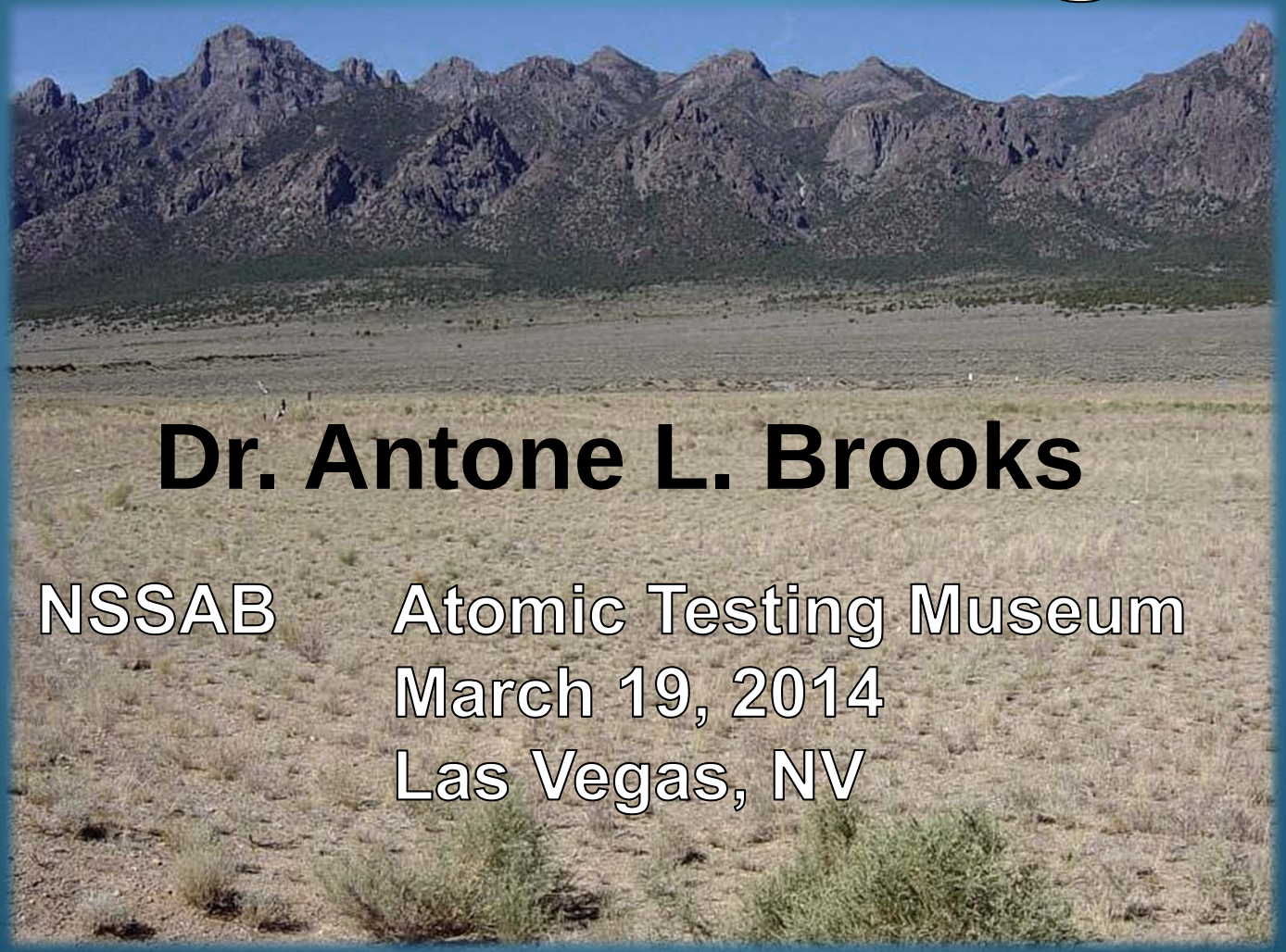
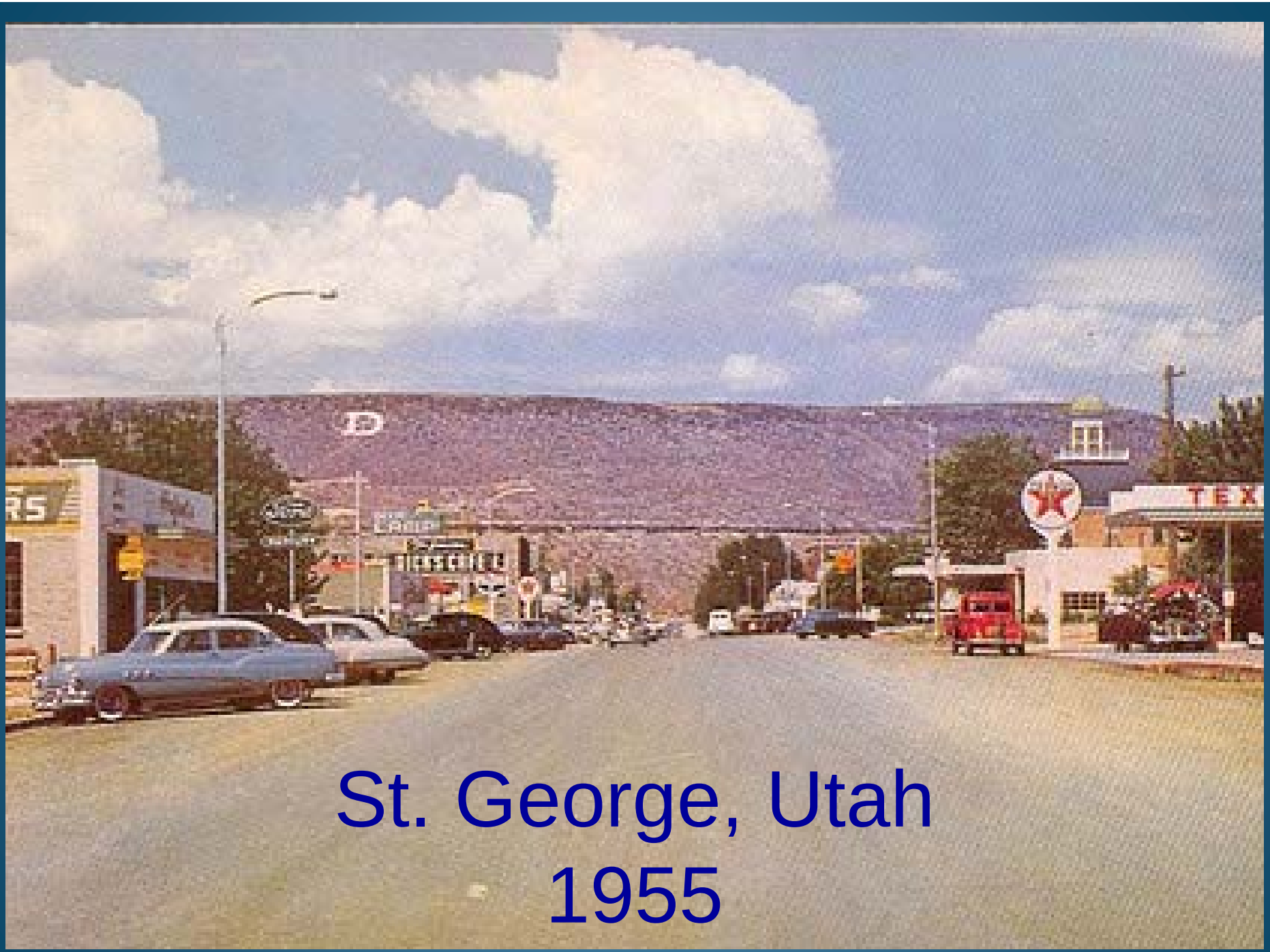
Radiation Biology In The Low Dose-region



Dr. Antone L. Brooks

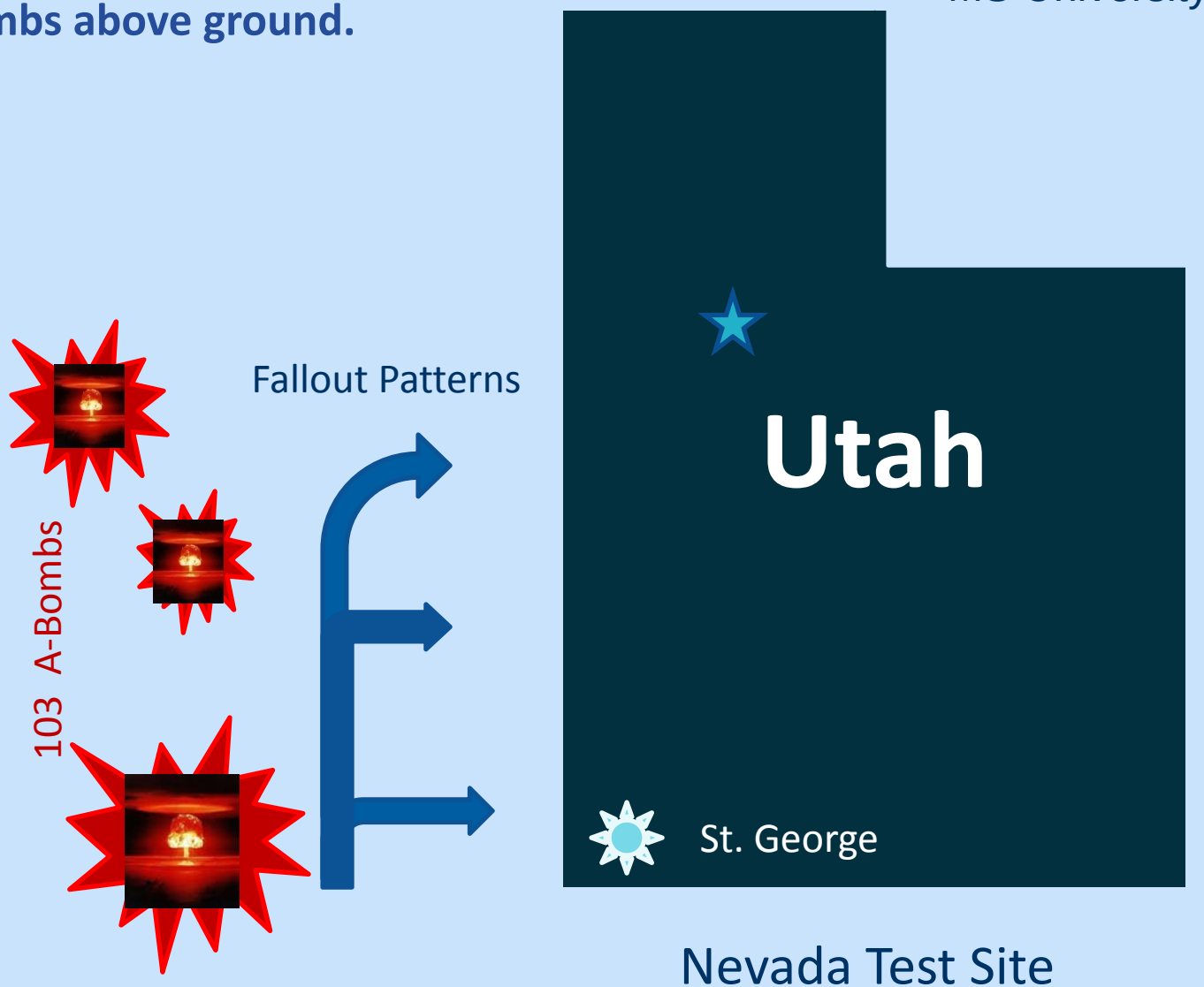
NSSAB Atomic Testing Museum
March 19, 2014
Las Vegas, NV


Nuclear weapons were part of my early life


St. George, Utah
1955

Fallout from over 100 A-bombs above ground.

MS University of Utah



Fallout was on everything and in everything!

My ecological research demonstrated lots of radioactive material in our bodies. We need to be sure we have not underestimated risk!!

What if…

internally deposited radioactive materials from fallout are more hazardous than external radiation?

(Fallout) Radionuclides of Concern

- Tritium
- Strontium-90
- Iodine-131
- Cesium-137
- Plutonium-239

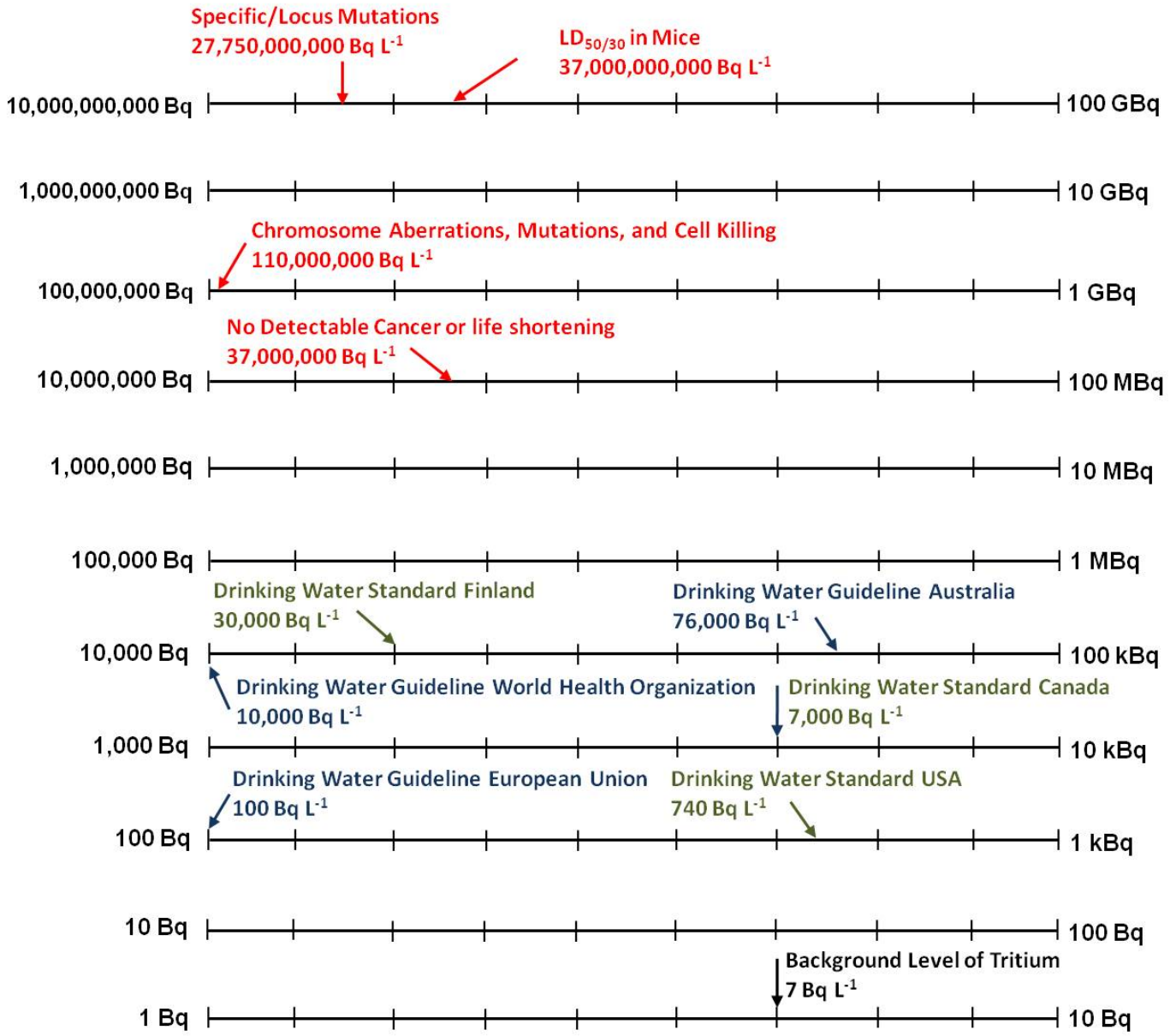
Conversion of Radiation Units

- Rad is a unit of Dose (Energy/Mass)

  100 Rad = 1 Gy

- Rem is a unit of Risk (Dose x Tissue x Rad type x dose-rate)
  - 100 Rem = 1 Sv
- Curie is a unit of activity
  - 1 pCi is equal to 2.2 Disintegrations / minute
  - 1 Bq is equal to 1 Disintegration/sec or 60 Dis/min
  - Bq is small while a Curie a very large

Tritium Activity, Biological Effects, and Regulations

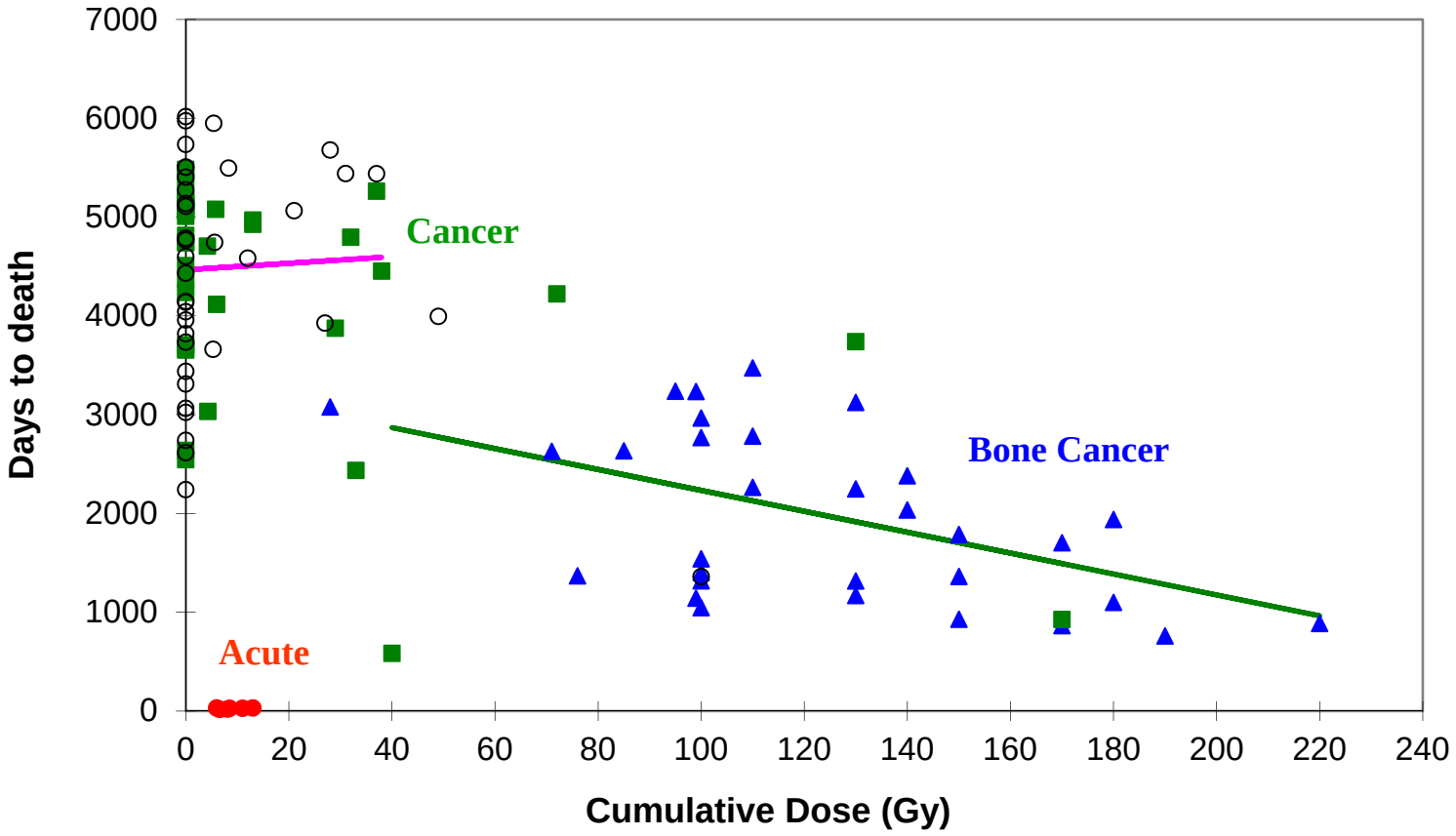


What if…

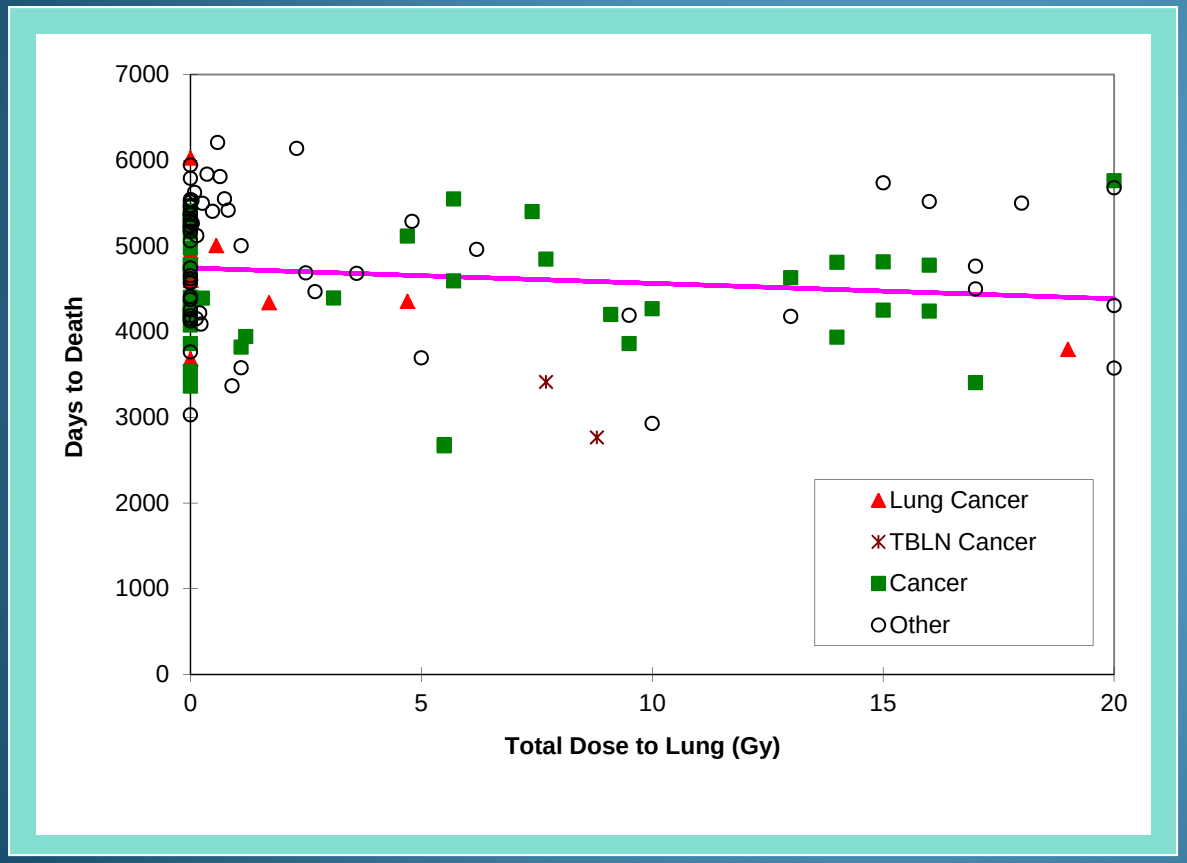
injected or inhaled ^{90}Sr-^{90}Y was much more hazardous than acute radiation?

- Samples from the environment were measured in pCi/liter or pCi/Kg range
- Chinese Hamsters were injected with μCi ^{90}Sr/g body weight (5-9 orders of magnitude higher than the environment) to study chromosome aberrations and cancer.

Dose Response for Life Shortening Following Inhalation of 90-Strontium Chloride



Dogs <20 Gy Dose to Lung after Inhalation of FAP



	Lung Cancer	Total Cancer
Control	8/54= **15%**	26/54= **48%**
Exposed	4/64= **6%**	29/64= **45%**

What if… Strontium-90 was More hazardous than acute exposure?

Answer:

- Huge doses were required to produce lung cancer from ^{90}Sr. Doses less than 20 Gy had no increase in lung cancer.
- Huge doses and dose rates were required to produce bone cancer from ^{90}Sr.

  Low dose rates did not increase bone cancer.

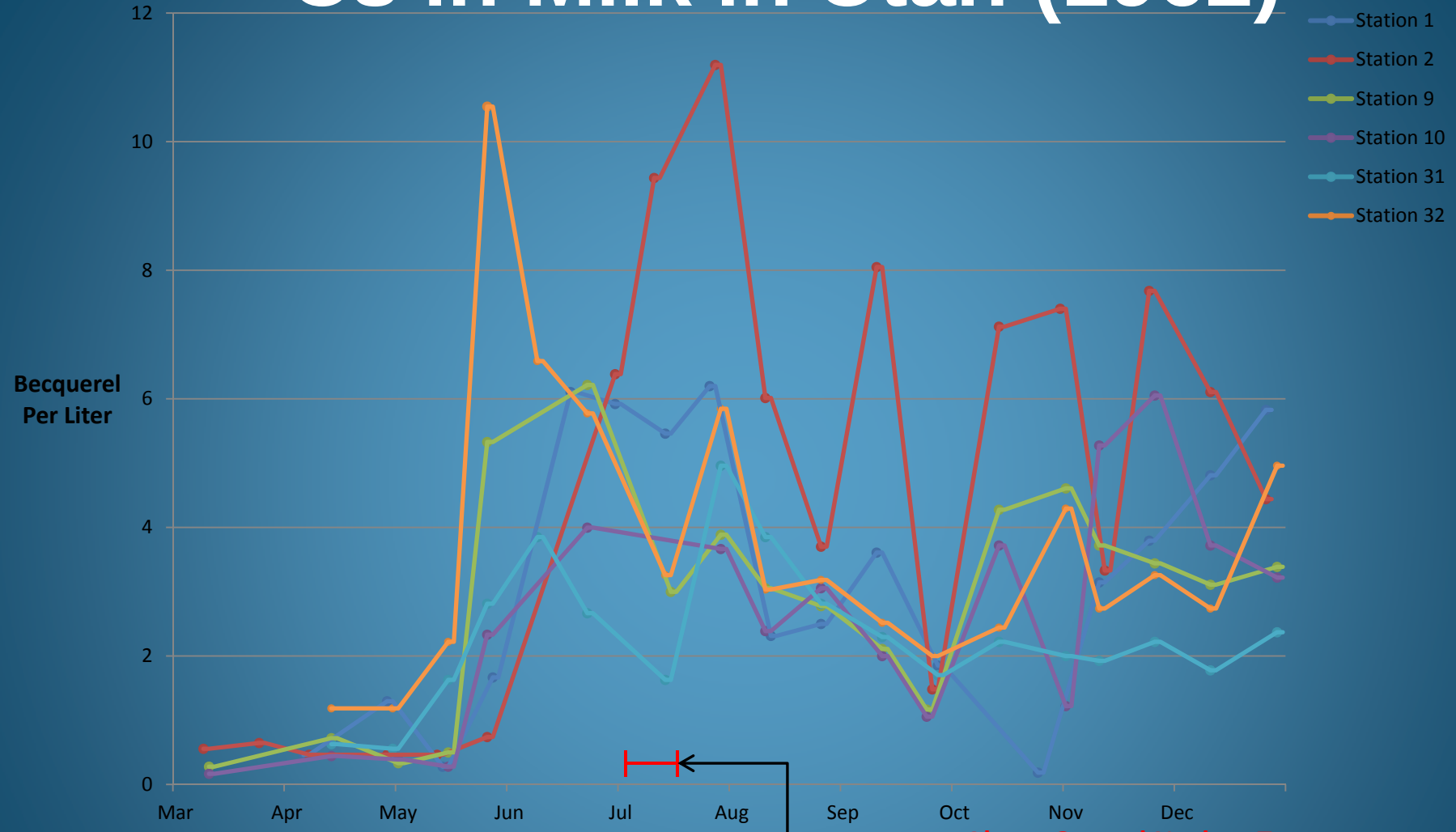
Health Effects of Iodine-131

- Iodine-131 concentrates in the Thyroid
- Short half-life results in high doses
- Chernobyl had very large doses of Iodine-131 to a large population
- Increased frequency of thyroid cancers in children exposed (7,000 excess cancers)
- Less than ten thyroid cancer deaths

Dose and health effects of Cesium-137

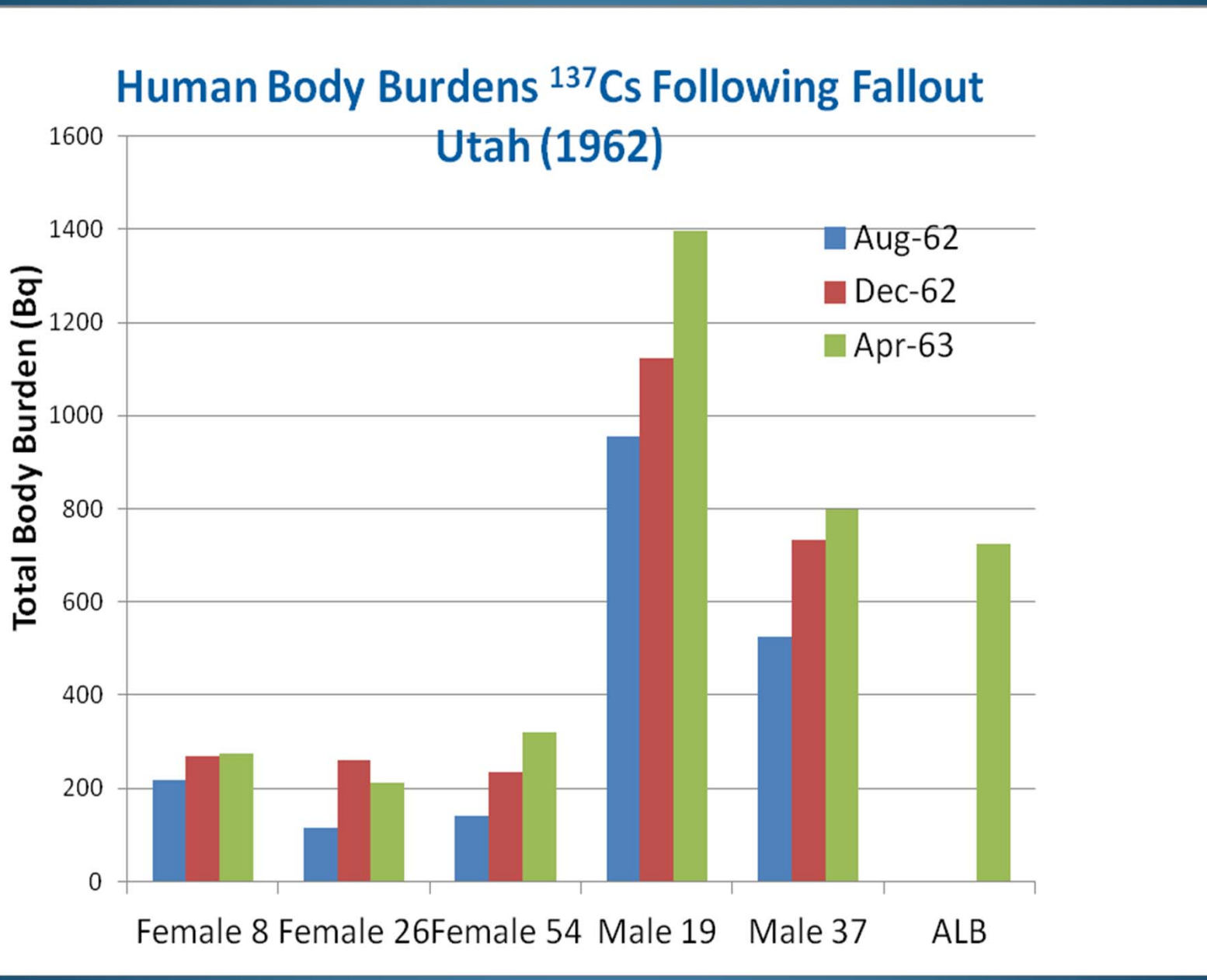
- Cesium-137 has long physical half-life and short effective half-life
- Cesium-137 is uniformly distributed in the body and results in a whole body dose
- Cesium-137 is a major component of fallout from nuclear weapons
- Cesium-137 can concentrate up the food chain
- Cesium binds to clay particles making it less biologically available

^{137}Cs in Milk in Utah (1962)



Above Ground Nuclear Tests

1.	Sedan	July 6	104 KT
2.	Little Feller II	July 7	22 T
3.	Jonnie Boy	July 11	500 T
4.	Small Boy	July 14	small
5.	Little Feller I	July 17	18 T


Human Body Burdens 137Cs Following Fallout
Utah (1962)
Total Body Burden (Bq)
1600
1400
1200
1000
800
600
400
200
0
Aug-62
Dec-62
Apr-63
Female 8
Female 26
Female 54
Male 19
Male 37
ALB

^{137}Cs Environmental and Effects Levels

Marked Life Shortening in Dogs
138,000,000 Bq/kg

100,000,000 Bq — 1 GBq

No Cancer Increase in Dogs
38,000,000 Bq/kg

No Life Shortening in Dogs
55,000,000 Bq/kg

10,000,000 Bq — 100 MBq

1,000,000 Bq — 10 MBq

100,000 Bq — 1 MBq

Highest Soil Concentration in Finland
78,000 Bq/m^2

10,000 Bq — 100 kBq

Action level for ^{137}Cs
1,200 Bq/kg

Global Fallout Reindeer Meat 1966
2,760 Bq/kg

Total ^{137}Cs Deposited from NTS (Nevada).
Total ^{137}Cs Deposited from Global Fallout
(Eastern US). > 3,000 Bq/m^2

Highest Concentration in Women, Chernobyl 1987
6,930 Bq (Whole Body Burden)

1000 Bq — 10 kBq

Highest level of ^{137}Cs in Cattle Fukushima

Highest Human, Utah
725 Bq/kg

General Consumption Limit for Adults
1,000 Bq/kg

100 Bq — 1 kBq

Lowest Chernobyl Reindeer Meat 2008
142 Bq/Liter

General Consumption Limit for Infants
100 Bq/kg

10 Bq — 100 Bq

Highest Peak in Milk, Utah
11 Bq/Liter

Highest Total Intake from Food, Utah
17.9 Bq/Week

1 Bq — 10 Bq

Bq/liter milk Seattle WA Chernobyl

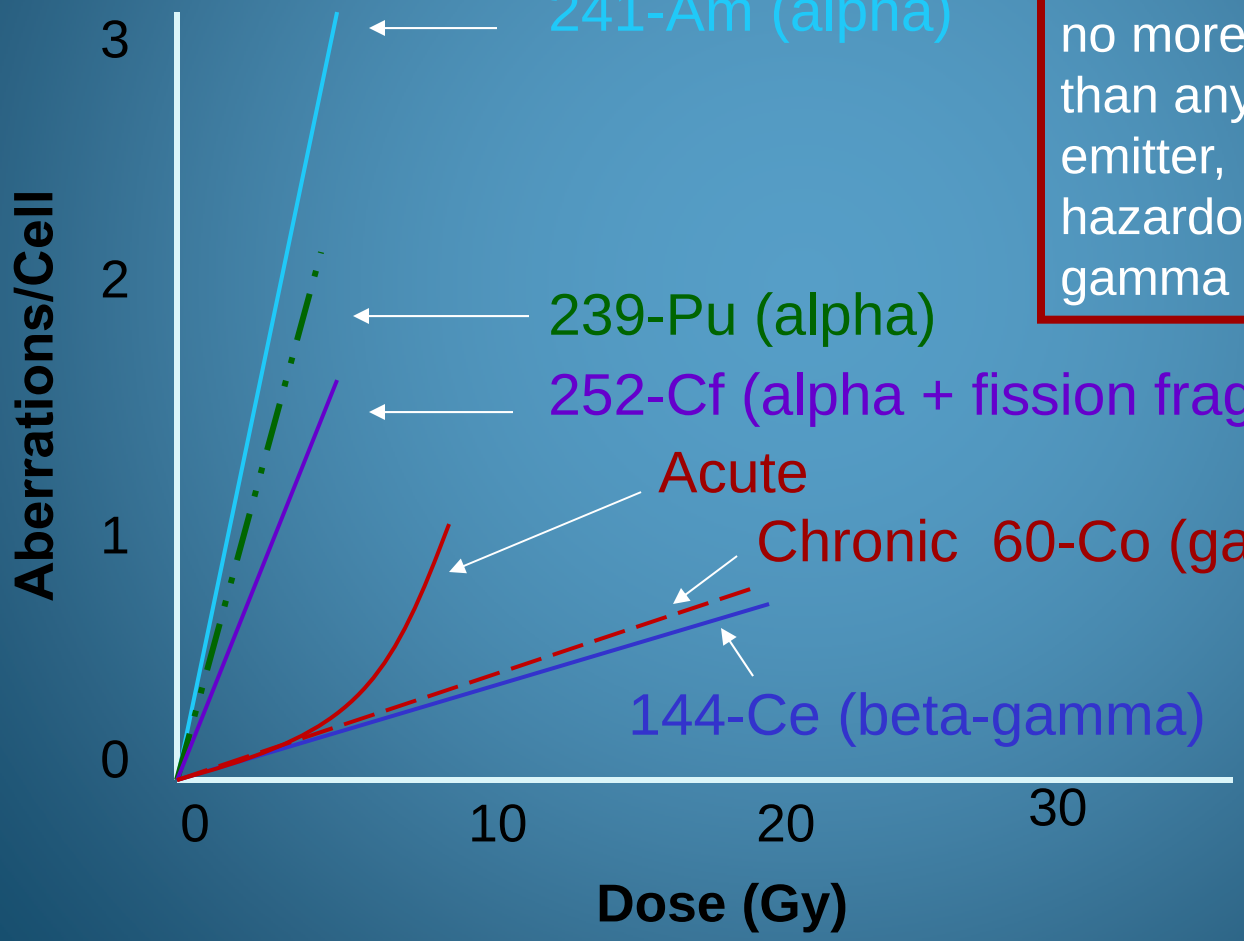
Heightened concern about Plutonium produced by fallout and nuclear power

- Plutonium is retained in the lung, bone and liver with long physical and biological half-lives.
- Plutonium produces a large dose to the target organs.
- Cells “hit” by a single alpha particle result in a large cellular dose.

What if…

^{239}Pu is the most hazardous substance known to man?

Dose Response for Radiation-Induced Chromosome Aberrations



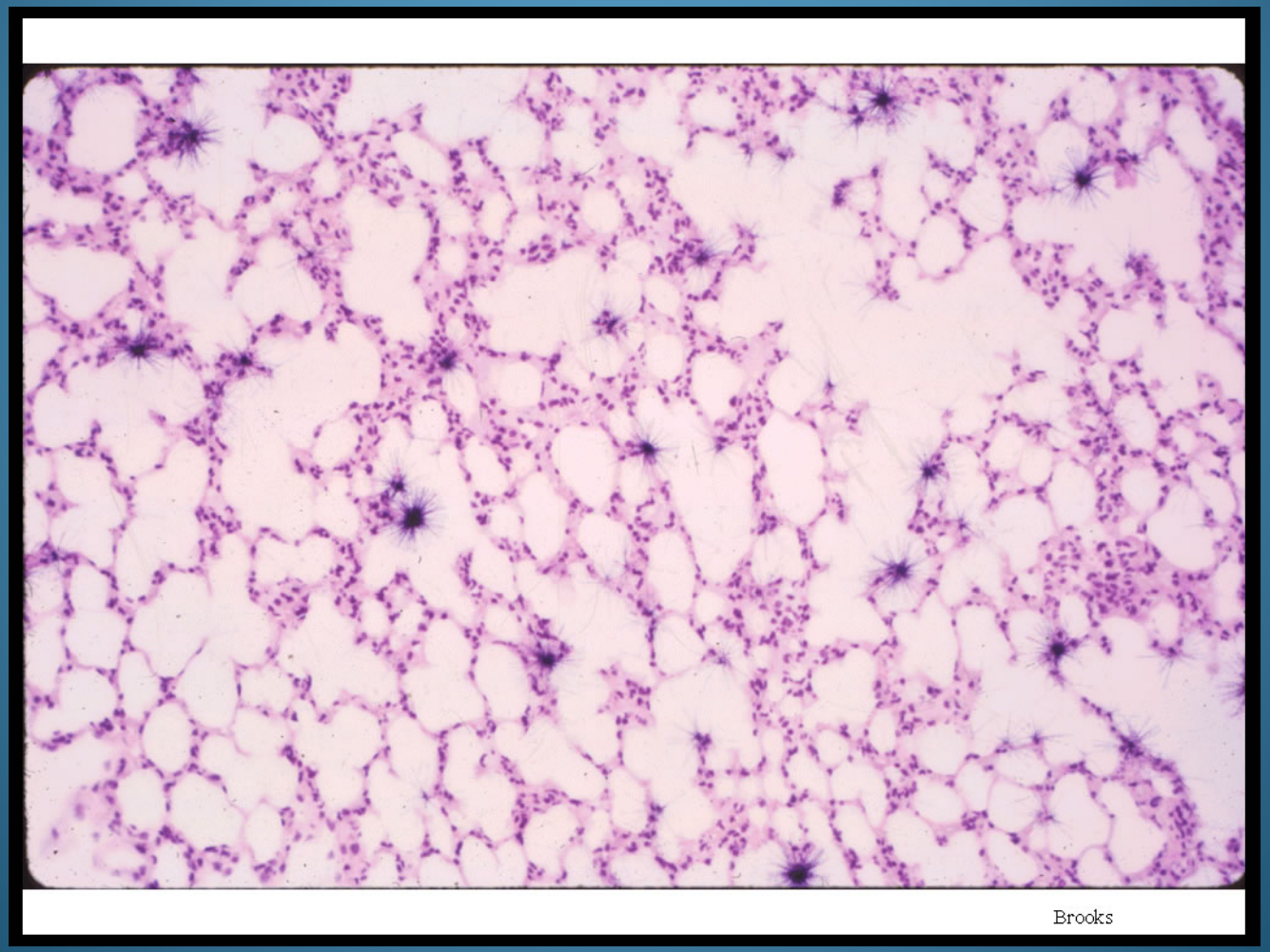
Wow!! Plutonium is no more hazardous than any other alpha emitter, more hazardous than beta-gamma emitters

What if…

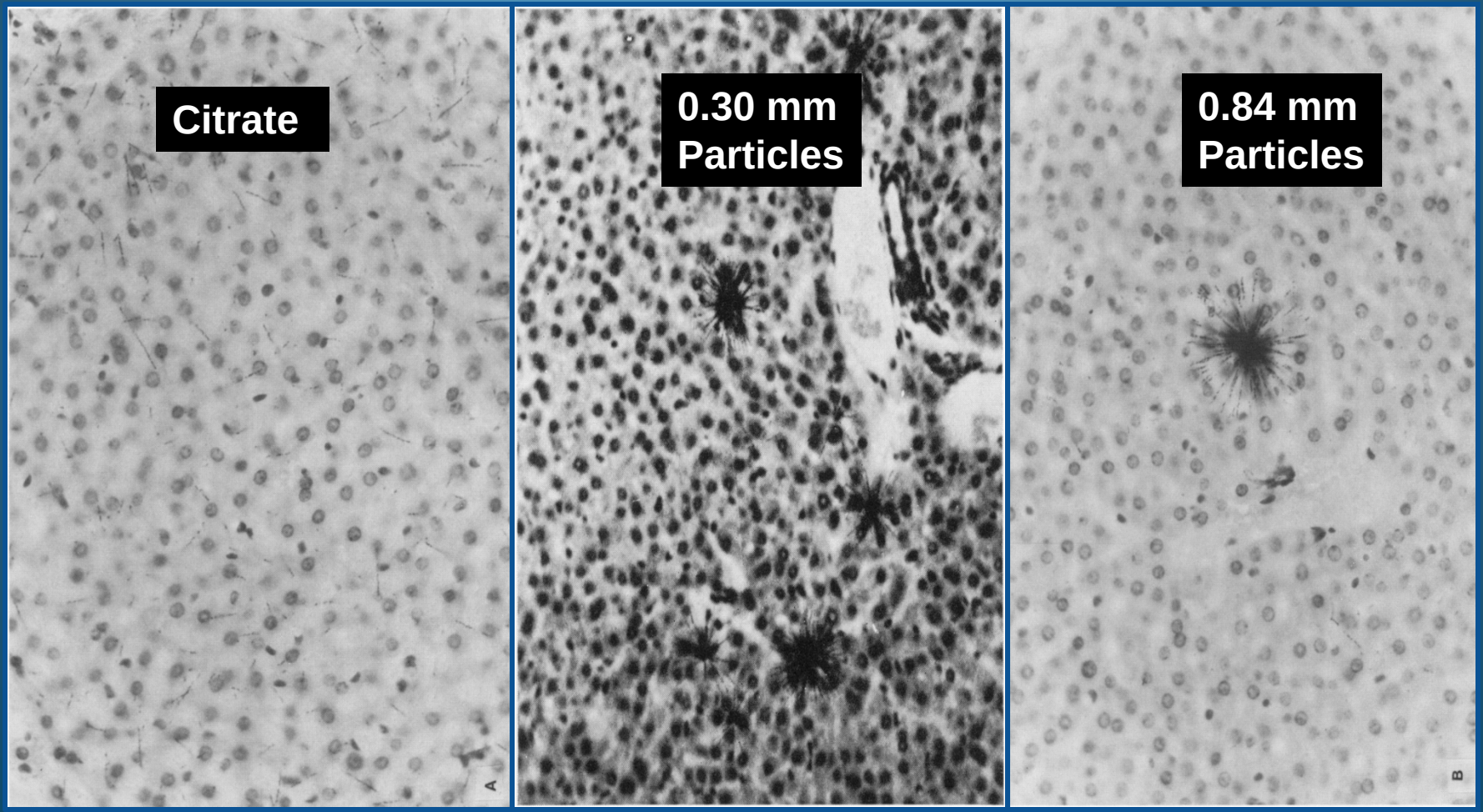
a single $^{239}PuO_2$ particle deposited in the lung can cause cancer?

"Hot Particle Hypothesis"

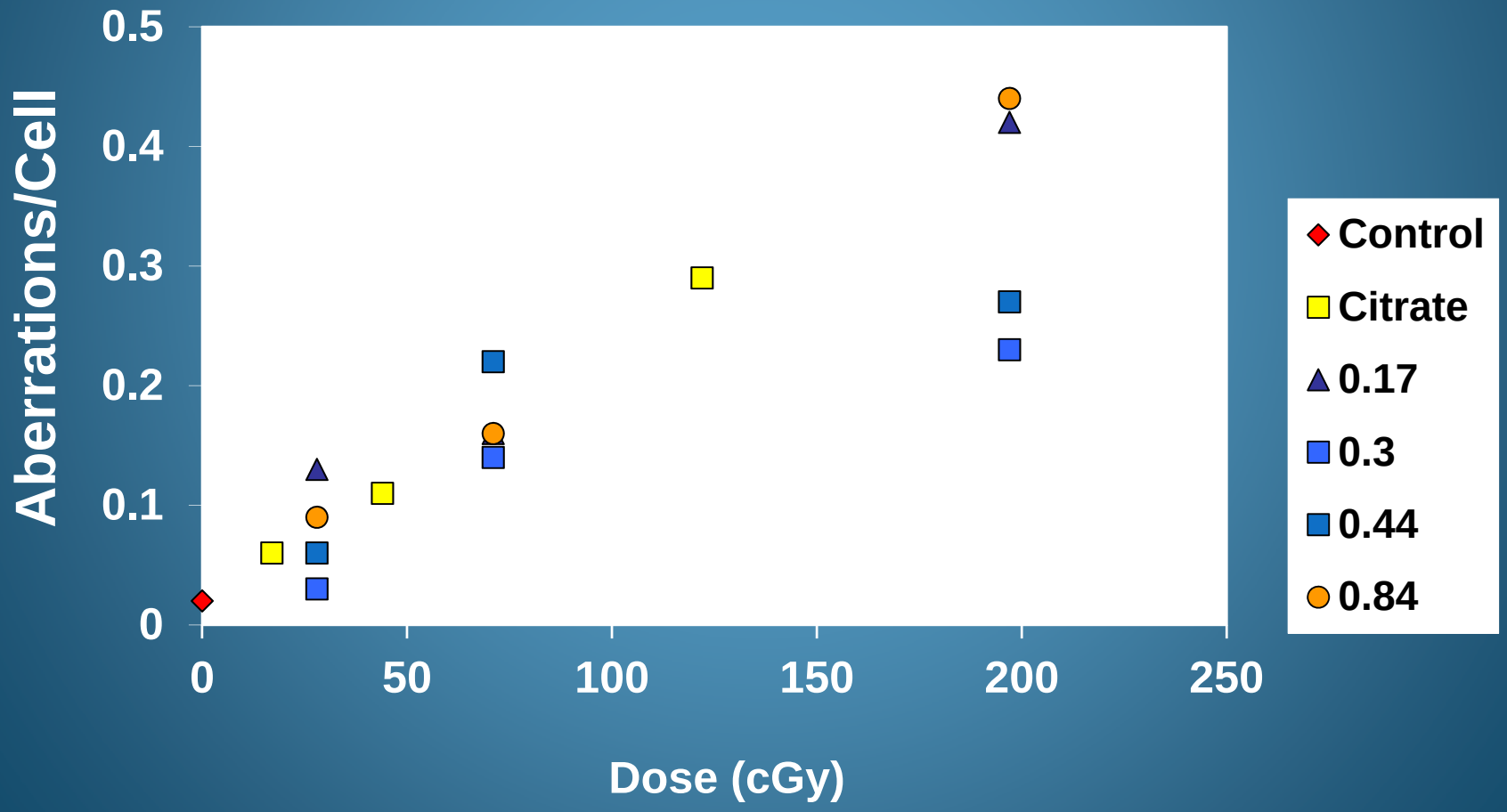
Non-Uniform Dose Distribution from Plutonium Inhalation



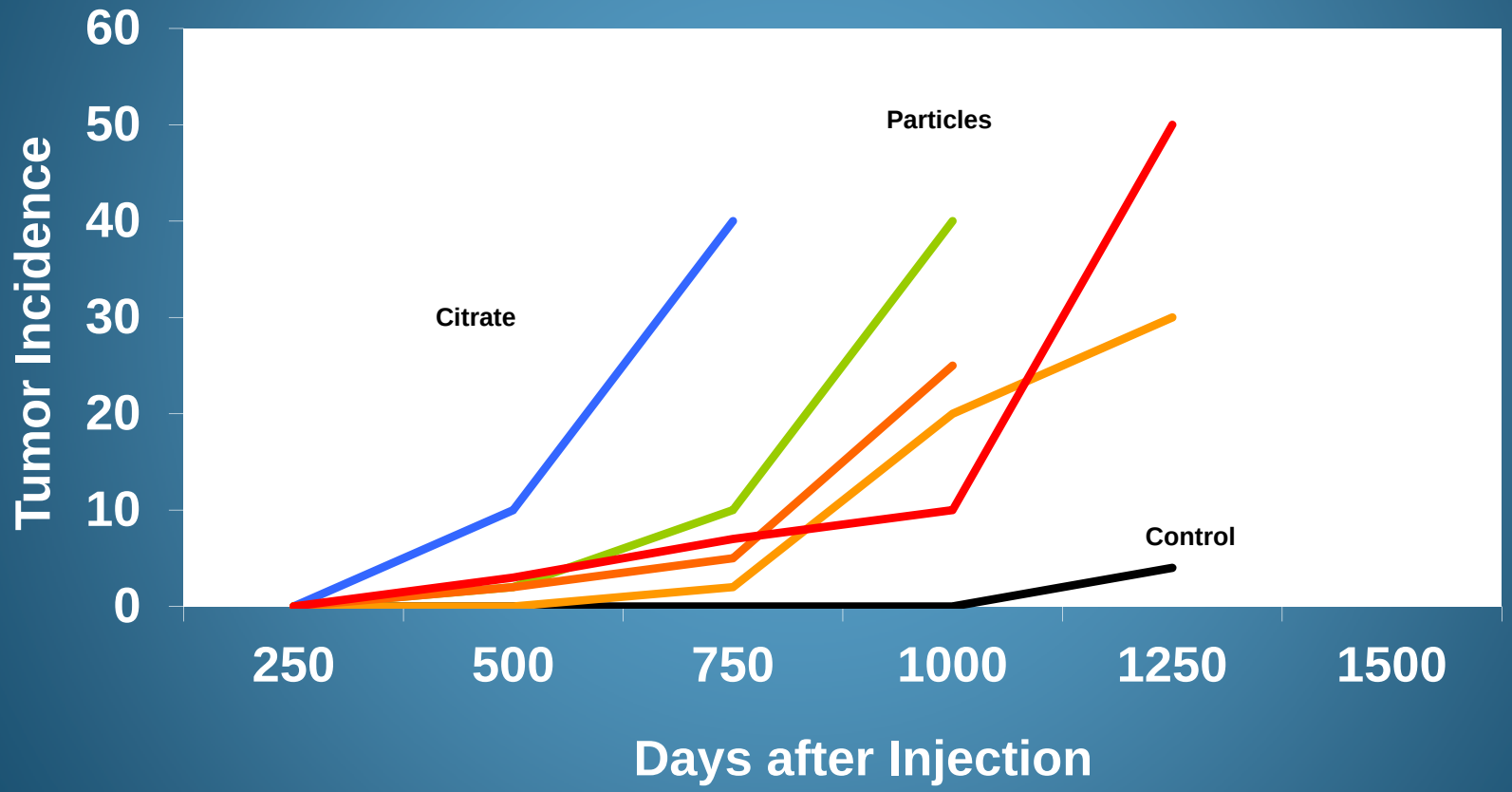
Non-Uniform Distribution of ^{239}Pu in the Liver of Chinese Hamsters following injection with citrate or oxide particles



The Influence of ^{239}Pu Dose-Distribution on Chromosome Aberration Frequency



Cumulative Liver Tumor Incidence After $^{239}PuO_2$ or ^{239}Pu Citrate Exposure



Concerns about Plutonium

- What if Plutonium is the most hazardous substance known to man? **It is not!!!**
- What if a single Plutonium particle will cause cancer. **It will not!!!**
- To get cancer from Plutonium, it is necessary to expose as many cells to alpha particles as possible.

What if Fallout is more Damaging than Acute External Radiation Exposure?

- Extensive Research on internally deposited radioactive materials, ^{90}Sr, ^{137}Cs, ^{144}Ce, ^{131}I, ^{230}Pu, ^{241}Am.
- All different routes of entry, Ingestion, Inhalation, wounds, injection.
- **Fallout is much less effective** in production of biological damage than single acute exposures (X-rays).
- **Decreased dose-rate decreased biological effects** at all levels of biological organization. Molecular, Cellular, Tissue, Organ, experimental animal.

New Technologies

- The Human Genome was sequenced
- New technologies, such as microbeams, were now available to test health risks in the low dose region, where it couldn't be measured before.

Can health risks in the low dose region now be understood?

What if…

the LNTH overestimates risk??

- Are the mechanisms of action the same for low and high doses of radiation?
- Do we need to change current paradigms in radiation biology?
- Is the LNTH an accurate scientific description for the dose-response relationship for cancer in the low dose region?

Research in Low Dose Region

- Extensive research on biological effects of low dose radiation resulted in many new observations making paradigm shifts in radiation biology essential.
  - Hit theory vs Bystander and tissue effects
  - Linear dose-responses vs Protective adaptation
  - Mutation theory vs Genomic instability
- The mechanisms of action of these phenomena are being carefully documented and understood.
- Low-dose responses are non-linear at all levels of biological organization (Molecular, Cellular, Tissue, Organism, Humans?) and suggest that LNT overestimates risk.

Are the mechanisms the same at low vs. high doses?

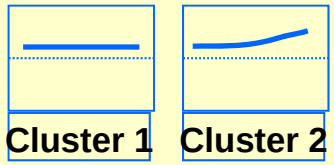
Three lines of evidence point to a transition in transcript expression profiles in the range of 10-25 cGy

All gene data (n = 22283)

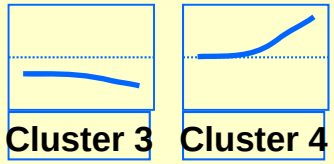
Filter for differential expression (FDR < 0.10)

Combine into one dataset N=420 genes

Cluster analyses

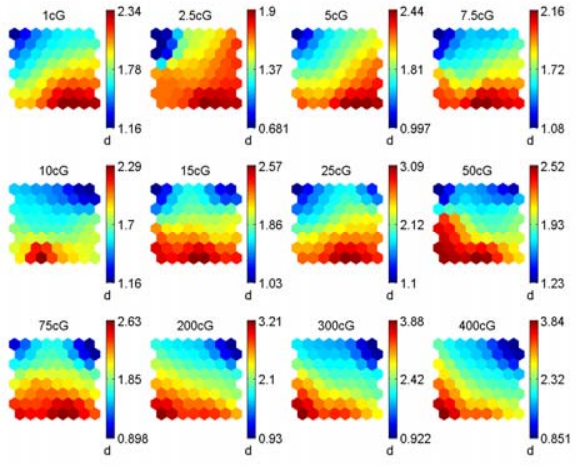


Cluster 1 **Cluster 2**



Cluster 3 **Cluster 4**

Self Organizing Maps



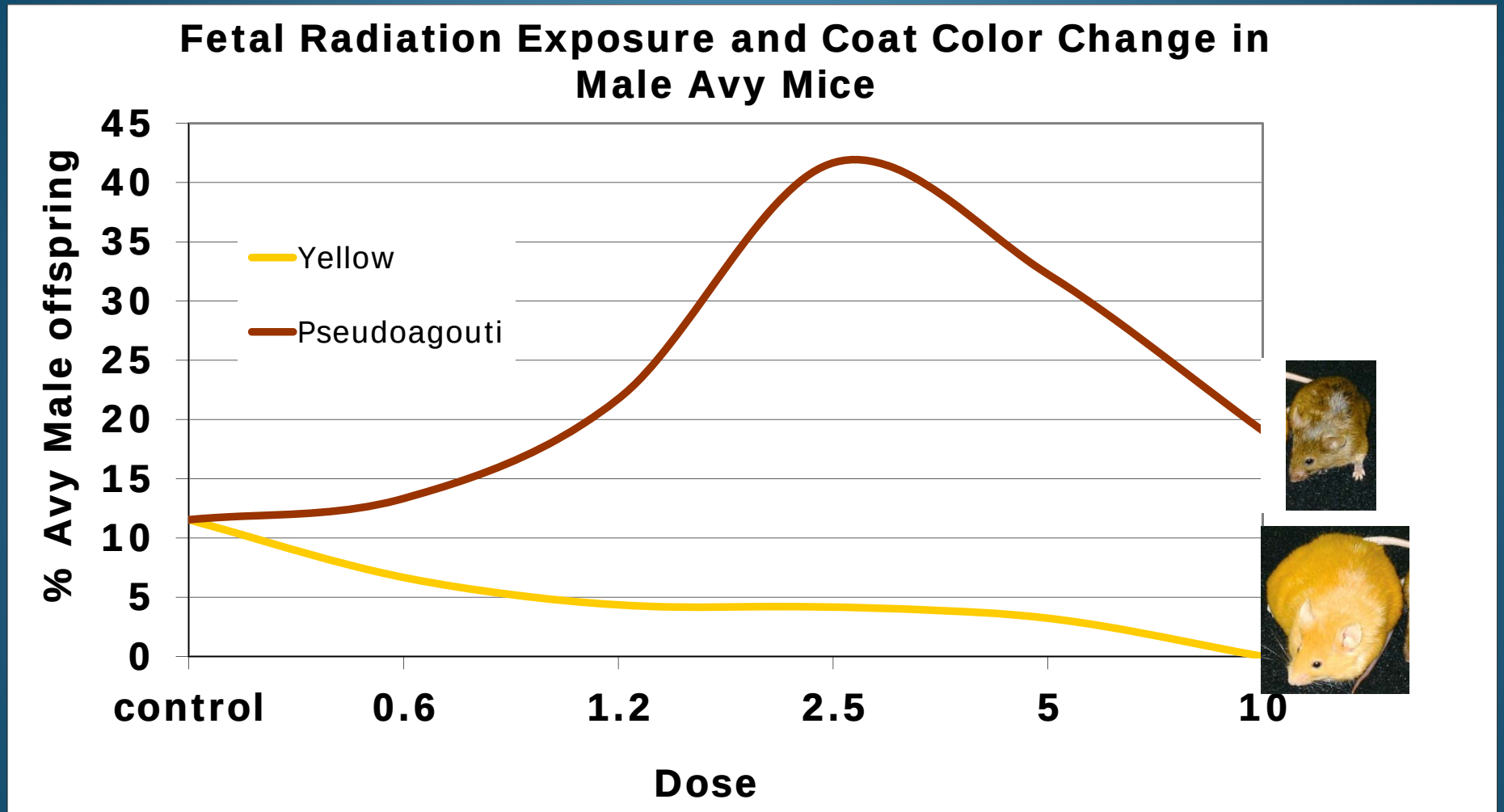
Near neighbor analyses

Row																		Uniqu
1	236		61		184		63		34		52		200		37		68		90		116		113	420
2		49		52		58		21		16		44		30		23		39		68		82		156
3			47		36		20		12		15		25		22		21		36		59			96
4				35		19		12		12		13		19		21		21		30				51
5					19		12		12		12		12		19		21		18					29
6						12		12		12		11		12		19		18						21
7							12		12		11		11		12		17							19
8								12		11		11		11		11								13
9									11		11		11		10									11
10										11		11		10										11
11											11		10											11
12												10												10
Dose/cGy	1.0		2.5		5.0		7.5		10		15		25		50		75		200		300		400	

Figure 1

In collaboration with D. Nelson, K. Krishnan

(Wyrobek, et al., LLNL)



Bernell and Jirtle 2011

What if…

mechanisms of action are different at high and low doses of radiation?

Differences between High- and Low-Dose Radiation Responses

High Dose > 0.2 Sv

Cell killing high
DNA damage high
Gene Expression (Damage?)
Epigenetic Effects?
Free Radical Increased
Direct Action

↑ Apoptosis (Increased)
↑ Mutation Frequency
↑ Cell Transformation
Immune response (-)
Cancer increased (5%/Sv)

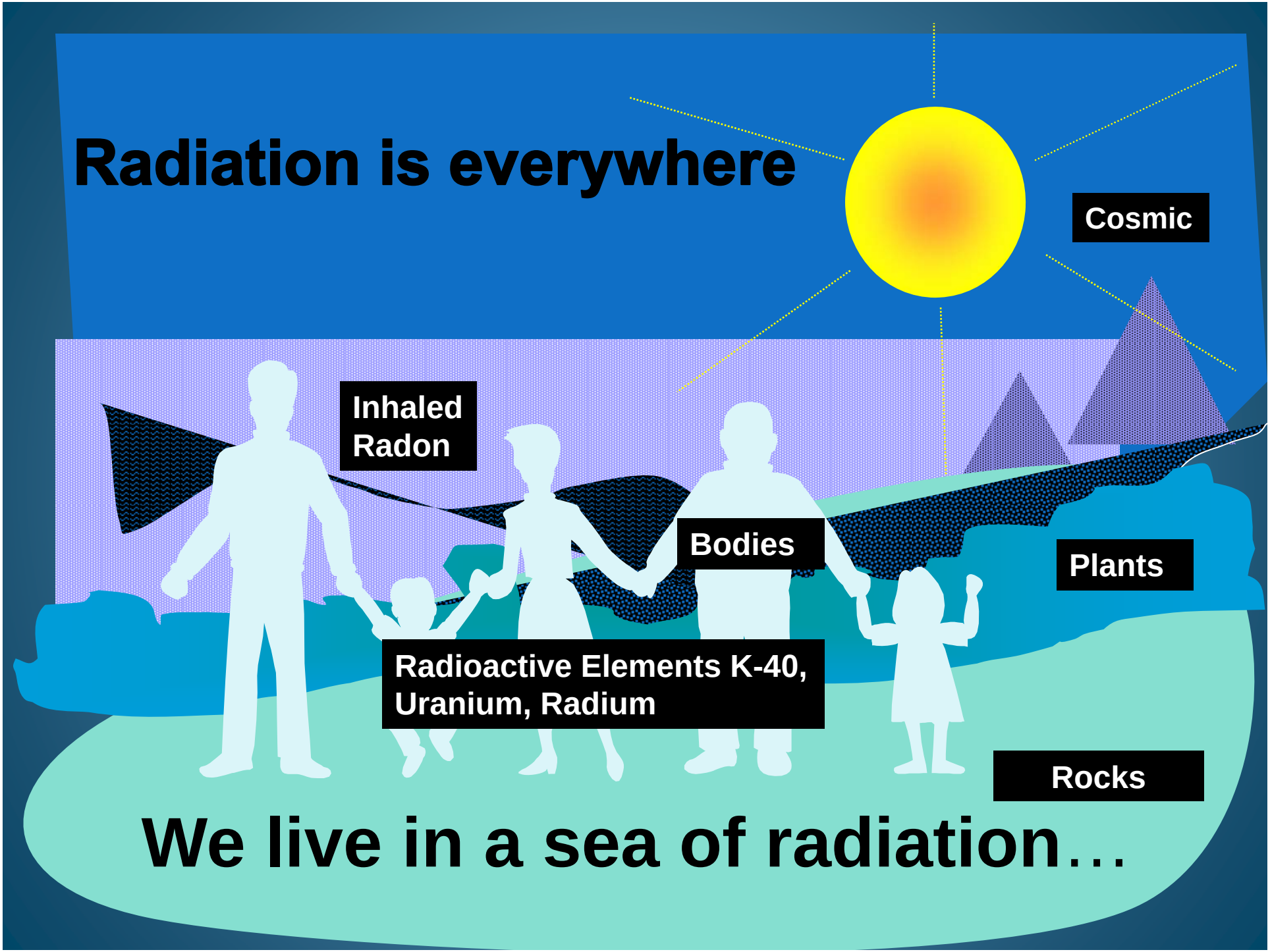
Mechanisms are different!!
(Repair Low dose vs Damage High Dose)

Low Dose < 0.2 Sv

Cell killing low
DNA damage low/not detected
Gene Expression (Protective?)
Epigenetic Effects (Protective)
Free Radicals decreased
Indirect Action
MnSOD
Glutathione

↑ Selective Apoptosis
↓ Mutation Frequency
↓ Cell Transformation
Immune response? (+)
Cancer (mSv)?

Radiation is everywhere

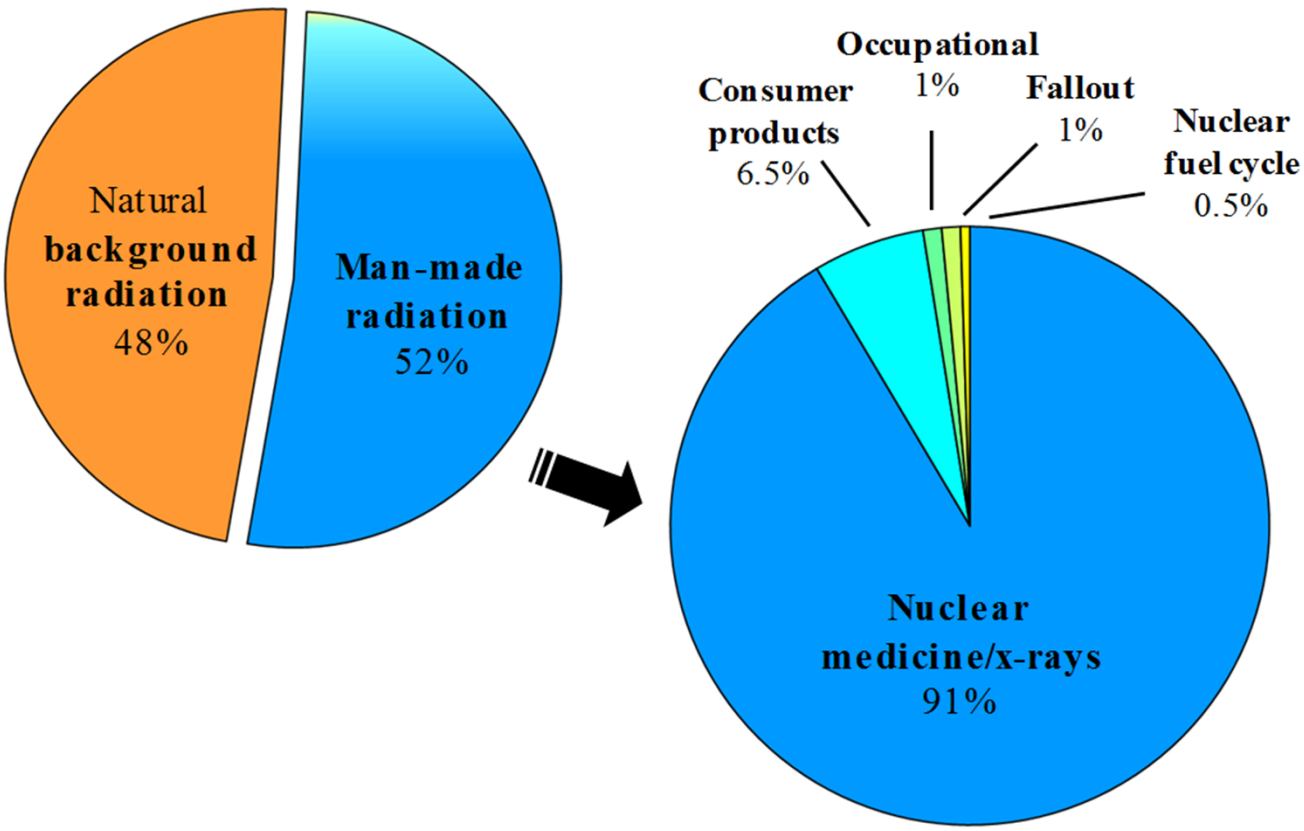


We live in a sea of radiation…

The question is: How much?

- **Compared to what?**
  - Fallout vs Natural Background
  - Fallout vs Nuclear power
  - Fallout vs Nuclear Accidents
  - Fallout vs Medical Exposures

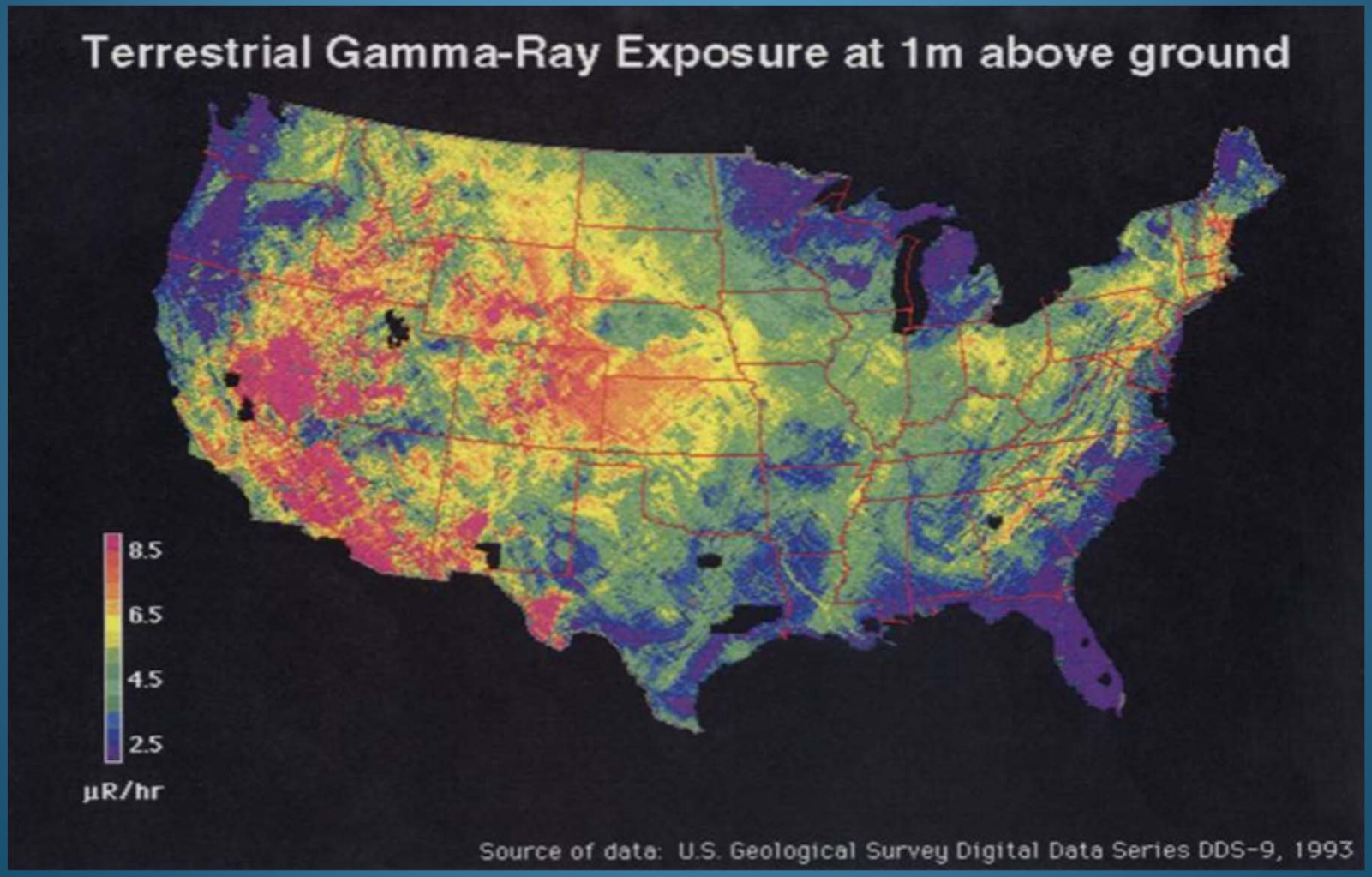
What Radiation Exposures Can we Modify?



Brenner and Hall 2008

Mettler 2007

U.S Dose Rates from Natural Background



Nevada Test Fallout

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

World wide fallout in the United States

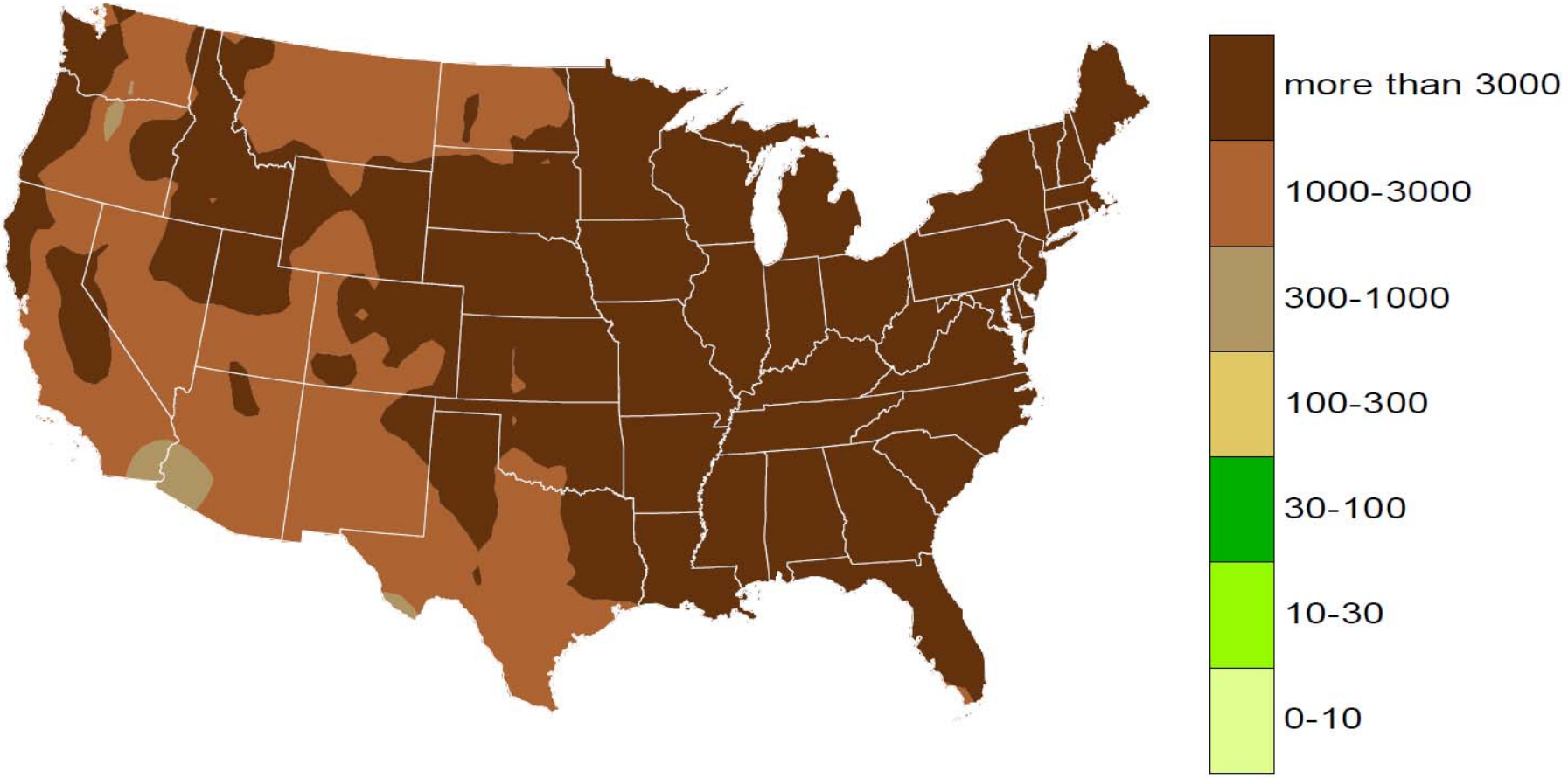
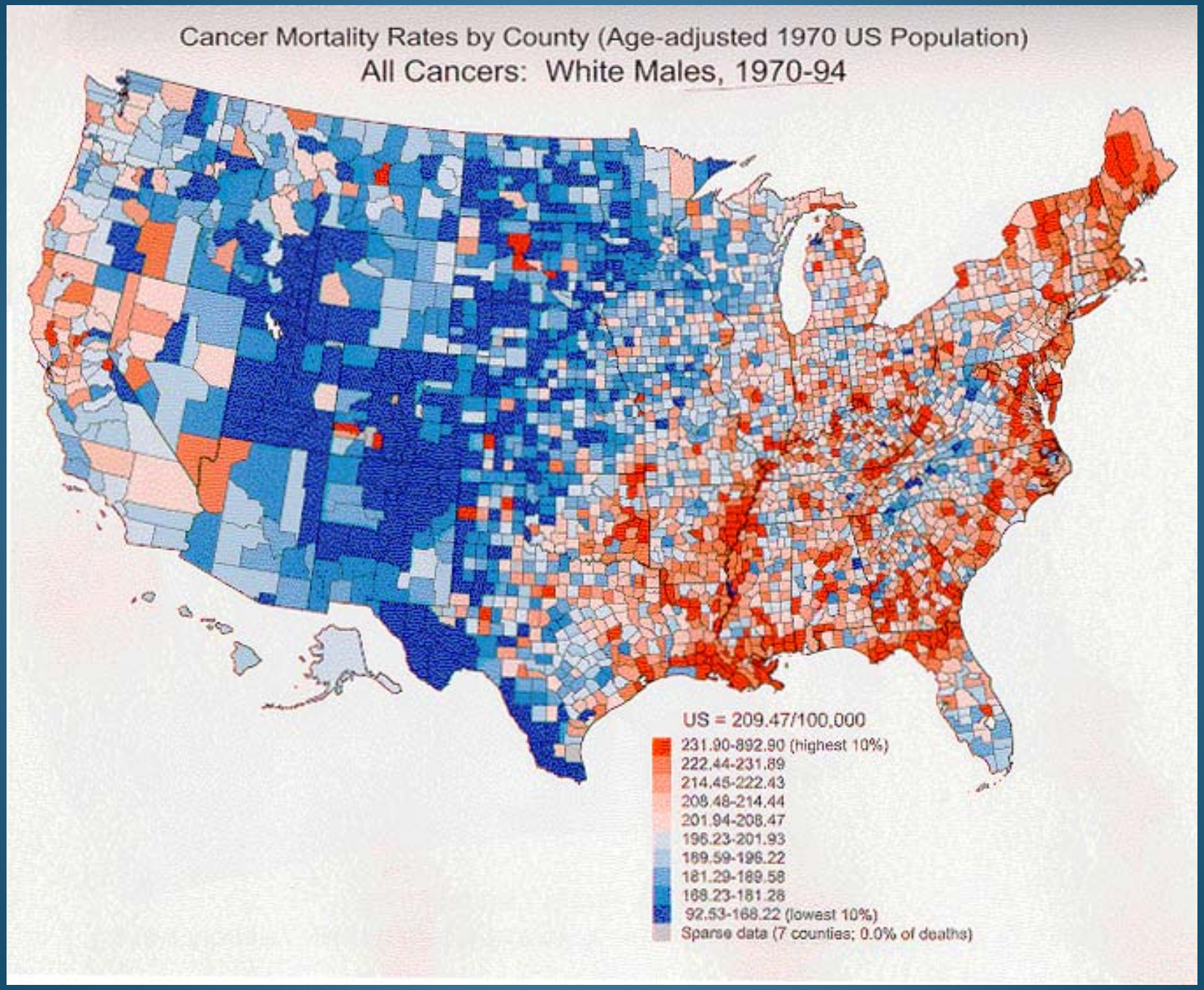
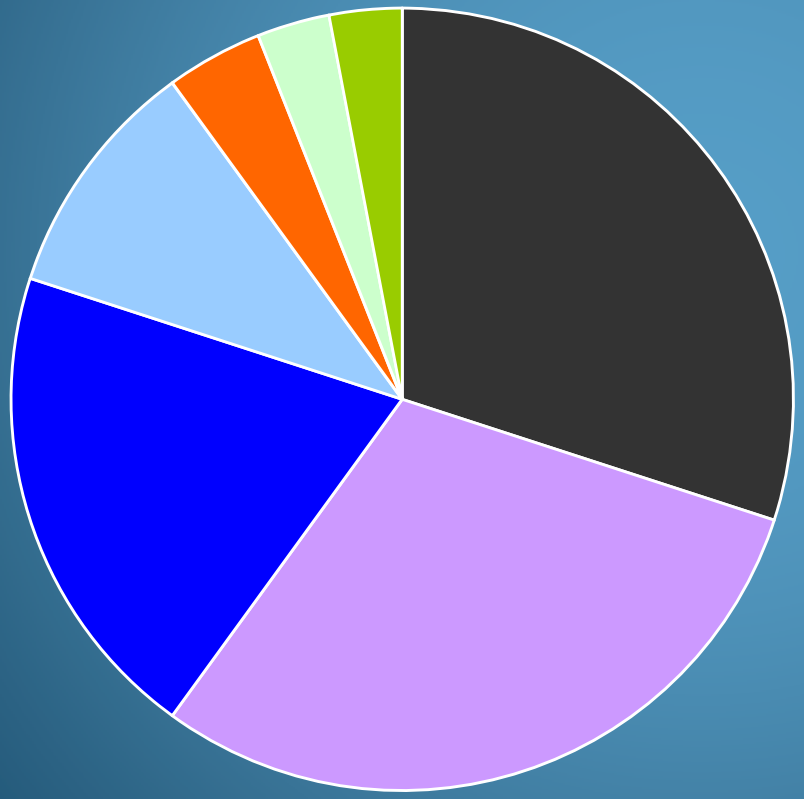


Figure 3.18. Cesium-137 deposition density (Bq/m^2) due to global fallout.


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?

Radiation is not a big hitter!!!



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

WHO

What I know now that I did not know then!!

- Strontium-90
  - Bone is very radiation resistant.
  - Risk per unit dose low
- Iodine-131
  - Adults thyroid very radiation resistant
  - Thyroid cancer seldom lethal
- Cesium-137
  - Cesium binds to clay making it less biologically available
  - Protracted dose-less effective than acute dose
- Plutonium-239
  - Is not absorbed across the G.I. Tract
  - Uniform distribution of dose more effective than particles

Summary

- We **live in a sea of radiation** and always have.
- Radiation is a **poor mutagen and Carcinogen.**
- Low dose responses seem to be **protective** and high dose responses damaging, thus **the body responds differently to high and low doses.**
- Cancer risks using LNTH are **conservative.**