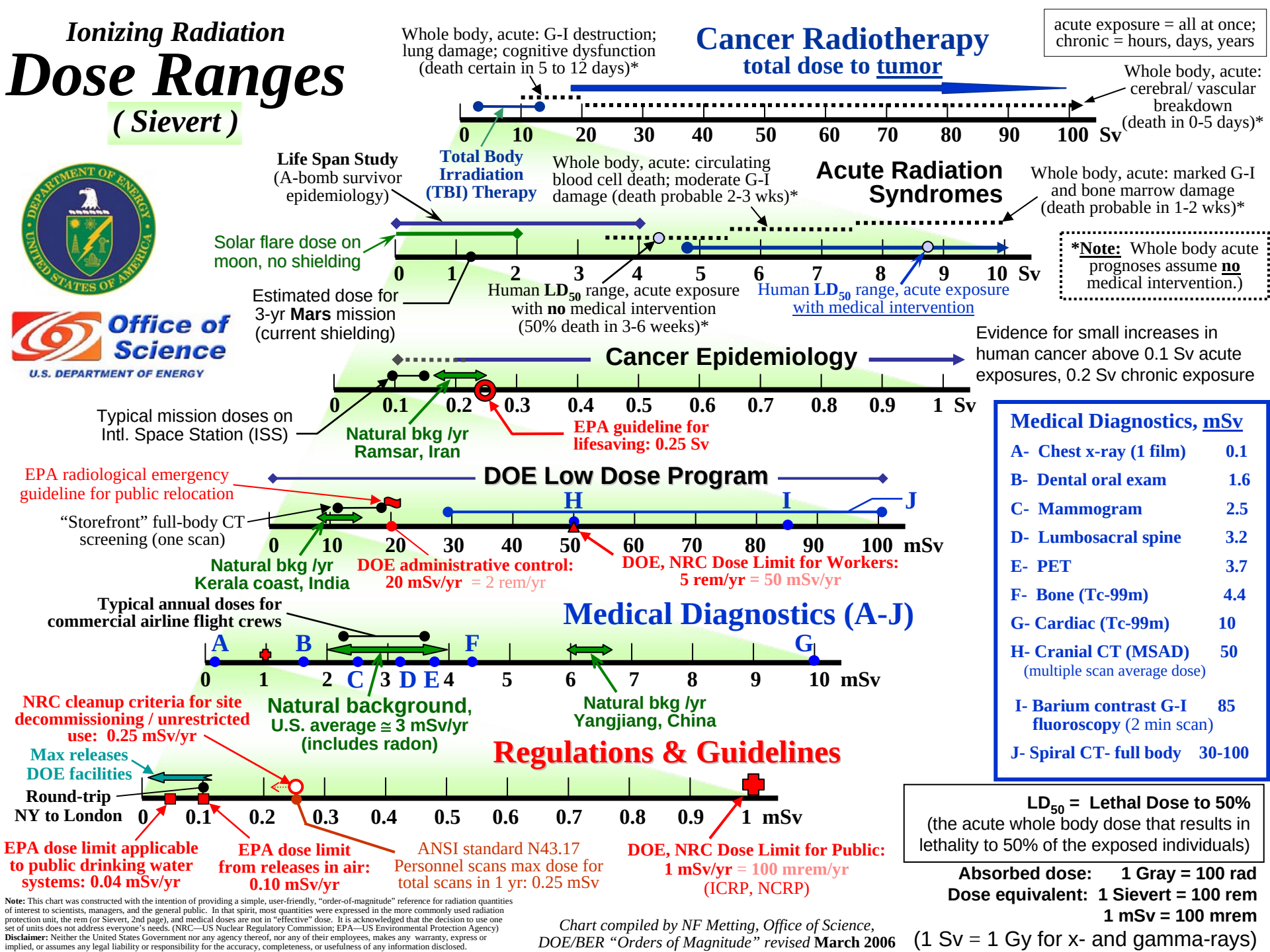
# *Ionizing Radiation*
# *Dose Ranges*
## *( Sievert )*

acute exposure = all at once; chronic = hours, days, years




### Medical Diagnostics, mSv

| | |
|---|---|
| A- Chest x-ray (1 film) | 0.1 |
| B- Dental oral exam | 1.6 |
| C- Mammogram | 2.5 |
| D- Lumbosacral spine | 3.2 |
| E- PET | 3.7 |
| F- Bone (Tc-99m) | 4.4 |
| G- Cardiac (Tc-99m) | 10 |
| H- Cranial CT (MSAD) (multiple scan average dose) | 50 |
| I- Barium contrast G-I fluoroscopy (2 min scan) | 85 |
| J- Spiral CT- full body | 30-100 |

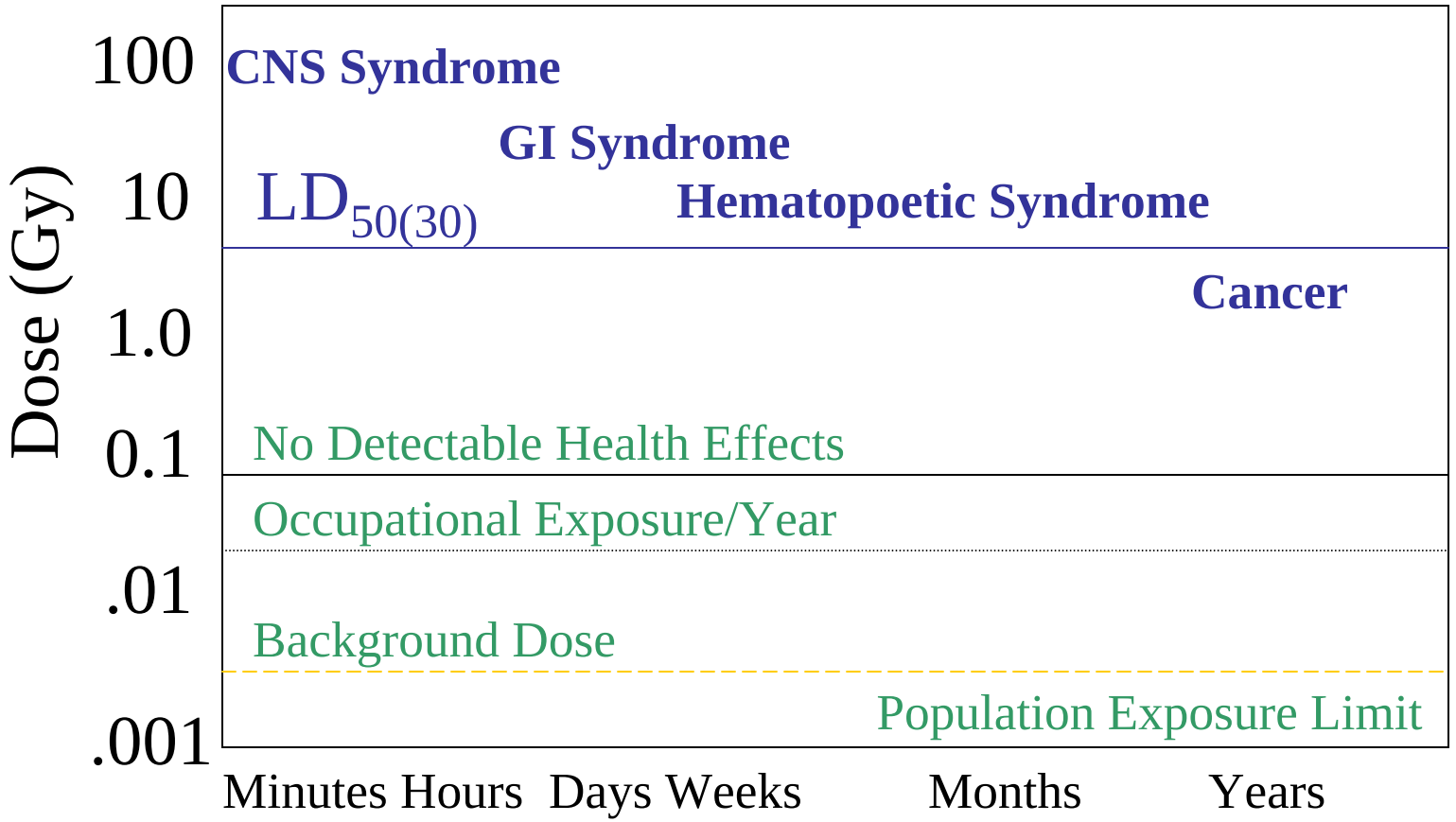
**$LD_{50}$ = Lethal Dose to 50%** (the acute whole body dose that results in lethality to 50% of the exposed individuals)

**Absorbed dose:** 1 Gray = 100 rad
**Dose equivalent:** 1 Sievert = 100 rem
1 mSv = 100 mrem
(1 Sv = 1 Gy for x- and gamma-rays)

**Note:** This chart was constructed with the intention of providing a simple, user-friendly, "order-of-magnitude" reference for radiation quantities of interest to scientists, managers, and the general public. In that spirit, most quantities were expressed in the more commonly used radiation protection unit, the rem (or Sievert, 2nd page), and medical doses are not in "effective" dose. It is acknowledged that the decision to use one set of units does not address everyone's needs. (NRC—US Nuclear Regulatory Commission; EPA—US Environmental Protection Agency)


*Chart compiled by NF Metting, Office of Science, DOE/BER "Orders of Magnitude" revised* **March 2006**

# Acute Effects of Radiation



# Cerebrovascular Syndrome

- Total body dose of 100 Gy or 10,000 rad of gamma rays (or less of neutrons) results in death in a matter of hours.
- All organ systems are also seriously damaged
- Gastrointestinal and hematopoietic systems would fail quickly at this level, but cerebral much faster

# Gastrointestinal Syndrome

- Death is caused by more than 10 Gy of gamma rays or neutrons. **There is no record of any human surviving over 10 Gy acute dose.**

- Symptoms and death are due to depopulation of epithelial lining of the gastrointestinal tract by radiation. Compartments of stem-cells.., differentiating compartment and mature functioning cells.

- 10 Gy doesn’t kill mature cells,but sterilizes dividing cells. As good cells are sloughed off and rubbed away, there are no replacement cells.

# Bone Marrow Syndrome

- Death from hematopoietic system failure can occur between 3-8 Gy…
- Mitotically active precursor cells are sterilized, therefore red cells, white cells and platelets are diminished.
- Immune impairment, bleeding and anemia from platelets because of depression of blood elements.
- Red blood cell anemia doesn’t occur.

# Summary of High Dose Effects

- No one has survived a dose of 10 Gy or 1,000 Rads without medical intervention
- Doses between 2 and 8 Gy kill dividing cells. If organs cannot replace these cells death occurs. Gut and Bone Marrow and the target organs.
- Doses below 1 Gy, 100 rads, 100,000 mrads produce little life shortening increase in cancer “risk”.

# Health Effects of Low Doses of Radiation?

- Cancer primary concern for Low doses of radiation
- Genetic Effects
- Birth Defects

# Late Non-Cancer Effects of Radiation

- Fetal Malformation
  - Spontaneous abortions
  - Birth defects
  - Developmental abnormalities
- Mental Retardation
  - Change in head size
  - Loss of I.Q.
- Cataracts
- Fibrosis

# Embryology of the developmental stages during pregnancy

**Preimplantation**

Cell proliferation & differentiation

**Embryo**

Differentiation & organogenesis

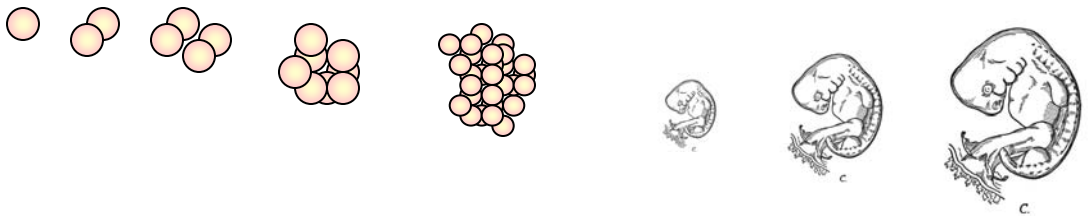
**Fetus**

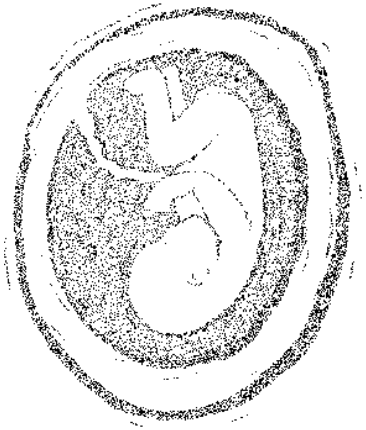
Growth

**Birth**

0 10 20 30 40 → 270

Time (Days)





**Endoderm, Mesoderm, Ectoderm**

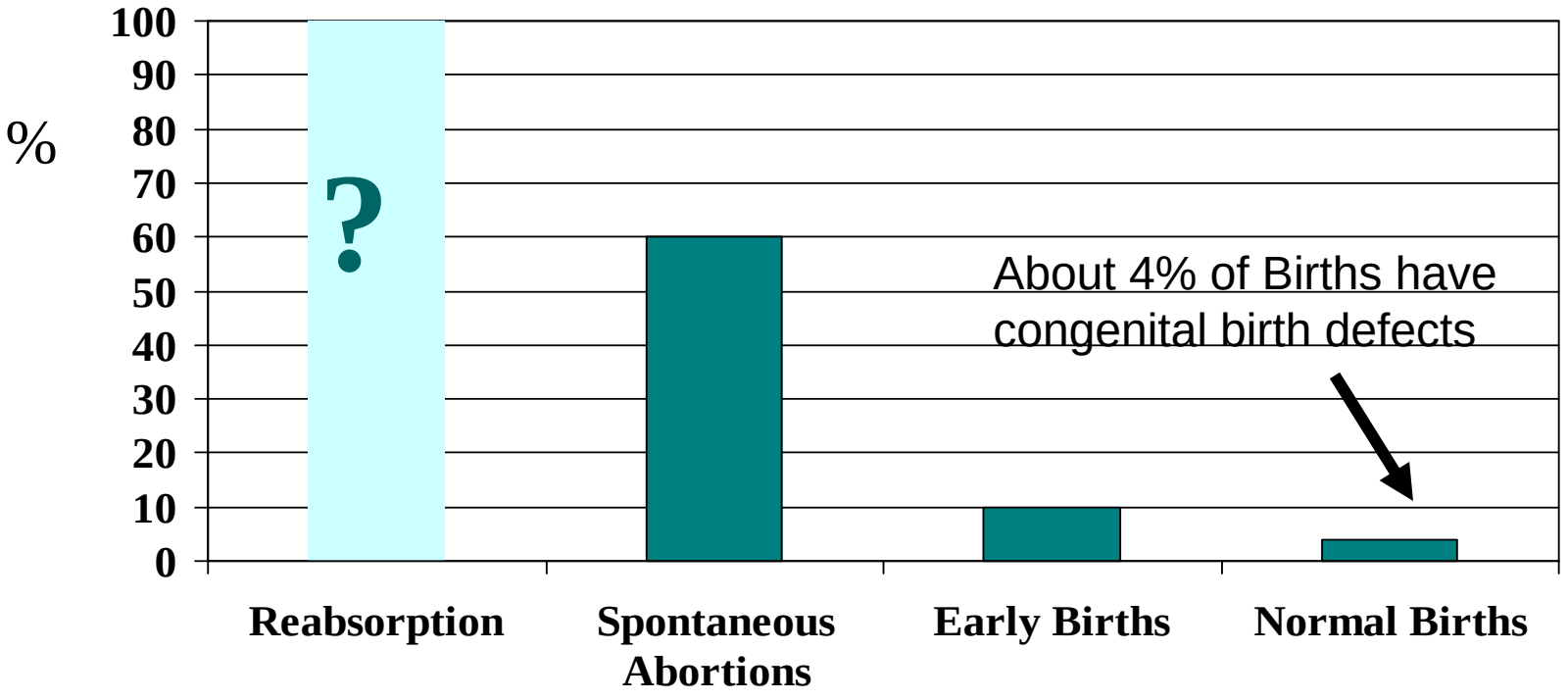
# The influence of Time of Exposure on the production of malformation

- There is a window of time when the fetus is in a stage that is sensitive to radiation
- This is related to the organs and tissues being formed at the time.
- High dose radiation exposure during this time window is very effective in producing congenital malformations.

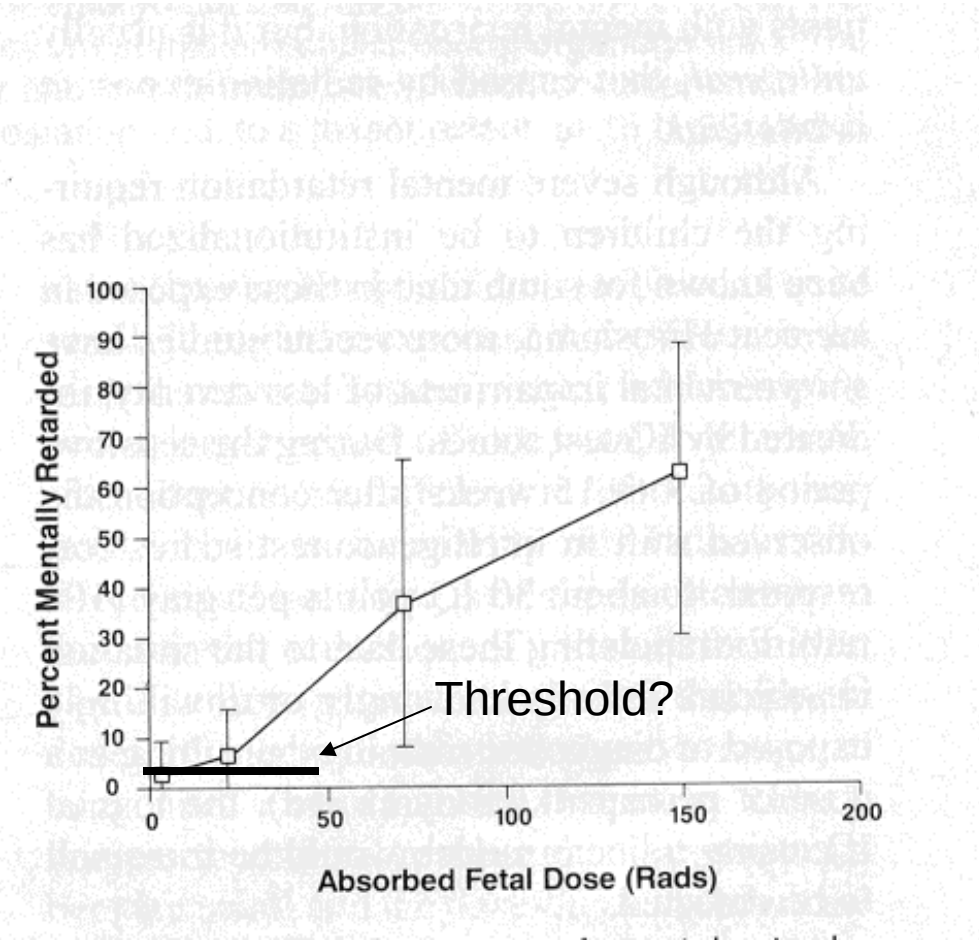
# Calculation of Risk using Real World Assumptions.

- 3.5 Radiation induced Cases in the population of 100,000 people followed over 10 years (Worst Case)
- 3.5 x 0.018 fraction of time in sensitive stage= 0.063
- 0.063 x 0.01 fraction of population receiving Maximal Dose =0.0063
- 0.0063 x 0.5 for dose rate effectiveness= 0.0032
- 0.0032 x the LNTH assumption=????
- Relate 0.0032 radiation induced malformations to the 2,800 “normal” cases.
- At what dose do you recommend an abortion????

# Natural processes protect against birth defects



# Radiation induced Mental Retardation




Hall

# Overview of Radiation Exposure of Tissues and Organs

403 accidents worldwide from 1944-1999

120 Acute deaths from these accidents

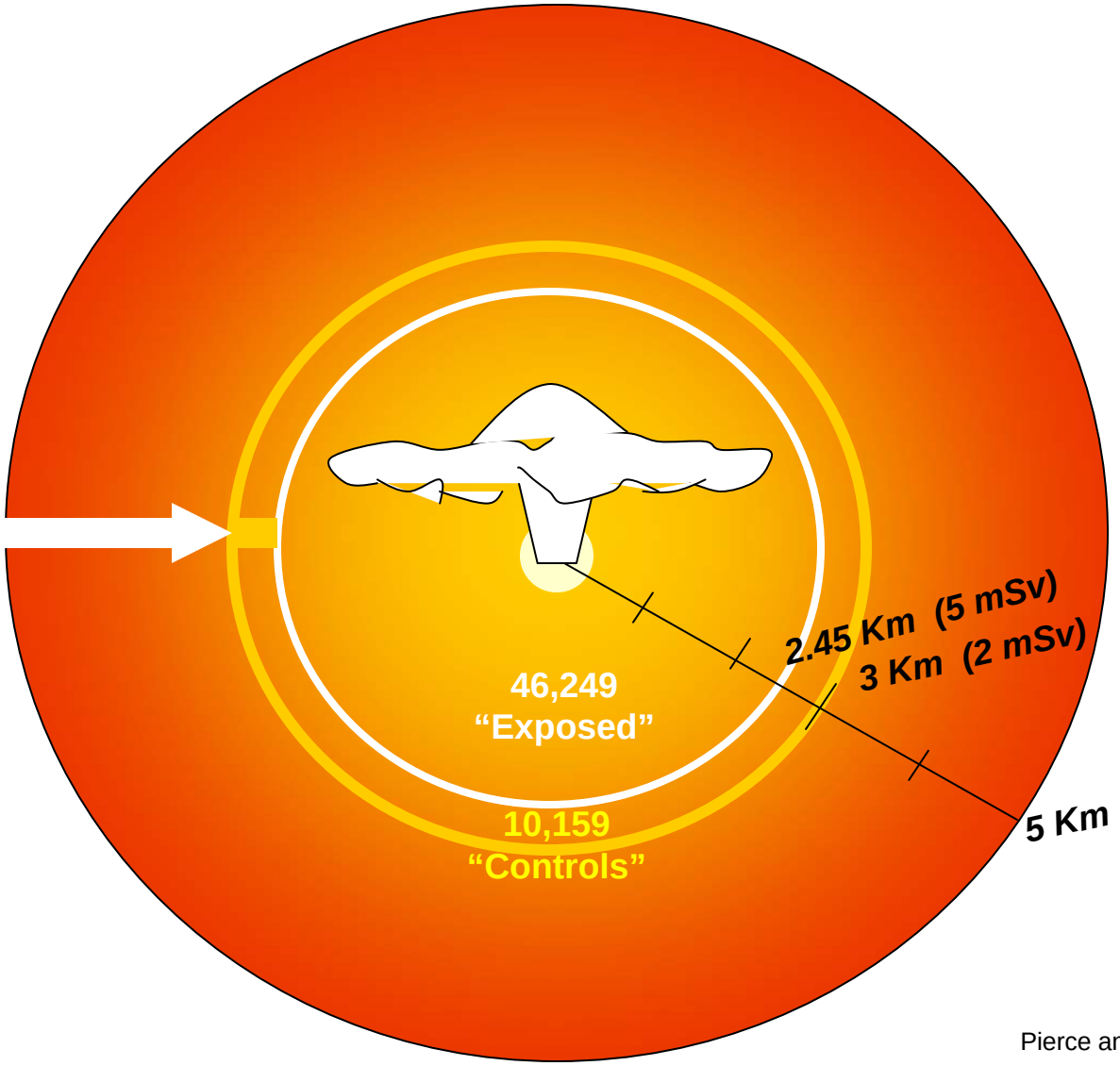
- 19 reactors
- 303 involved radiation devices, sealed sources or x-ray machines
- 81 radioisotopes

# Effects of Atomic Bomb

- **Killed outright by the bomb or acute radiation effects.** — **About 200,000 people**
- **Survived for lifespan study** — **86,572 people**

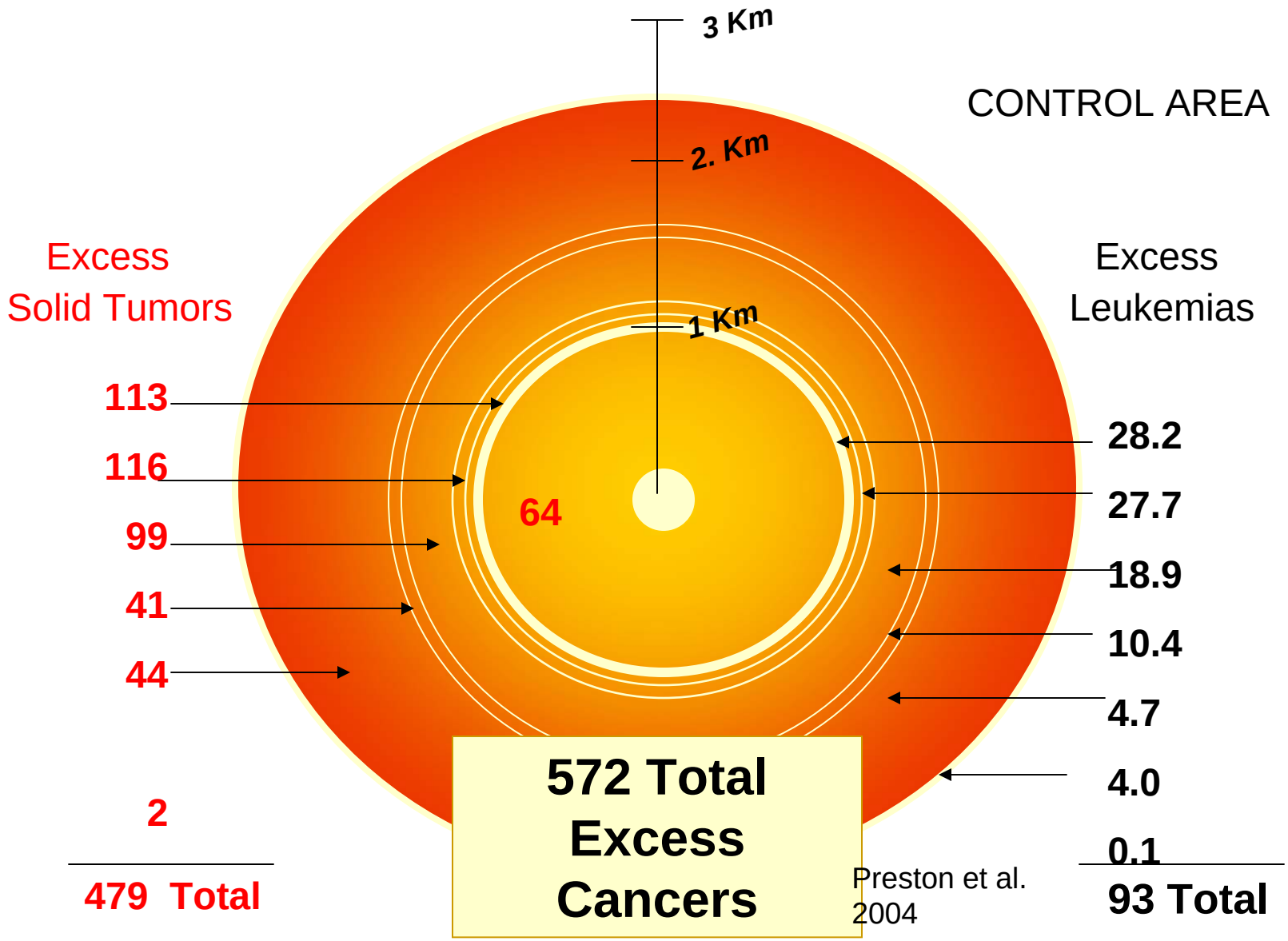
# A-BOMB SURVIVOR STUDIES

5% less cancer than total controls




Pierce and Preston 2000

# A-BOMB SURVIVOR STUDIES



# Atomic Bomb Survivor Excess Cancer

Population of Survivors Studied **86,572**

40% of these people are still alive 60 years after the bomb

| | |
|---|---|
| Cancer Mortality observed after the Bomb | 10,127 |
| Cancers Mortality Expected without Bomb | 9,555 |
| **Total Cancer Mortality Excess** | **572** |

| Excess Tumor | | Excess Leukemia | | |
|---|---|---|---|---|
| 479 | + | 94 | = | 572 |

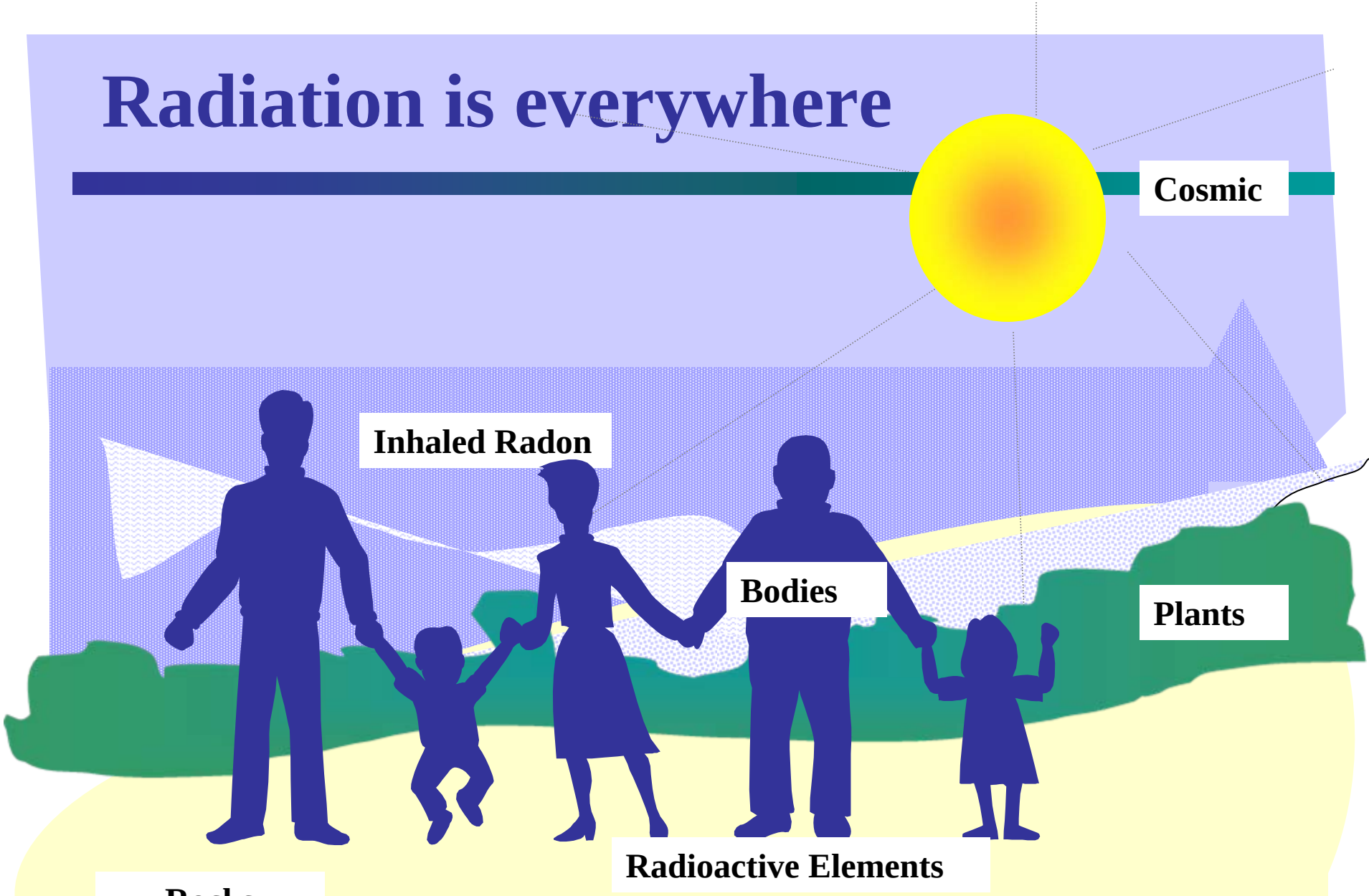
# Problems with Detection of Cancer following Low Doses

- Background radiation
- Background cancer
- High signal to noise ratio

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

# Background Radiation

# Radiation is everywhere




## We live in a sea of radiation…

# Normal annual exposure from natural radiation

## About 300 mrem/yr

| | |
|---|---|
| Radon gas | 200 mrem |
| Human body | 40 mrem |
| Rocks, soil | 28 mrem |
| Cosmic rays | 27 mrem |

# Normal annual exposure from man-made radiation

## About 70 mrem/yr

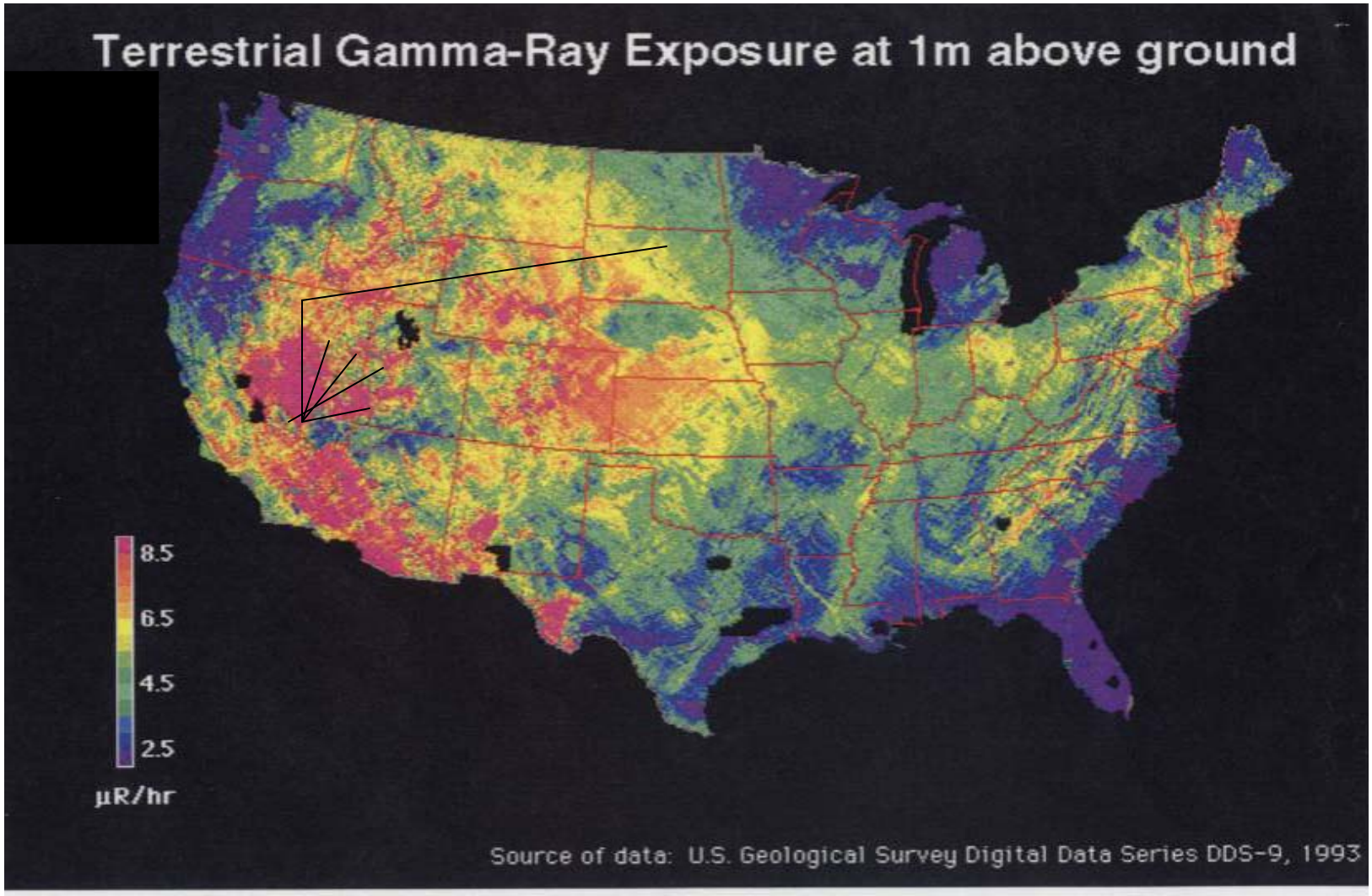
| | |
|---|---|
| Medical procedures | 53 mrems |
| Consumer products | 10 mrems |
| One coast to coast airplane flight | 2 mrems |
| Watching color TV | 1 mrem |
| Sleeping with another person | 1 mrem |
| Weapons test fallout | less that 1 mrem |
| Nuclear industry | less than 1 mrem |

# Medical Radiation Exposures

- 300 million medical x-rays/year
  - X-ray 0.1 mGy
- 100 million dental x-rays/year
  - Dental 0.06 mGy
- 10 million doses of radiopharmaceuticals/yr
- 37 million CT scans/year
  - Head scan 4-6 mGy/scan
  - Body scan 40-100 mGy/scan
- Large doses from radiation therapy

# Background Cancer

# U.S Dose Rates from Natural Background



# Nevada Test Fallout

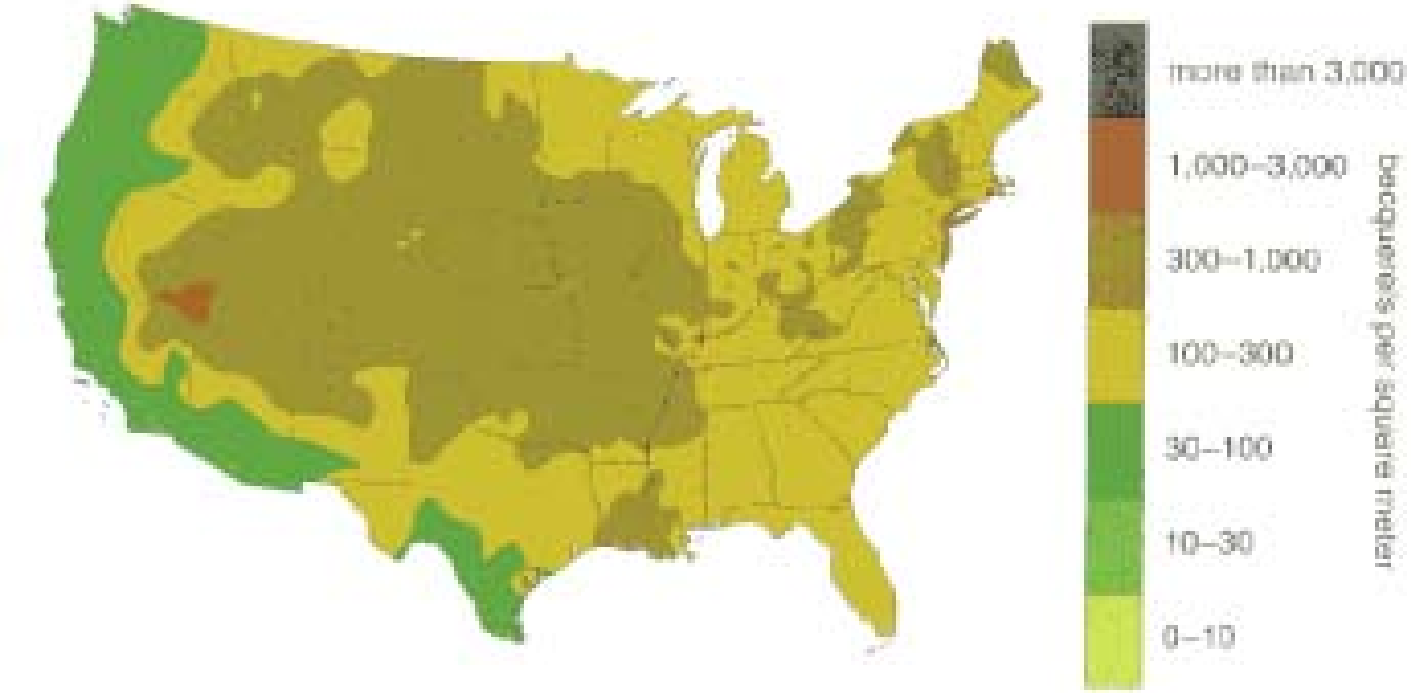
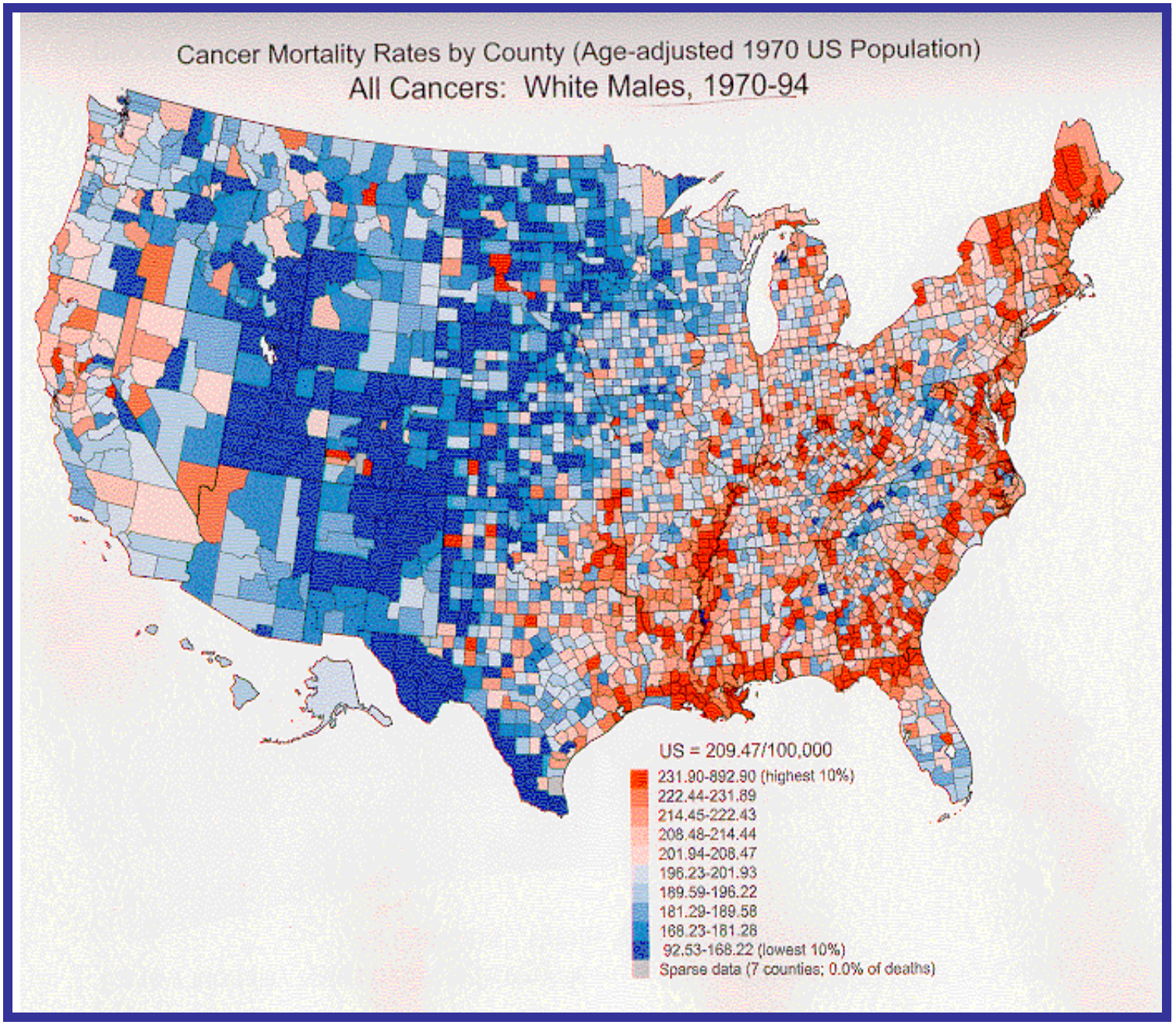
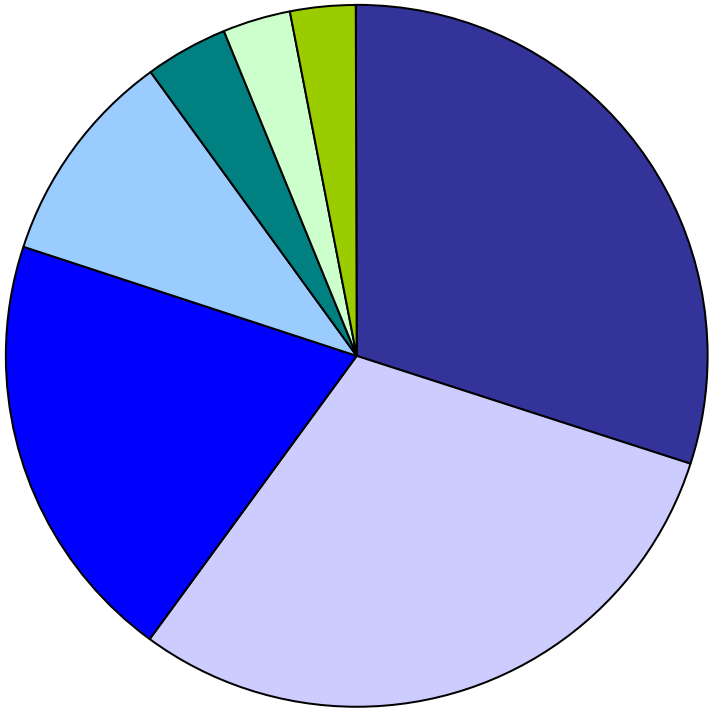



Figure 7. Cesium-137 deposition density resulting from the cumulative effect of the Nevada tests generally decreases with distance from the test site in the direction of the prevailing wind across North America, although isolated locations received significant deposition as a result of rainfall.

Simon et al. 2006


Cancer Mortality Rates by County (Age-adjusted 1970 US Population)
All Cancers: White Males, 1970-94
US = 209.47/100,000
231.90-892.90 (highest 10%)
222.44-231.89
214.45-222.43
208.48-214.44
201.94-208.47
196.23-201.93
189.59-196.22
181.29-189.58
168.23-181.28
92.53-168.22 (lowest 10%)
Sparse data (7 counties; 0.0% of deaths)

# What Causes Cancer?



- Cigarette smoke
- Diet & nutrition
- Chronic infection
- Occupational exposure
- Genetic
- Alcohol drinking
- Environmental factors including radiation

# How Much Radiation?

- It is very difficult to understand units
- Huge range of every day exposures
- How much radiation does it take to significantly increase cancer frequency?

# It takes a lot of radiation to produce cancer!!!

| Number of people | Dose/Person (Gy) | Amount/ Person (J) | Amount (J) | Background Cancer | Excess Cancer |
|---|---|---|---|---|---|
| **1** | 10 | *700 | 700 | 0.42 | 0.0 |
| **10** | 1 | 70 | 700 | 4.2 | 1.0 |
| **100** | 0.1 | 7 | 700 | 42 | 1.0 |
| **1,000** | 0.01 | 0.7 | 700 | 420 | 1.0 |
| **10,000** | **0.001 | 0.07 | 700 | 4,200 | 1.0 |
| **100,000** | 0.0001 | 0.007 | 700 | 42,000 | 1.0 |

***This is a large lethal amount of radiation given to one person. Cancer can never be detected with this quantity of radiation regardless of population size!!!**

****Background low LET dose/person**

# It takes a lot of radiation to produce Cancer!!!

| Number of people | Dose / Person (Gy) | Quantity/ Person (J) | Quantity (J) | Background Cancer | Excess Cancer |
|---|---|---|---|---|---|
| **1** | 0.1 | 7.0 | 7.0 | 0.42 | 0.01 |
| **10** | 0.1 | 7.0 | 70 | 4.2 | 0.1 |
| ***100** | 0.1 | 7.0 | 700 | 42 | 1.0 |
| **1,000** | 0.1 | 7.0 | 7000 | 420 | 10 |
| **10,000** | 0.1 | 7.0 | 70,000 | 4,200 | 100 |
| **100,000** | 0.1 | 7.0 | 700,000 | 42,000 | 1000 |
| **86,611** | 0.14 | 10.3 | 894,557 | 10,127 | **572 |

**Amount per person and the population size is below the level to detect cancer**

**Cancer is detectable in this range of population, dose, exposure.**

*BEIR VII

**** A-bomb observed response.**

# DOE Low-Dose Radiation Research Program

- A 10 year program, running for 7 years.
- Focused on biological mechanisms of low-dose (< 0.1 Gy) and low dose-rate (< 0.1 Gy / Yr) radiation
- International in scope (currently 80 projects)
- To develop a scientific basis for radiation standards

***http://lowdose.tricity.wsu.edu***

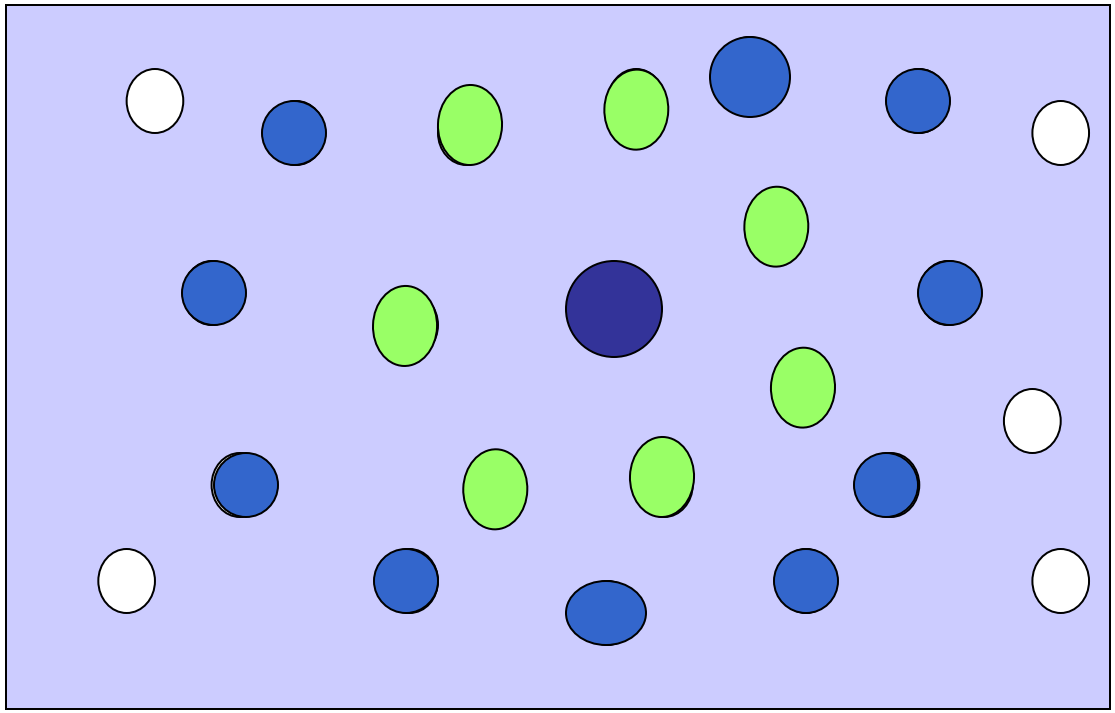
# Key Research Areas

- Technological Advances
- Biological Advances

# Cellular Changes

- **Bystander Effects**
  - Cells respond without energy deposition
  - Cell-cell communication
  - Materials into the media
- **Adaptive Response**
  - Small dose alters response to large dose
  - Small dose decreases spontaneous damage
- **Genomic Instability**
  - Loss of genetic control many cell generations after the radiation exposure

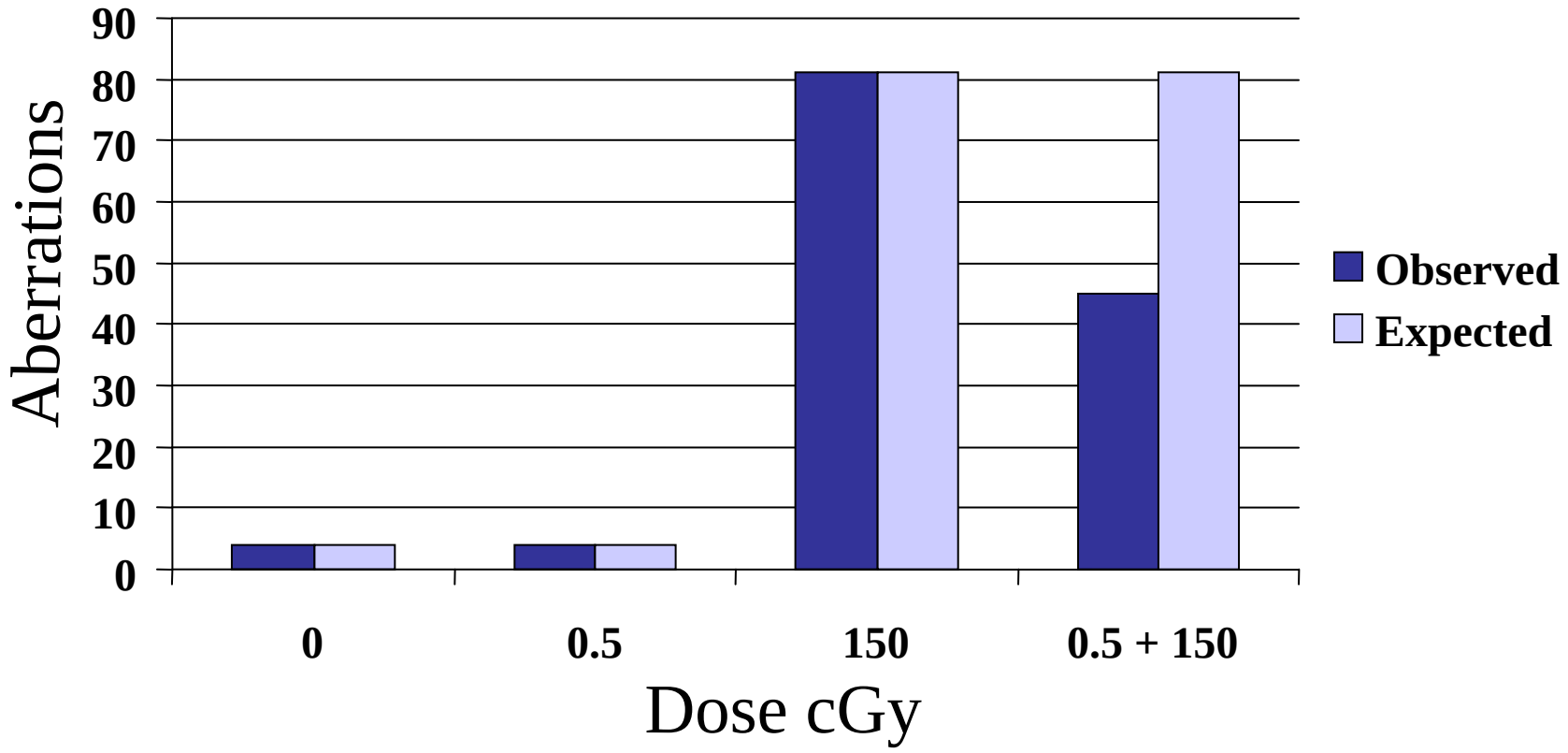
# Bystander Effects *in vitro*



# Low Dose Rate exposures: No Bystander Effects in unexposed Tissues or Organs

- Cancer from internal emitters are at the site of radionuclide deposition
- Secondary cancers from radio-therapy located at the exposure site
- At low dose rates there is little evidence for cancer in non-exposed tissues

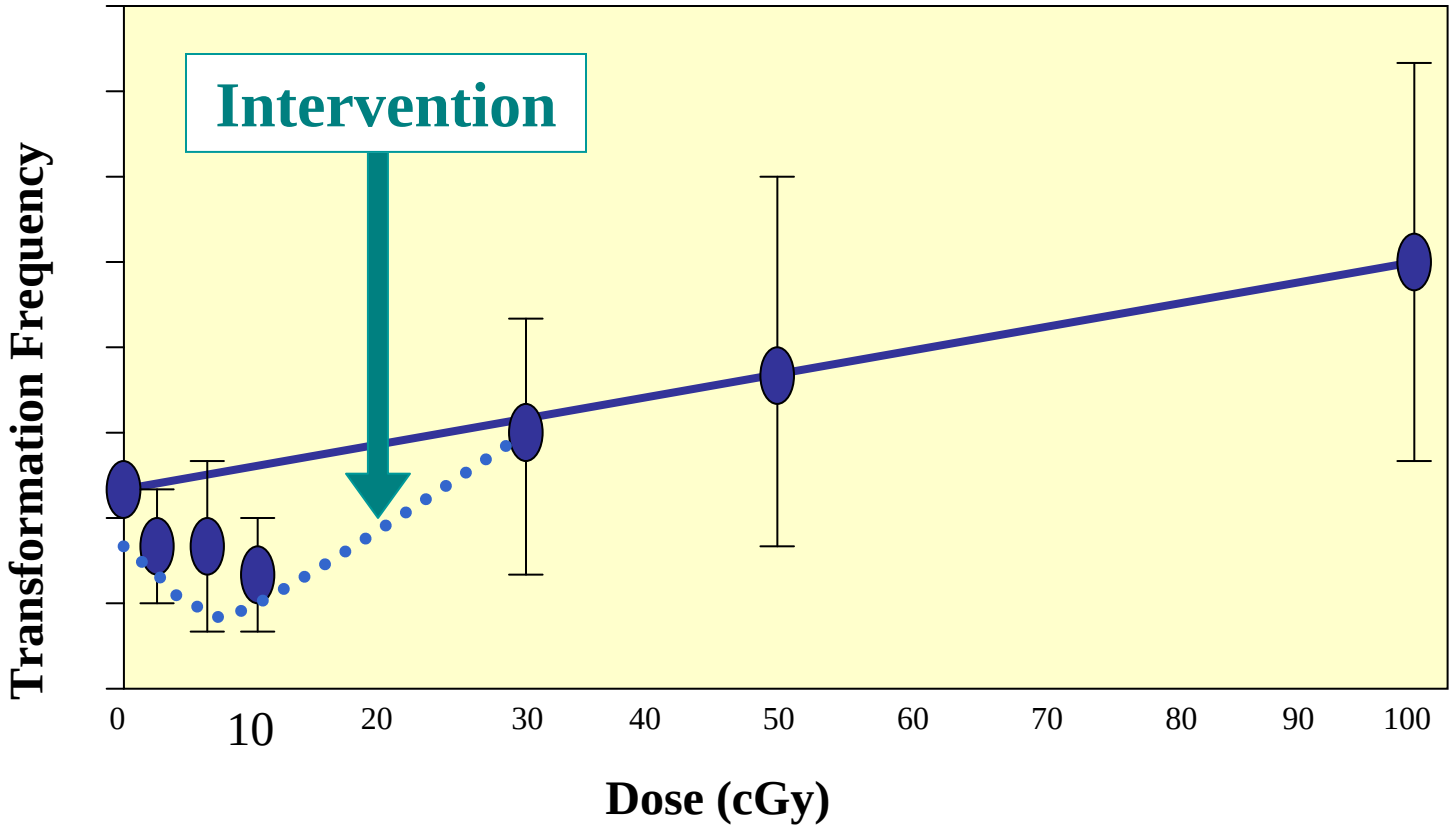
# What Genes are Responsible for the Adaptive Response ?




**Shadley and Wolff 1987**

# Adaptive Response

## Sub-linear dose response



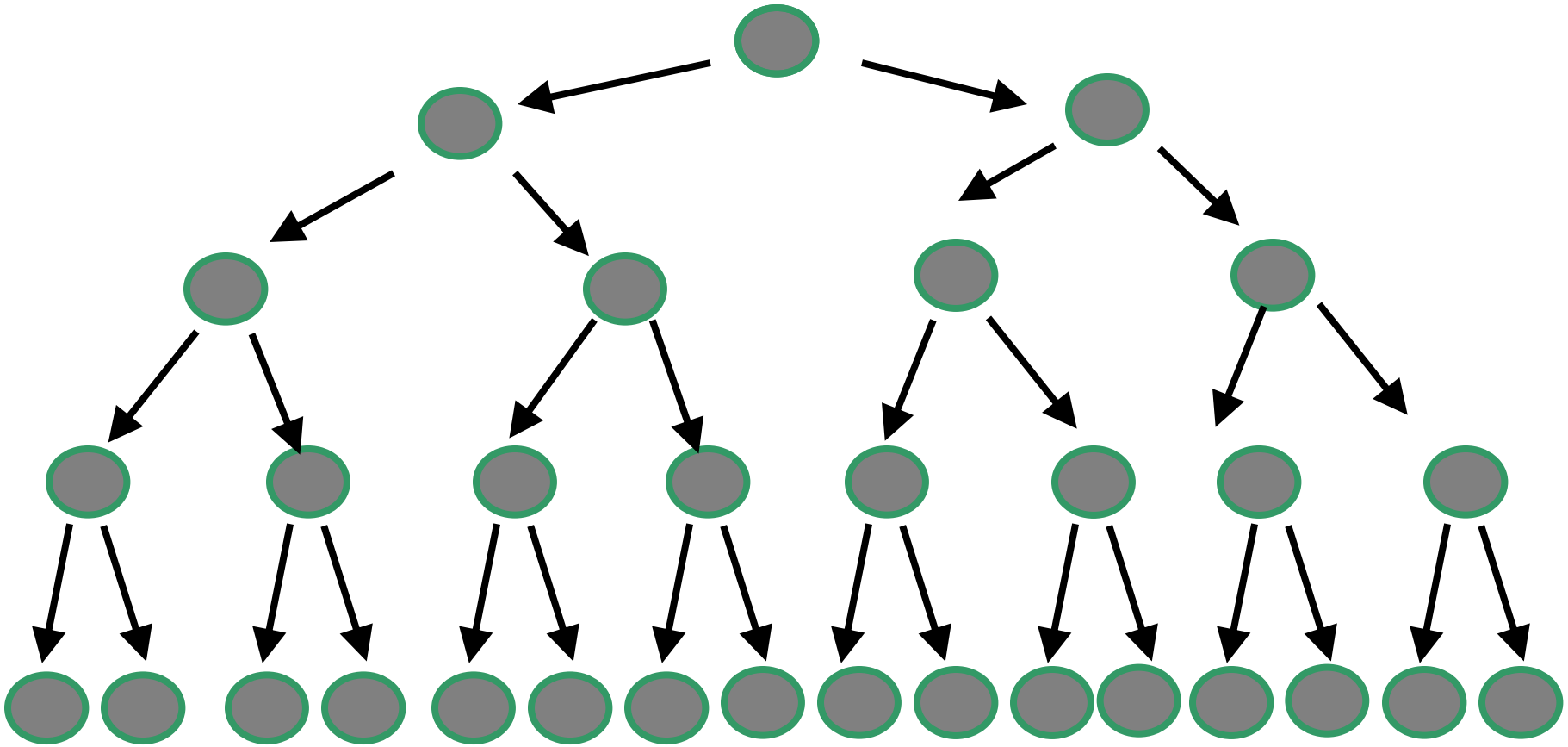

Redpath et al. 2001

# Radiation-induced Genetic Damage

## Old Paradigm

After a cell is mutated by radiation, all of its prodigy are mutated

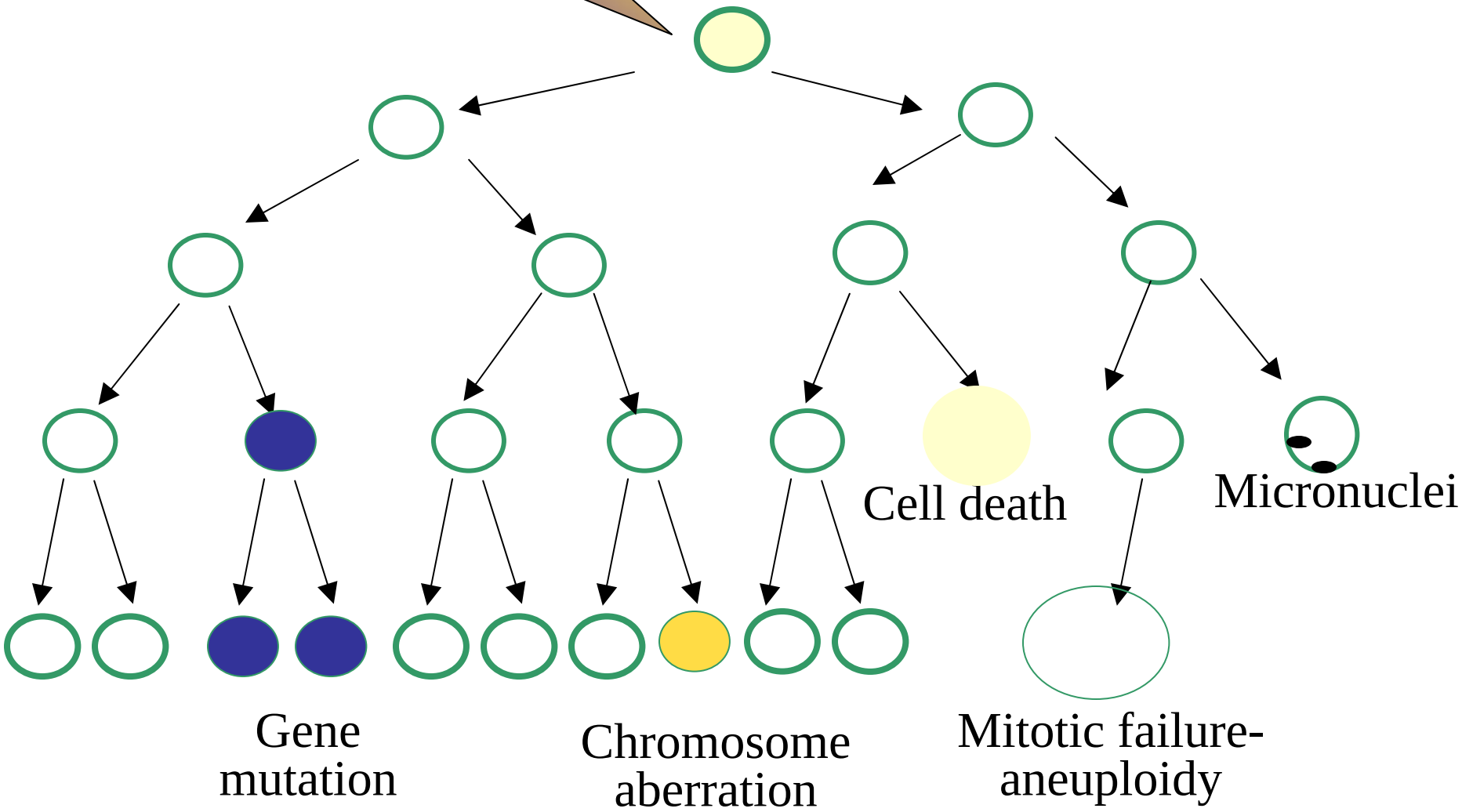
Mutation is a rare event



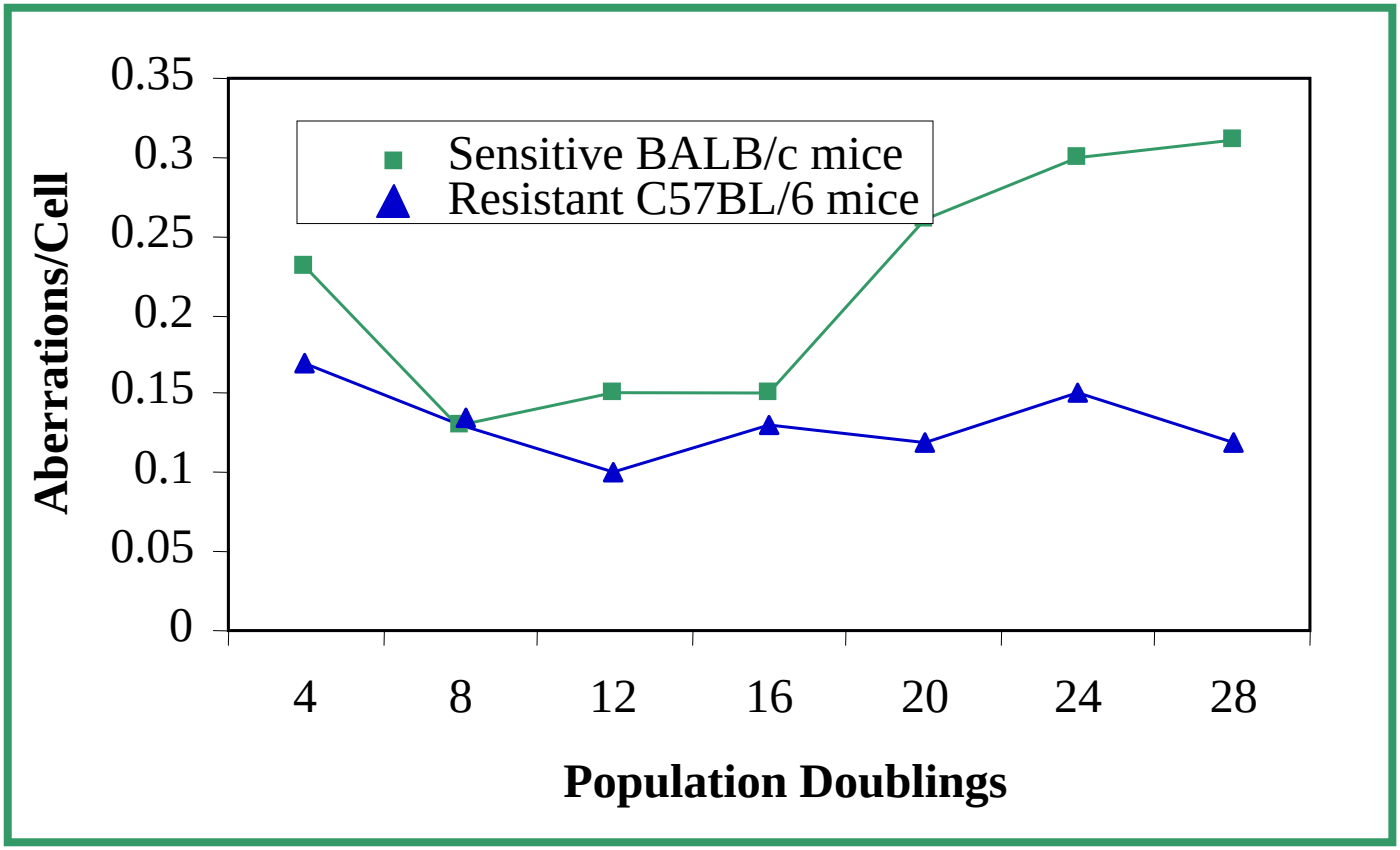
# Genomic Instability

New Paradigm

After a cell is exposed to radiation, different things can happen …sometimes after many cell divisions. This is a frequent event.



# Genomic Instability can be demonstrated in some strains of mice




B. Ponnaiya & R.L. Ullrich, 1998

# Radiation-related Gene Induction

It has been shown that certain genes are inappropriately induced, or “turned on” or “turned off” by radiation.

The genes involved depend on the radiation dose delivered.

# Protective Response

It was found that low-dose IR exposures modulated genes involved in stress response, synaptic signaling, cell-cycle control and DNA synthesis/repair, suggesting that low-dose IR may activate protective and reparative mechanisms as well as depressing signaling activity.

Yin 2003

# Summary of New Paradigms

- **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

# Radiation is a rather poor mutagen and Carcinogen

- It is a very good cell killer
  - Induction of apoptosis
  - Chromosome cell death
  - Necrosis
  - Wide use in radiation therapy

# Summary: "My View on Low Dose Cancer Risk"

- Radiation is not a major environmental carcinogen. It takes a large amount of radiation to produce an increase in cancer frequency.
- Both non-linear and linear models must be considered in determining dose-response relationships for radiation-related human cancer.
- Single hit, single DNA damage/mutation, single cancer biophysical model must be modified to accommodate modern molecular biology.
- Additional research is needed to define mechanisms of action for observed low dose biological responses before they can be used in cancer risk estimates.
- Scientific basis for radiation standards is needed to help define the shape of the dose-response relationships in the low dose regions.