From the Field to the Laboratory and Back:

The "What ifs", "Wows" and "Who Cares" of Radiation Biology

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Dr. Antone L. Brooks

Thanks

- Thanks to NCRP for selecting me to give this presentation, especially Drs. Tenforde and Morgan who have supported me at NCRP.

- Thanks to Dr. Roger O. McClellan for the introduction and helping me get a good start in science.

- Thanks to the scientists I have worked and published with over the years.

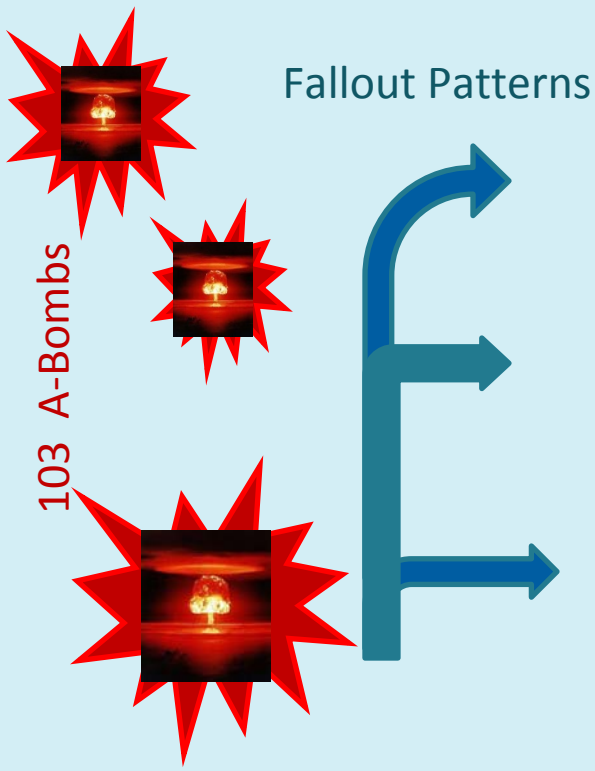
- Thanks to the funding agencies that have funded my research.

Nuclear weapons were part of my early life


St. George, Utah
1955

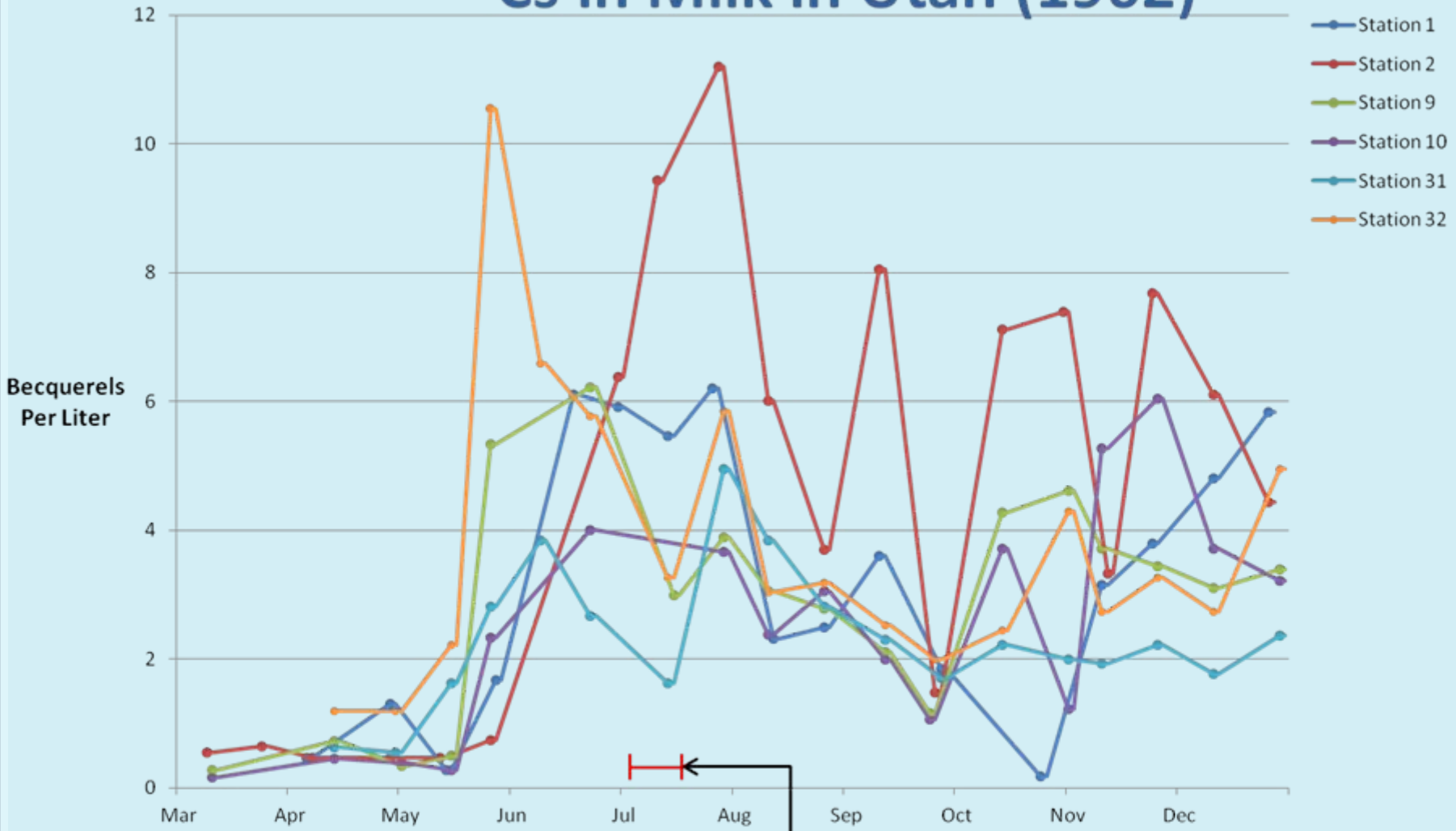
Fallout from over 100 A-bombs above ground.

MS University of Utah



Nevada Test Site

^{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	1.65 KT
5.	Little Feller I	July 17	18 T

Human Body Burdens ^{137}Cs Following Fallout Utah (1962)

Wow!!

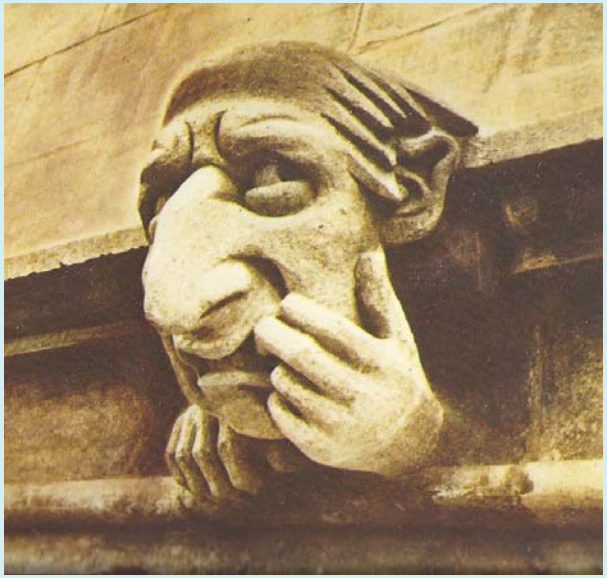
It was on everything and in everything!

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

What can I do to help understand the effects of internally deposited radioactive materials?

My First Scientific Meeting

- How much is a pCi?
- How much is a Bq?

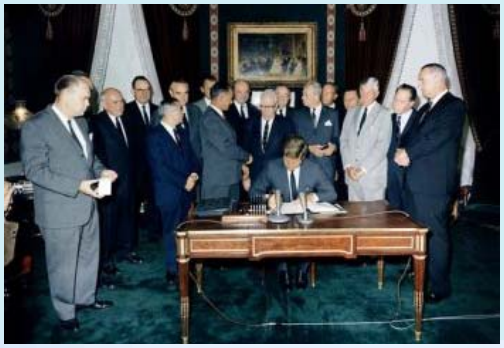


WHAT IF…

- I get cancer?
- my children are not OK?
- fallout causes a cancer epidemic?

Who Cares?

Everyone!



1963

The limited nuclear test-ban treaty was signed.

To Cornell for PhD!

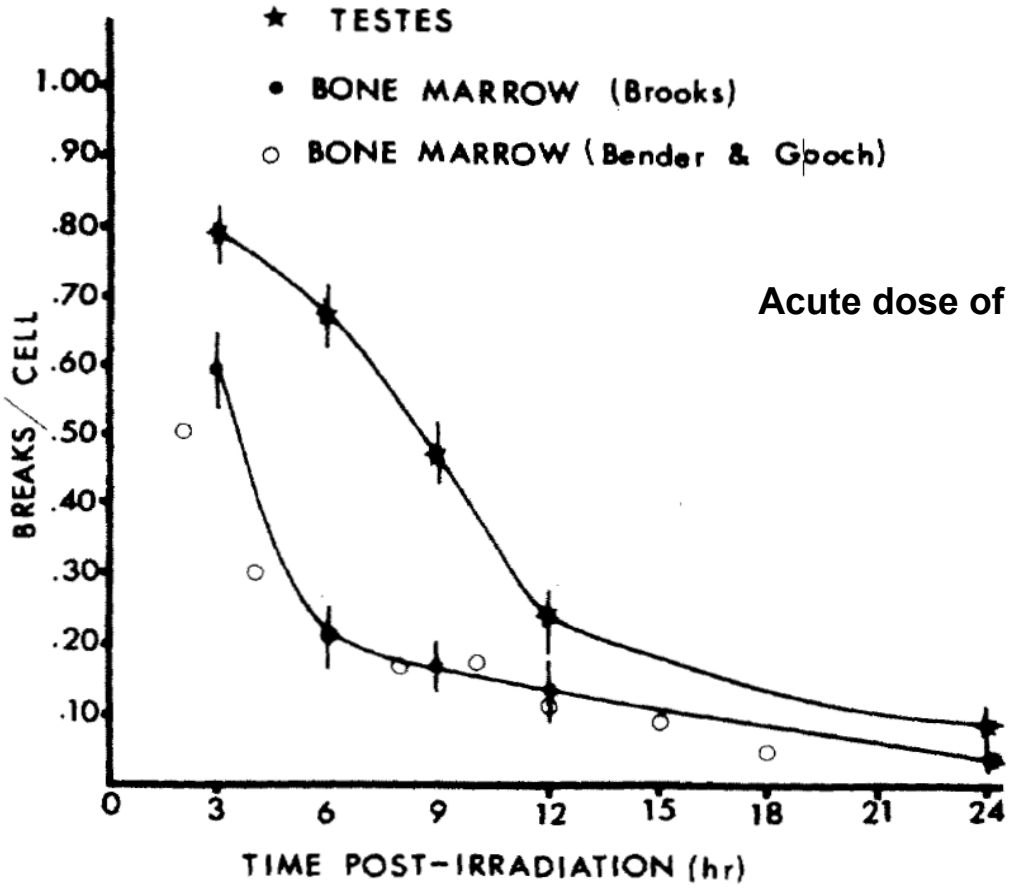
WHAT IF…

The radiation we have all been exposed to causes genetic damage?

Use of Chromosome aberrations as a measure of biological change induced by radiation

- Made measurements *in vivo,* Chinese hamsters
- Made measurements in both somatic and genetic tissue (Risk thought to be similar at this time)
- Made measurements as a function of both dose and time after exposure

CHROMATID ABERRATIONS



Acute dose of 1.0 Gy

BREAKS = CHROMATID + ISOCHROMATID DELETIONS + (2) (EXCHANGES)

Cornell

But people breathe and eat fallout…

What if…

internally deposited radioactive materials are more hazardous than external radiation?

Lovelace Inhalation Toxicology Research Institute (ITRI)

Internal Emitters

- Most research at this time was following single acute exposure
- Very little information on the biological changes induced by internally deposited radioactive material was available

What if…

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

^{90}Sr-^{90}Y

- Long physical and biological half-life
- Deposits and stays in the bone and lung
- Large dose to the bone or lung at a low dose-rate
- Potential for leukemia as well as lung and bone cancer

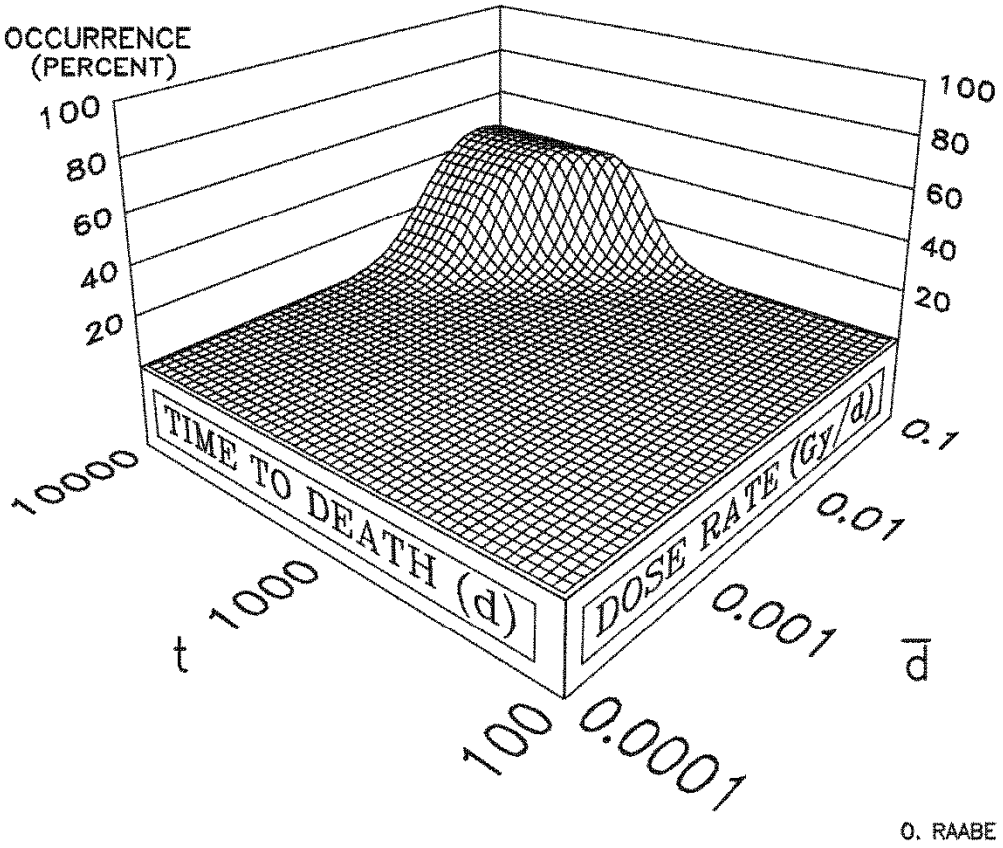
- Samples from the environment were measured in pCi/liter or pCi/kg range

- 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.

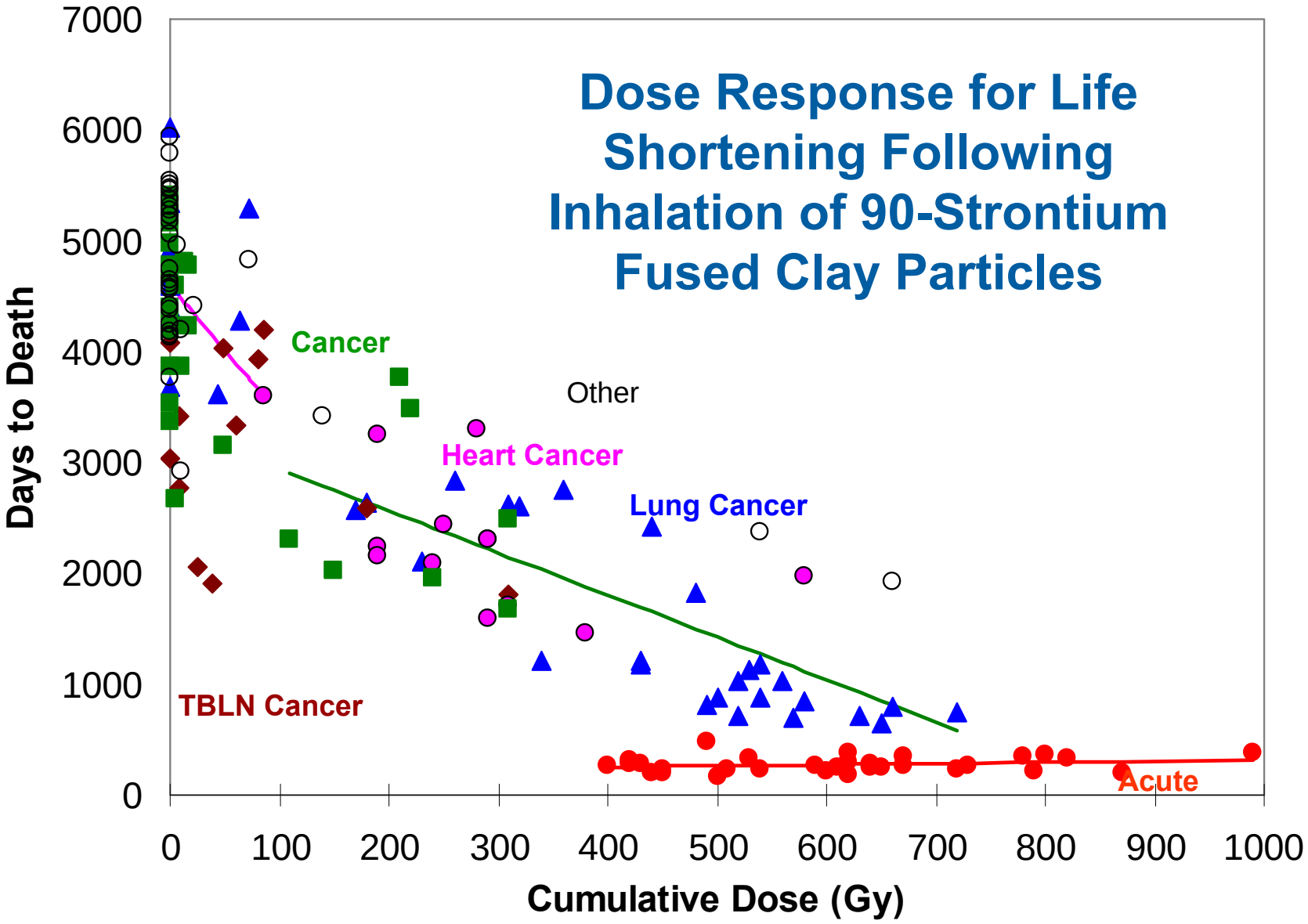
Low-LET Studies

	Utah	Davis	Argonne	ITRI
Injection	1954 ^{90}Sr	1963 ^{90}Sr	1956 ^{90}Sr (Transplacental) 1957 ^{90}Sr (Subcutaneous) 1960 ^{144}Ce 1961 ^{137}Cs	
Ingestion		1961 ^{90}Sr		
Inhalation				1970 ^{90}Sr(insol) 1967 ^{144}Ce (insol) 1970 ^{91}Y (insol) 1969 ^{90}Y (insol) 1965 ^{90} Sr (soluble) 1966 ^{144}Ce (soluble) 1972 ^{144}Ce (juvenile) 1972 ^{144}Ce (aged) 1972 ^{144}Ce (multiple exposures) 1968 ^{137}Cs (soluble) 1966 ^{91}Y (soluble)

OCCURRENCE OF DEATHS FROM BONE CANCER FOR BEAGLES FED ^{90}Sr AT DAVIS



TIME AFTER BIRTH & AVERAGE BETA DOSE RATE TO SKELETON (LOG SCALES)

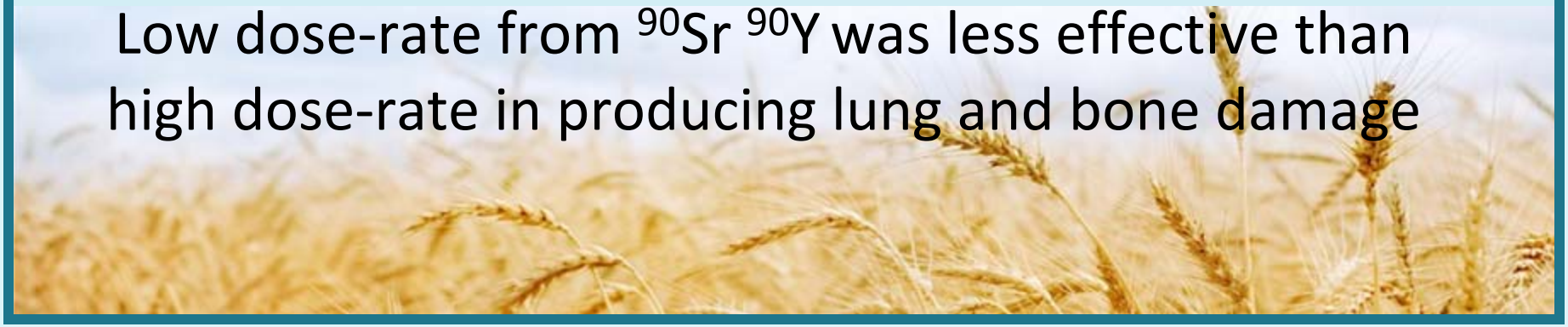

Dose Response for Life Shortening Following Inhalation of 90-Strontium Fused Clay Particles
Days to Death
Cumulative Dose (Gy)
7000
6000
5000
4000
3000
2000
1000
0
0
100
200
300
400
500
600
700
800
900
1000
Cancer
Other
Heart Cancer
Lung Cancer
TBLN Cancer
Acute

Wow!!

It takes a lot of radioactive material to produce biological changes!

It takes a lot of disintegrations to make a Sv!!!

Low dose-rate from ^{90}Sr ^{90}Y was less effective than high dose-rate in producing lung and bone damage



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…

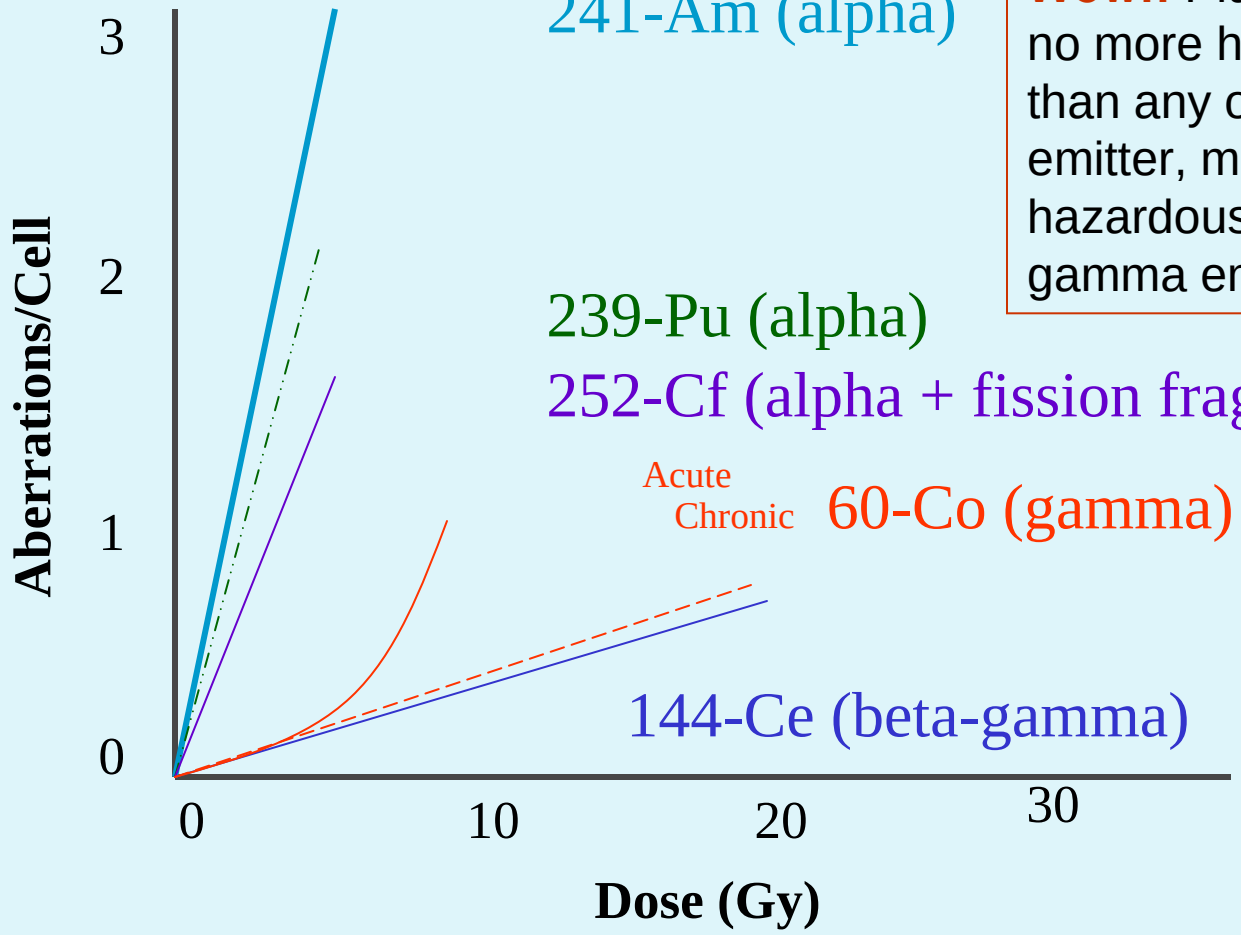
^{239}Pu

is the most

hazardous substance

known to man?

Dose Response for Radiation-Induced Chromosome Aberrations



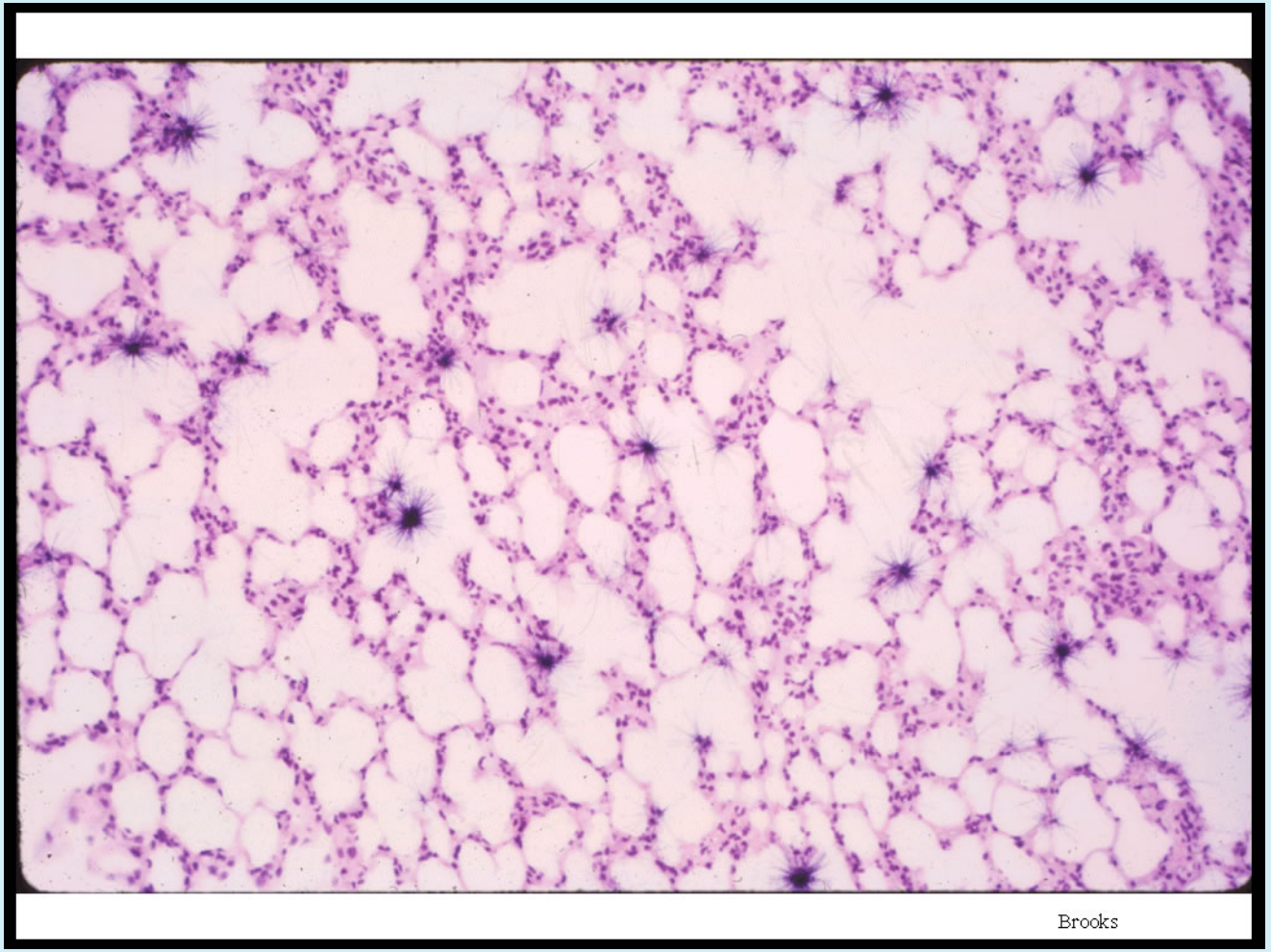
Wow!! Plutonium is no more hazardous than any other alpha emitter, more hazardous than beta-gamma emitters

What if…

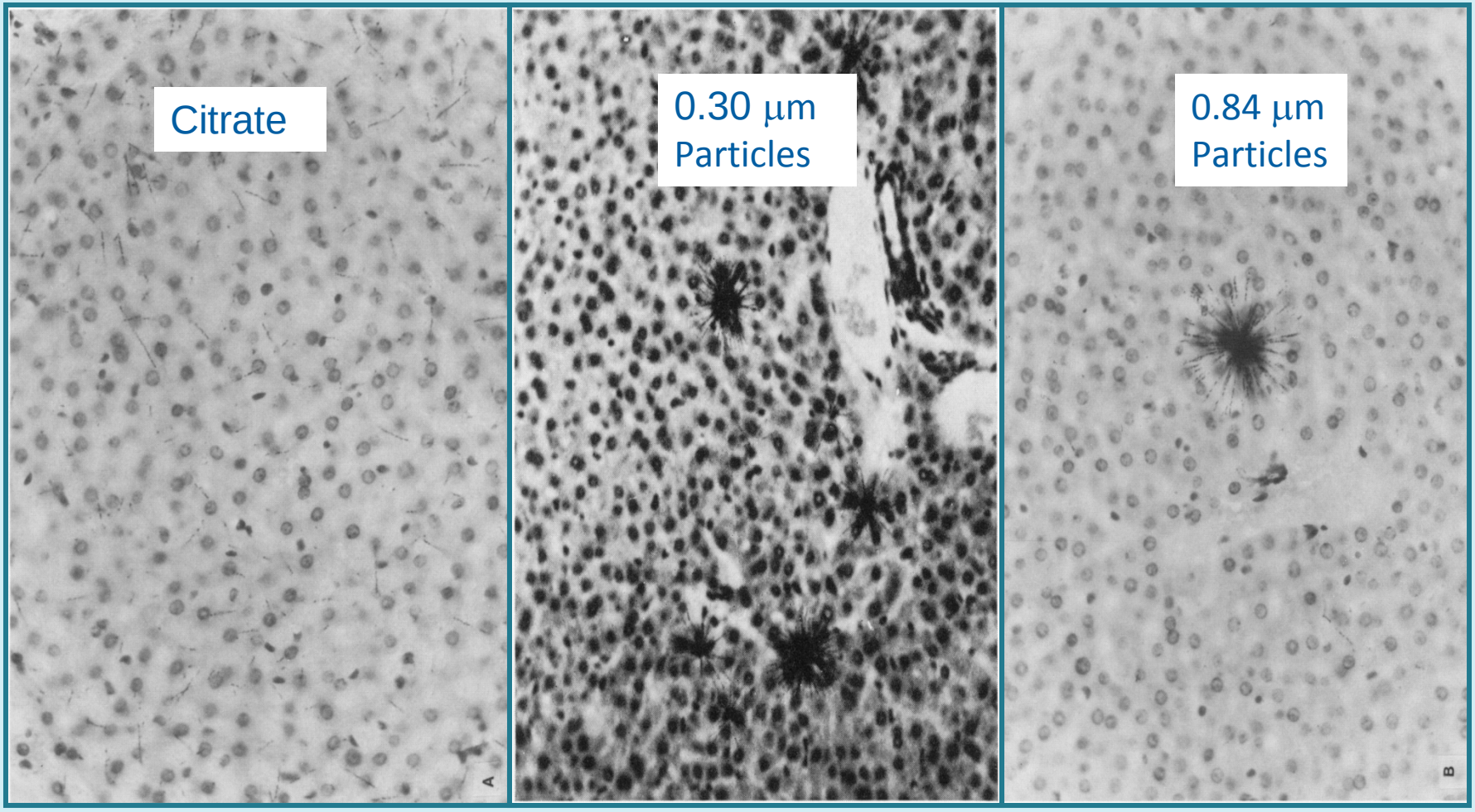
a single $^{239}PuO_2$ particle deposited in the lung can cause cancer?

"Hot Particle Hypothesis"

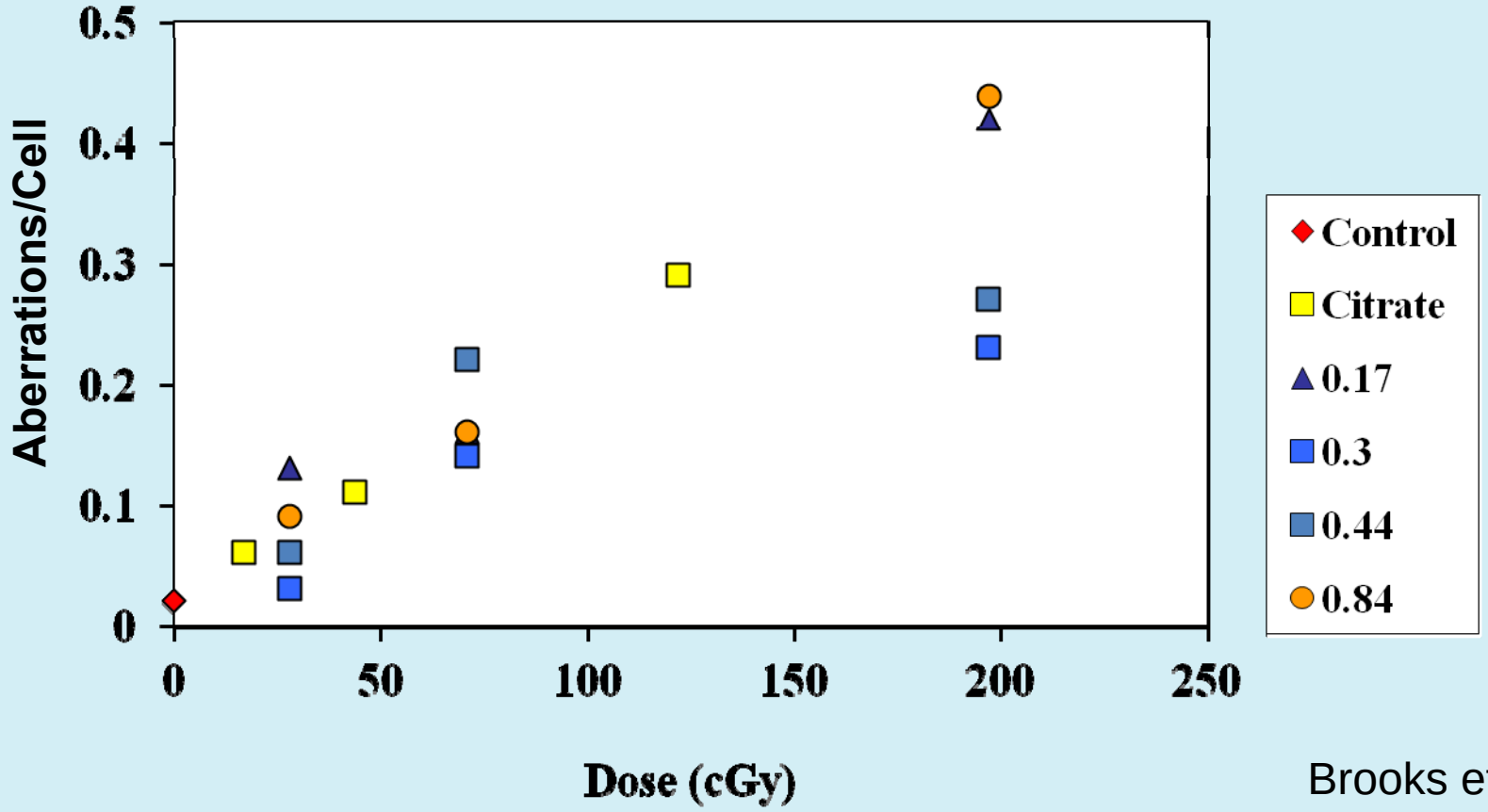
Non-Uniform Dose Distribution from Plutonium Inhalation



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



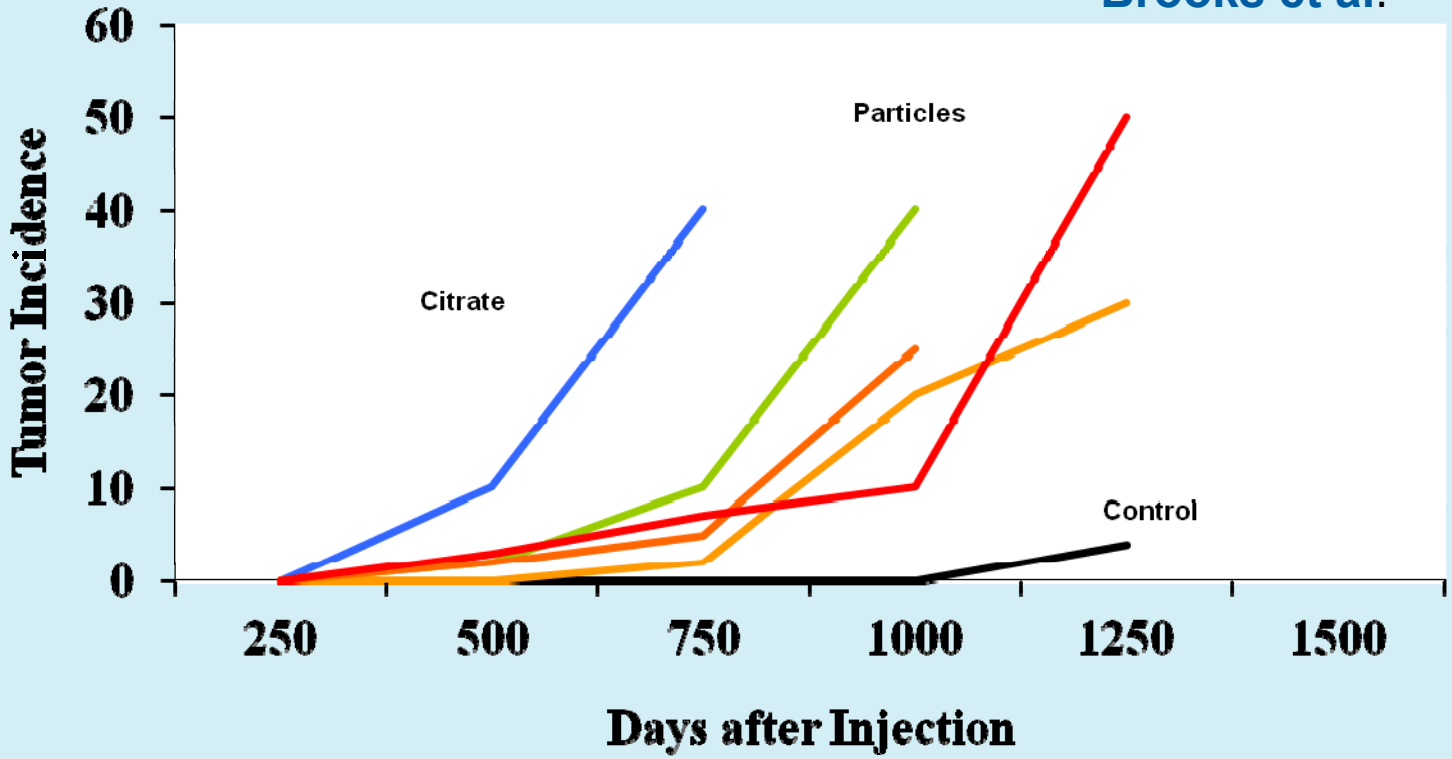
The Influence of ^{239}Pu Dose-Distribution on Chromosome Aberration Frequency



Brooks et al

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

Brooks et al.

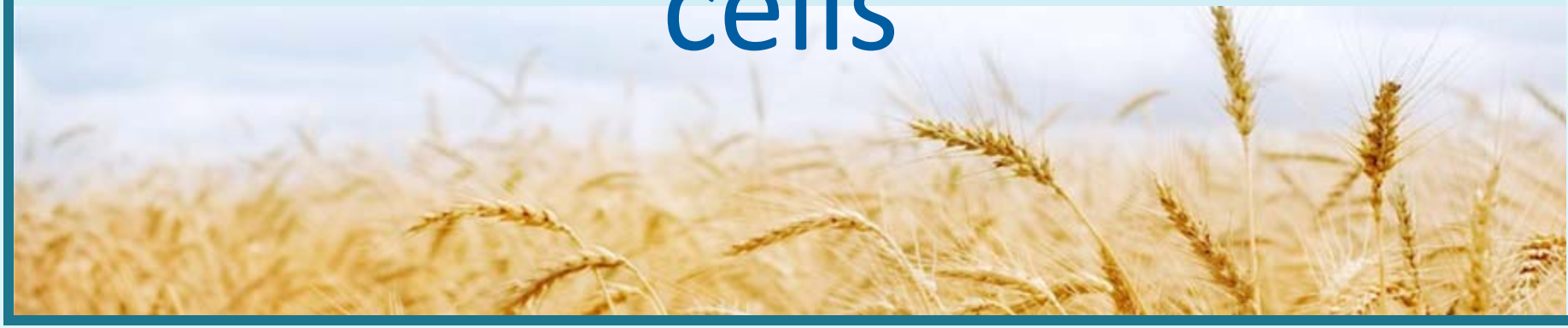


Results of Research

- The “hot particle hypothesis” is not supported by the data.
- To get cancer, it is necessary to expose as many cells to alpha particles as possible
- How do we resolve such observations with the “hit theory”?

Wow!!

The tissue is responding as a unit, not as single cells



Health Risks of Radon

- Radon is responsible for more than half of the background radiation

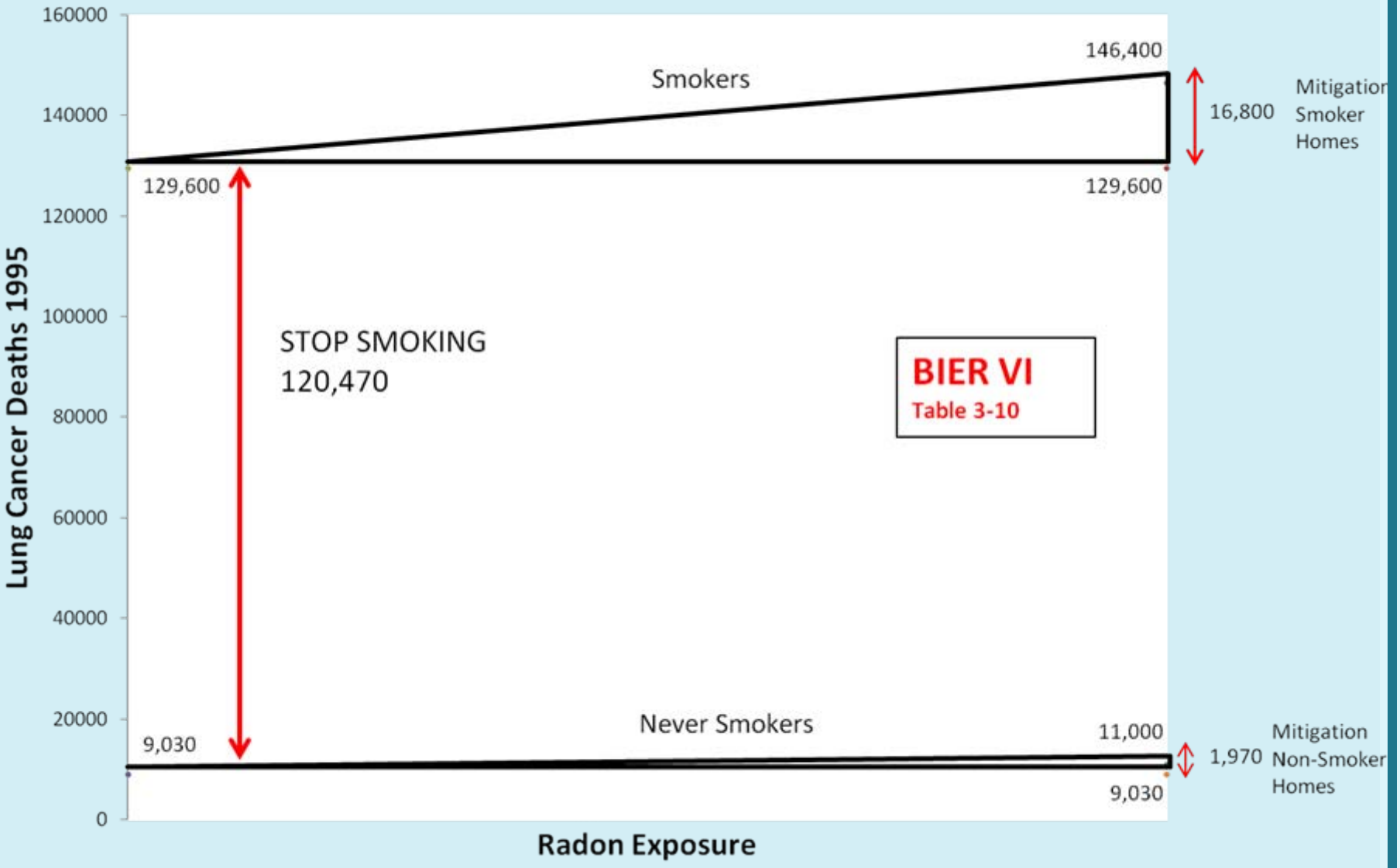
- Uranium miners were developing a high frequency of lung cancer

Move to PNNL

What if…

Radon is killing us in our homes?

Radon Mitigation and Lung Cancer Risks



Wow!!

Radon alone is not the second (or third!) cause of lung cancer

Who Cares?

EPA and Congress

passed laws to make testing of homes mandatory and mitigation in high level homes. BEIR VI calculated risk from collective dose. Most of the dose is from homes with levels below the EPA action level.

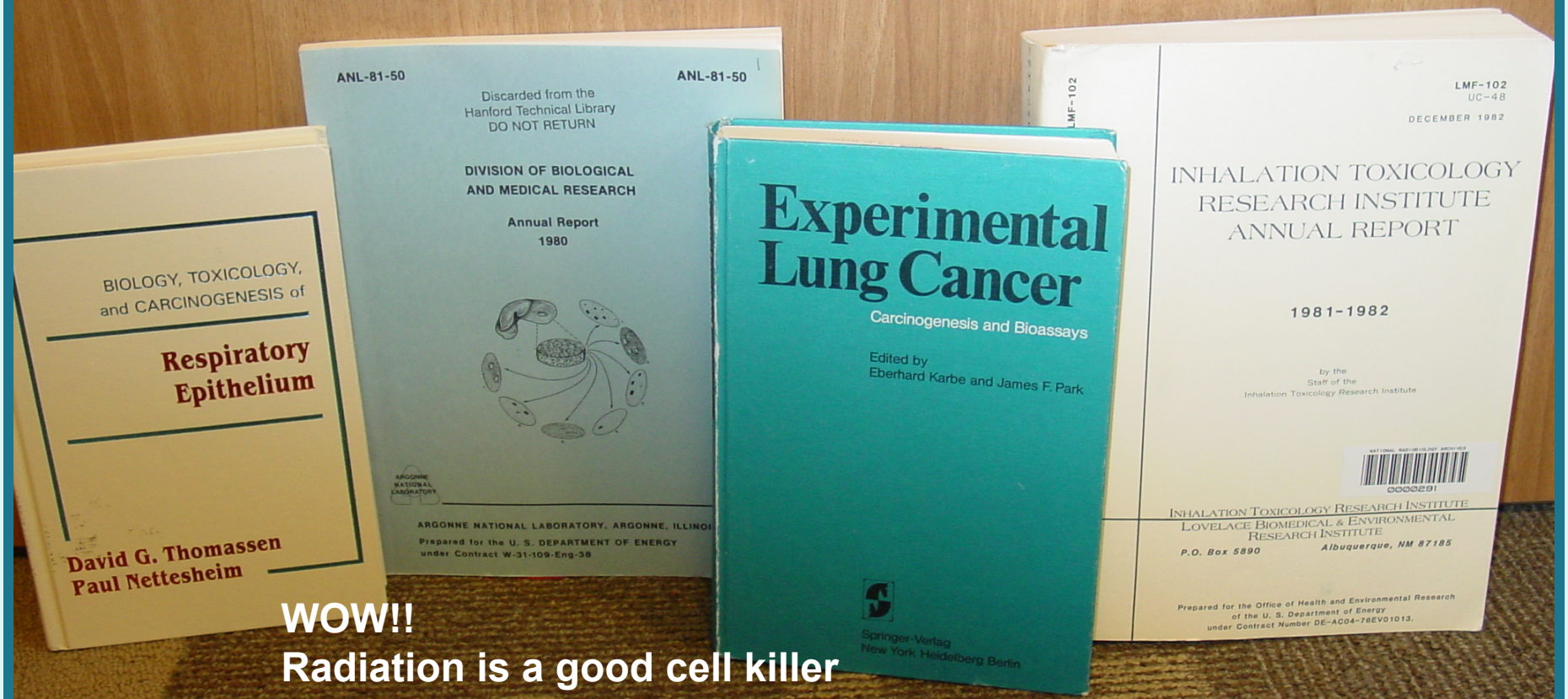
What if…

health risks from environmental contamination from other energy sources was greater than the health risk from nuclear power?

Toxicology of Energy Production

- Each national laboratory was assigned an energy source.
- Our techniques were applied to evaluate the risks associated with the energy source.
- Cell killing, mutations, SCE's chromosome aberrations, lung damage, cancer were end points.
- ITRI was given "Diesel Exhaust" and "Fluidized Bed Coal Combustion".

Biological Effects of Non-Nuclear Energy Production



WOW!!
Radiation is a good cell killer
Compared to chemicals
radiation is a poor mutagen
and Carcinogen

Who Cares??

Nuclear Waste Cleanup

- Is expensive $$$$!
- Senator Peter Domenici
- Washington State University

- Are our low dose regulations based on real science ?

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?

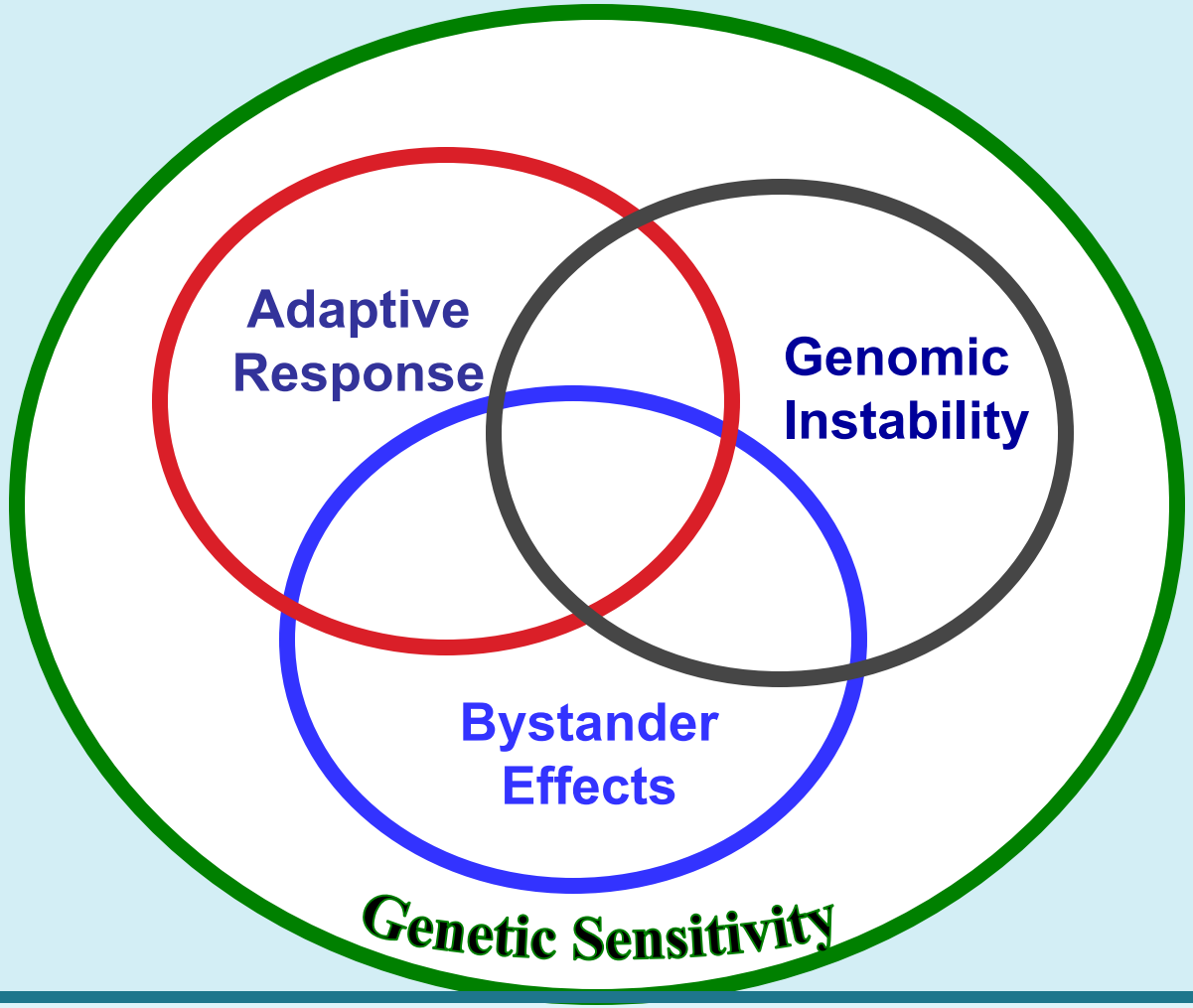
What if…

the LNTH overestimates risk??”

Chief Scientist for DOE Low Dose Radiation Research Program

- 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?

Biological Responses Induced by Low Doses of Radiation



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?

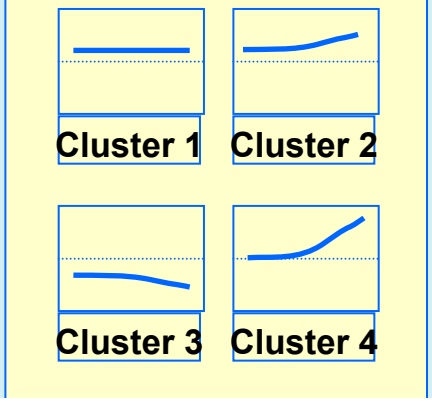
Three lines of evidence point to a transition in transcript expression profiles in the range of 10-25 cGy

All gene data (n = 22283)

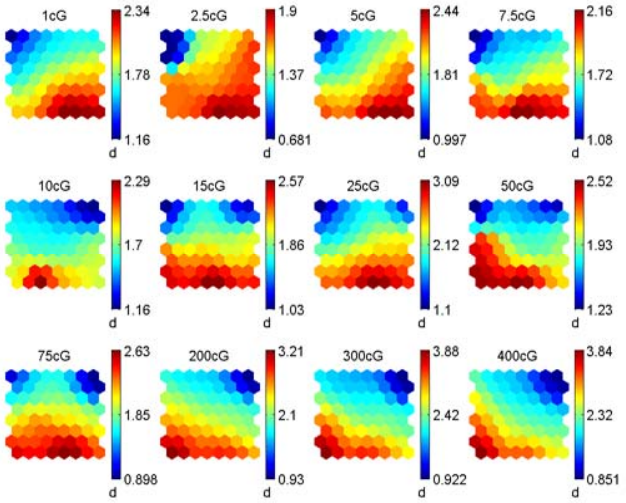
Filter for differential expression (FDR < 0.10)

Combine into one dataset N=420 genes

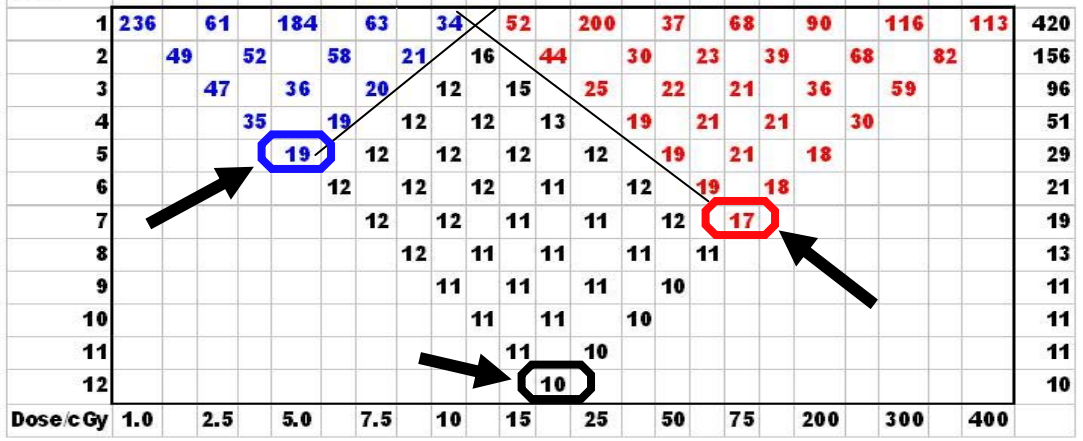
Cluster analyses



Self Organizing Maps

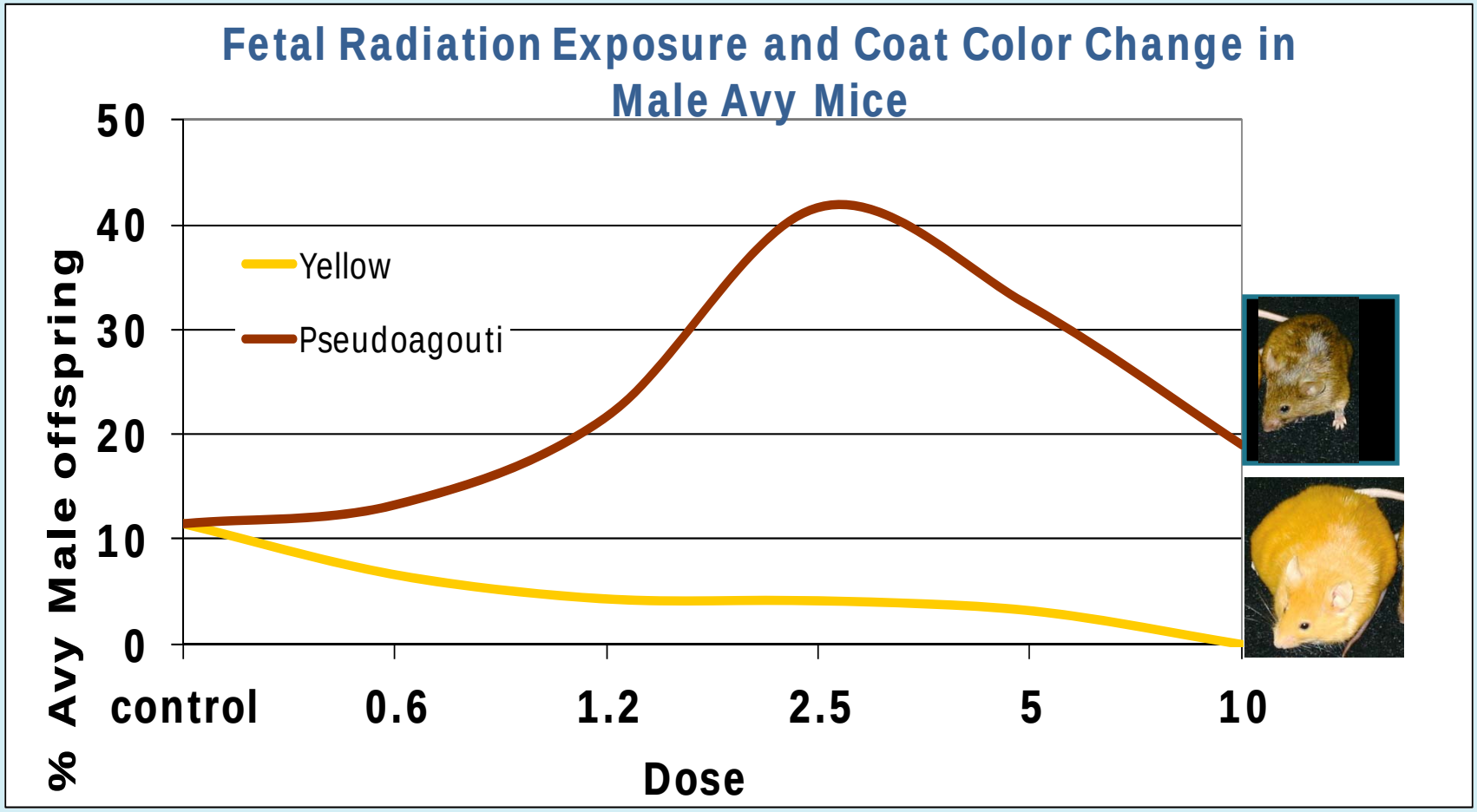


Near neighbor analyses



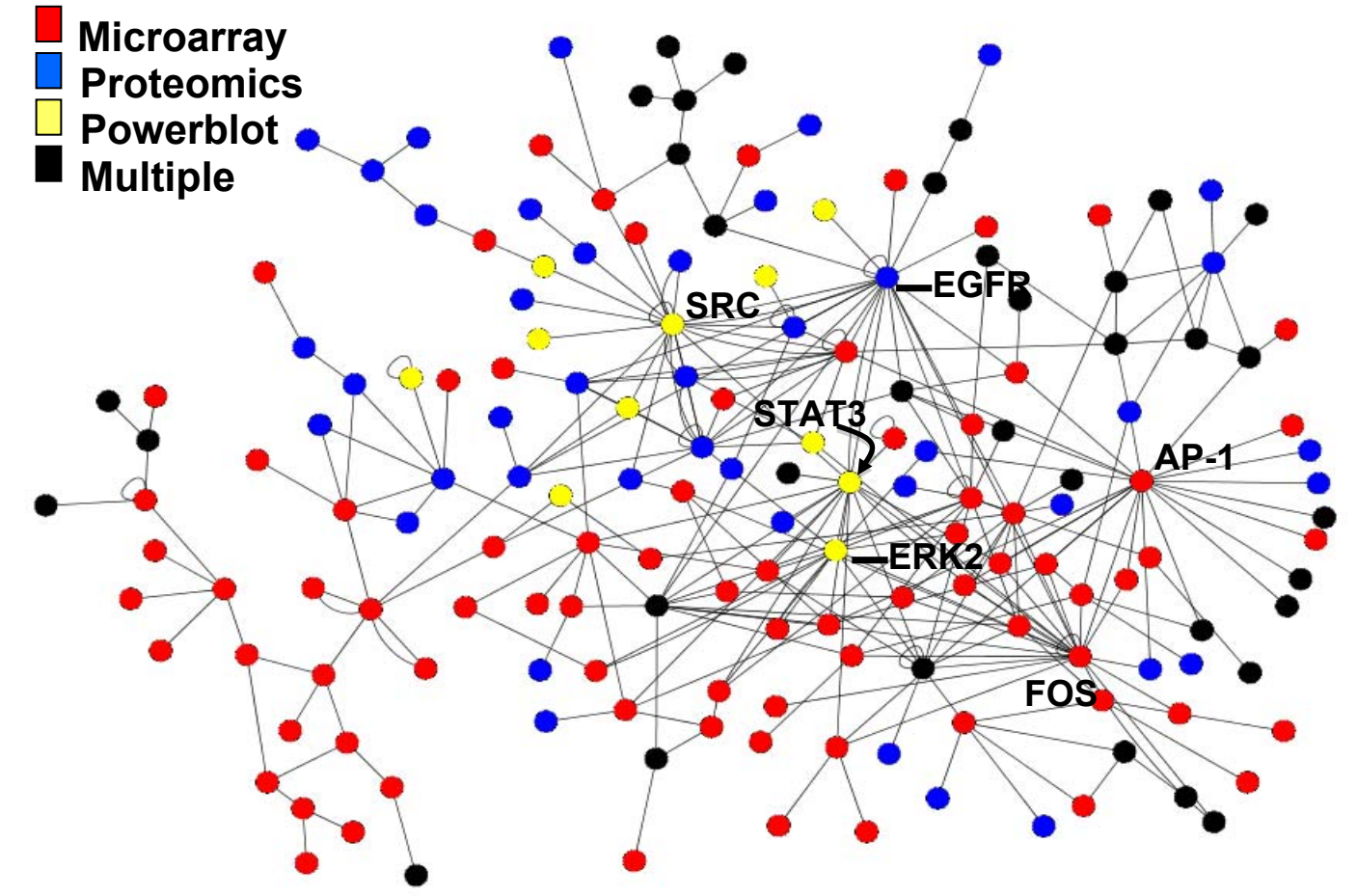
In collaboration with D. Nelson, K. Krishnan

(Wyrobek, et al., LLNL)



Bernell and Jirtle 2011

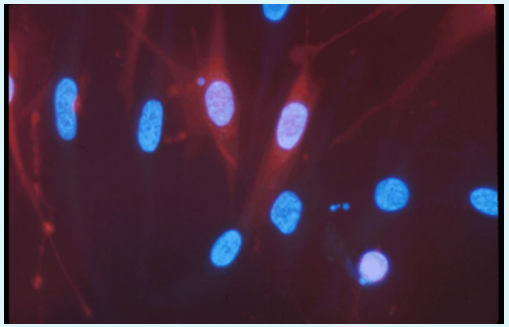
Network reconstruction using Integrated data are more comprehensive and accurate (Systems Biology)



What if…

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

Mechanisms of Action



- At low doses genomics, proteomics, micrornaome, metabolomics, etc. show different responses at low doses and high doses.
- Many low dose responses are known to be involved in reducing damage
- Altered post-transcriptional protein modification
- Epigenetic changes
- Impact of oxidative status of the cell
- Radiation-induced changes in selective apoptosis
- Cell/cell, cell/matrix interactions

Wow!!

World-wide low dose research has defined many mechanisms involved in new low dose biological phenomena.

(US-DOE, European Union, Japan, Korea)

Who Cares?

Regulators and Scientists

Meeting with the regulators from federal agencies and the DOE Low Dose Research Program.

- First Day Scientists talked, Regulators slept
- Second Day Regulators talked, Scientist slept
- Third day DOE talked and everyone else slept

Who Cares?

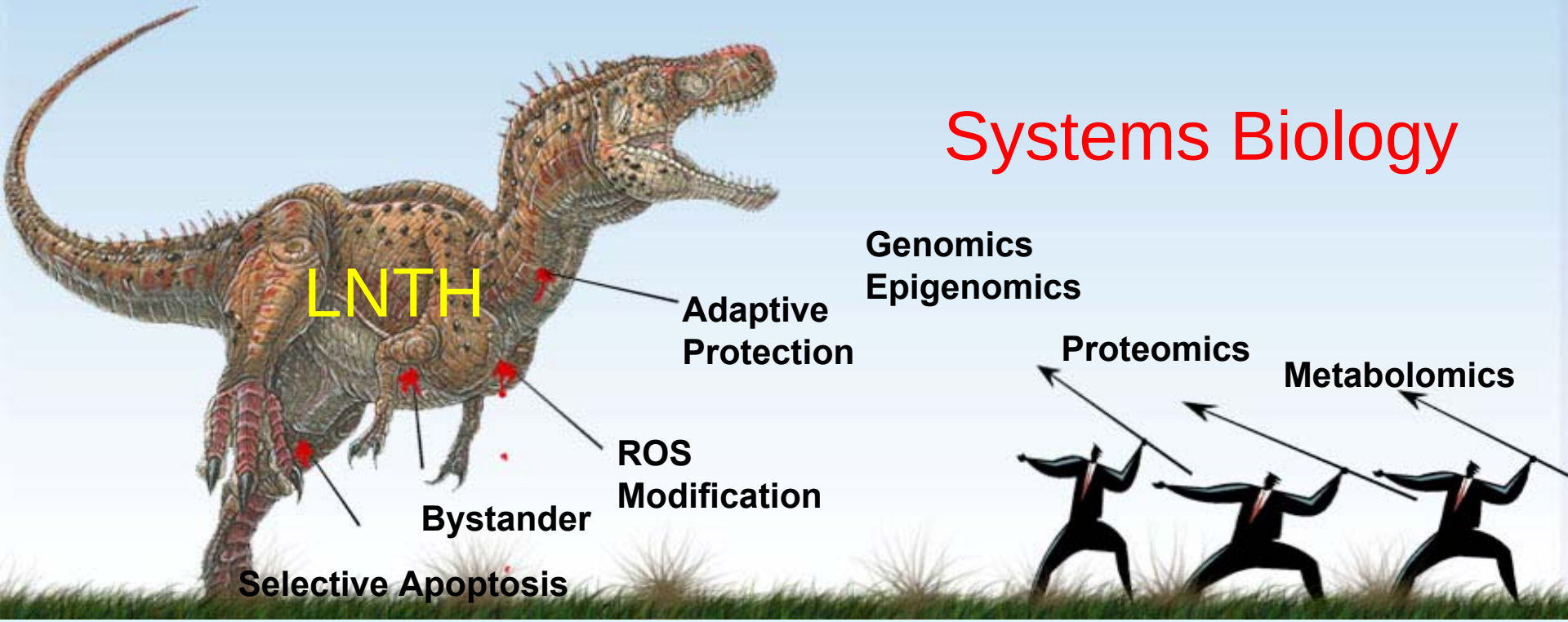
News reporters, media editors and scientists

- Much of the scientific data suggested that the risk was not as high as LNTH
- After the scientific presentations the News reporters suggested, “Very interesting but I cannot get such information by my Editor.”
- What would the response be if the risk was much higher than LNTH?

The Dinosaur of LNTH remains useful for regulations

but is scientifically dead for low-dose risk assessment.

All these cell and molecular responses are radio-protective !!!



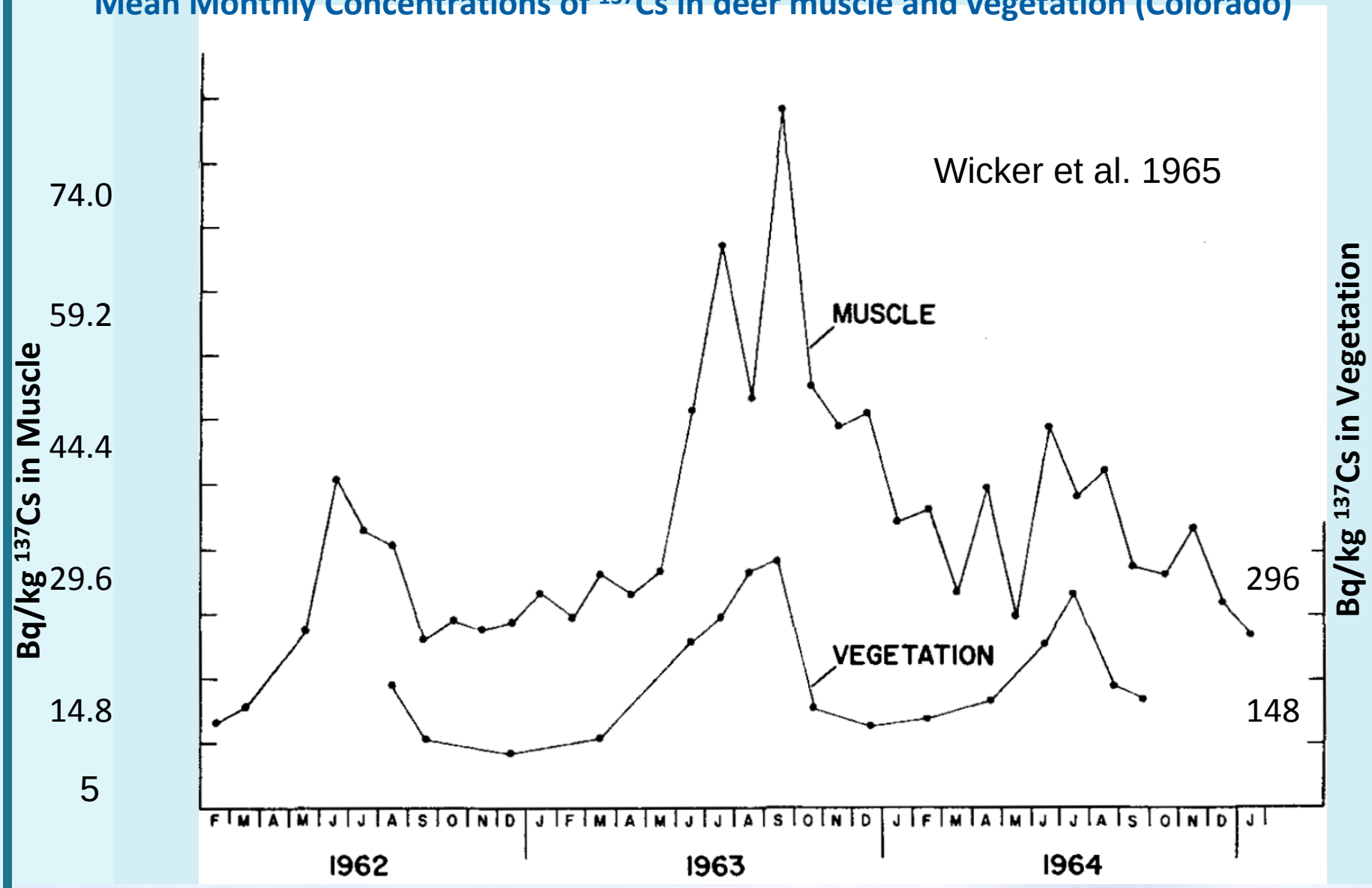
Back to the Field- Fukushima

- Appreciate all the information

  at this meeting.

- Interesting to compare to

Mean Monthly Concentrations of ^{137}Cs in deer muscle and vegetation (Colorado)



Correlation of ^{137}Cs radioactivity between peripheral blood and organs

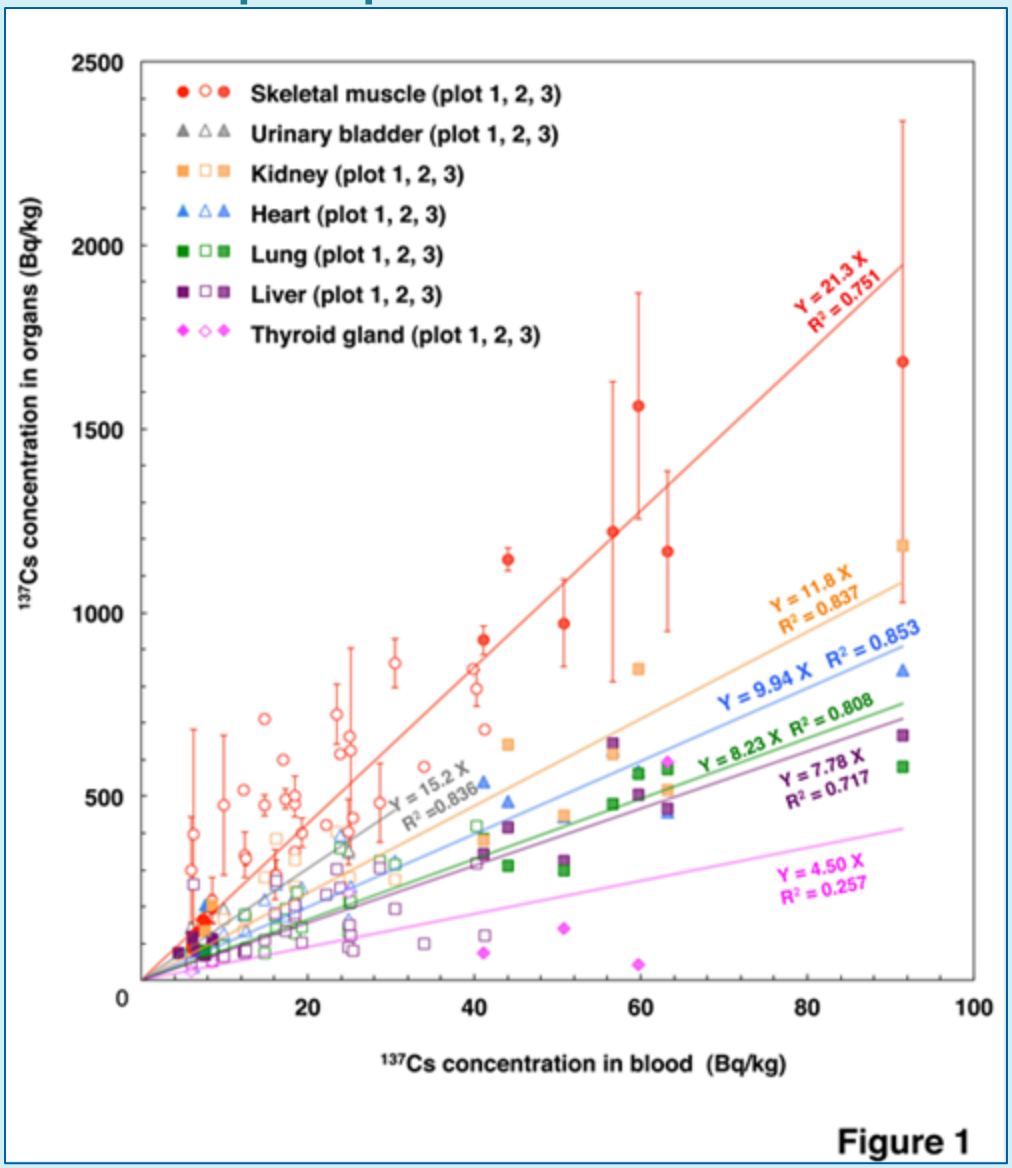


Figure 1

Manabu Fukumoto
2012

^{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

Nevada Fallout

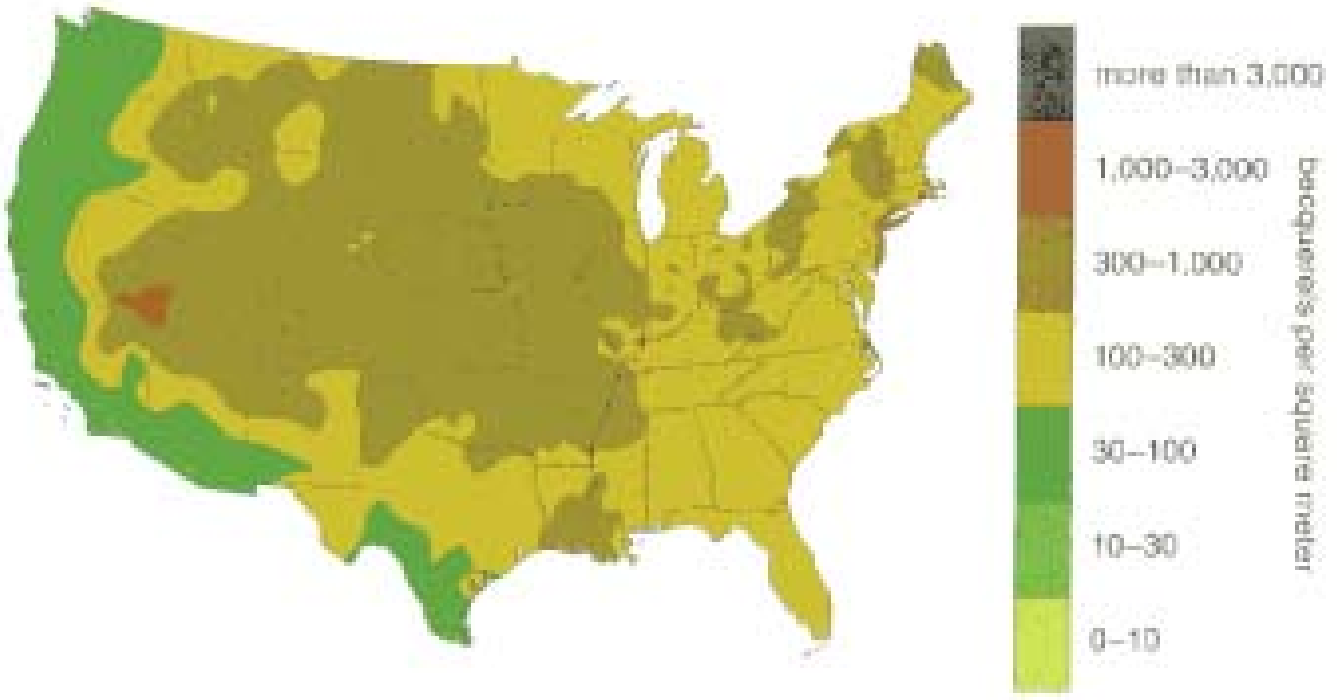


Figure 7. Cesium-137 deposition density resulting from the cumulative effect of the Nevada tests generally decreases with distance from the test site in the direction of the prevailing wind across North America, although isolated locations received significant deposition as a result of rainfall.

Simon et al. 2006

World wide fallout in the United States

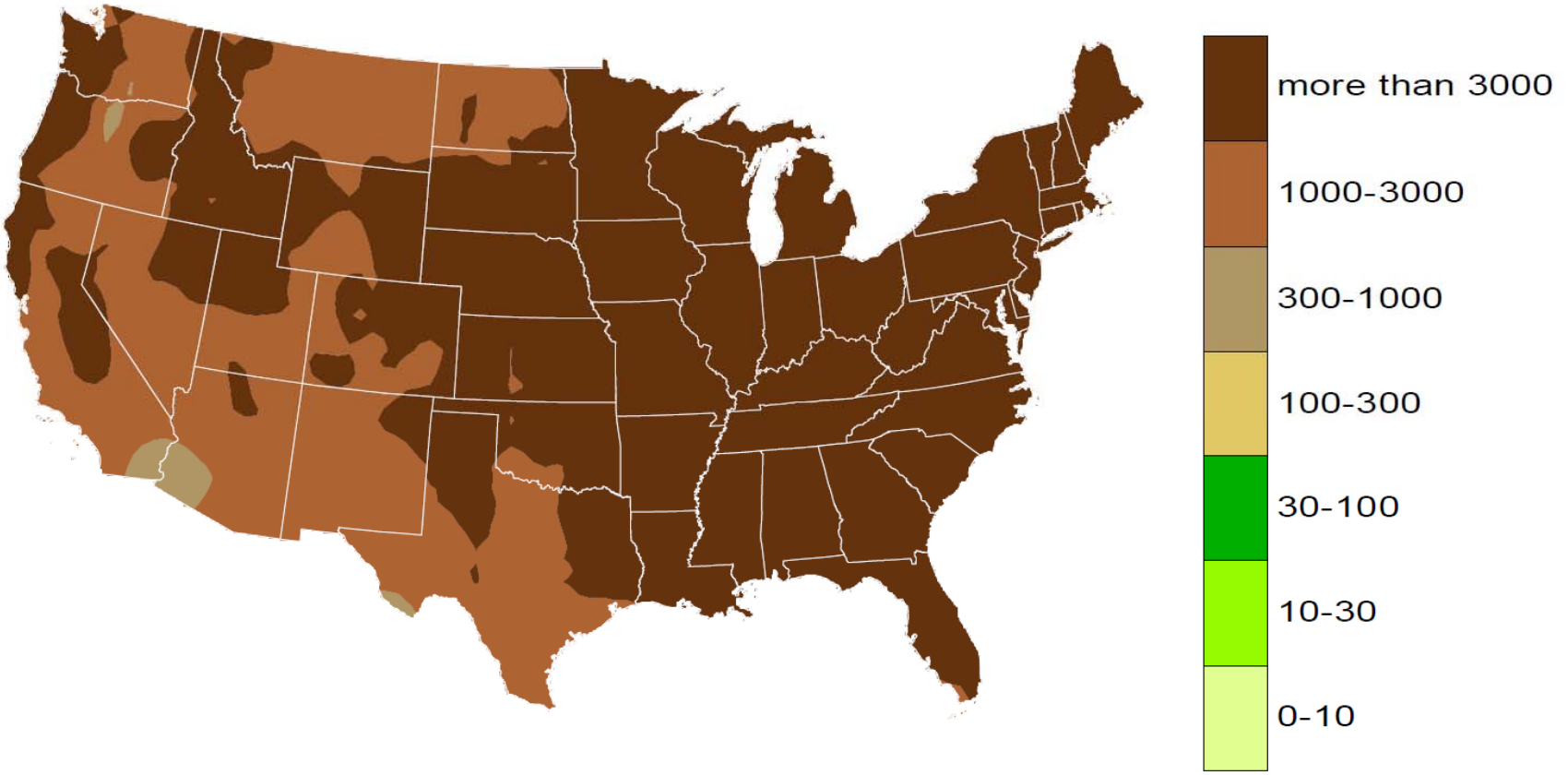
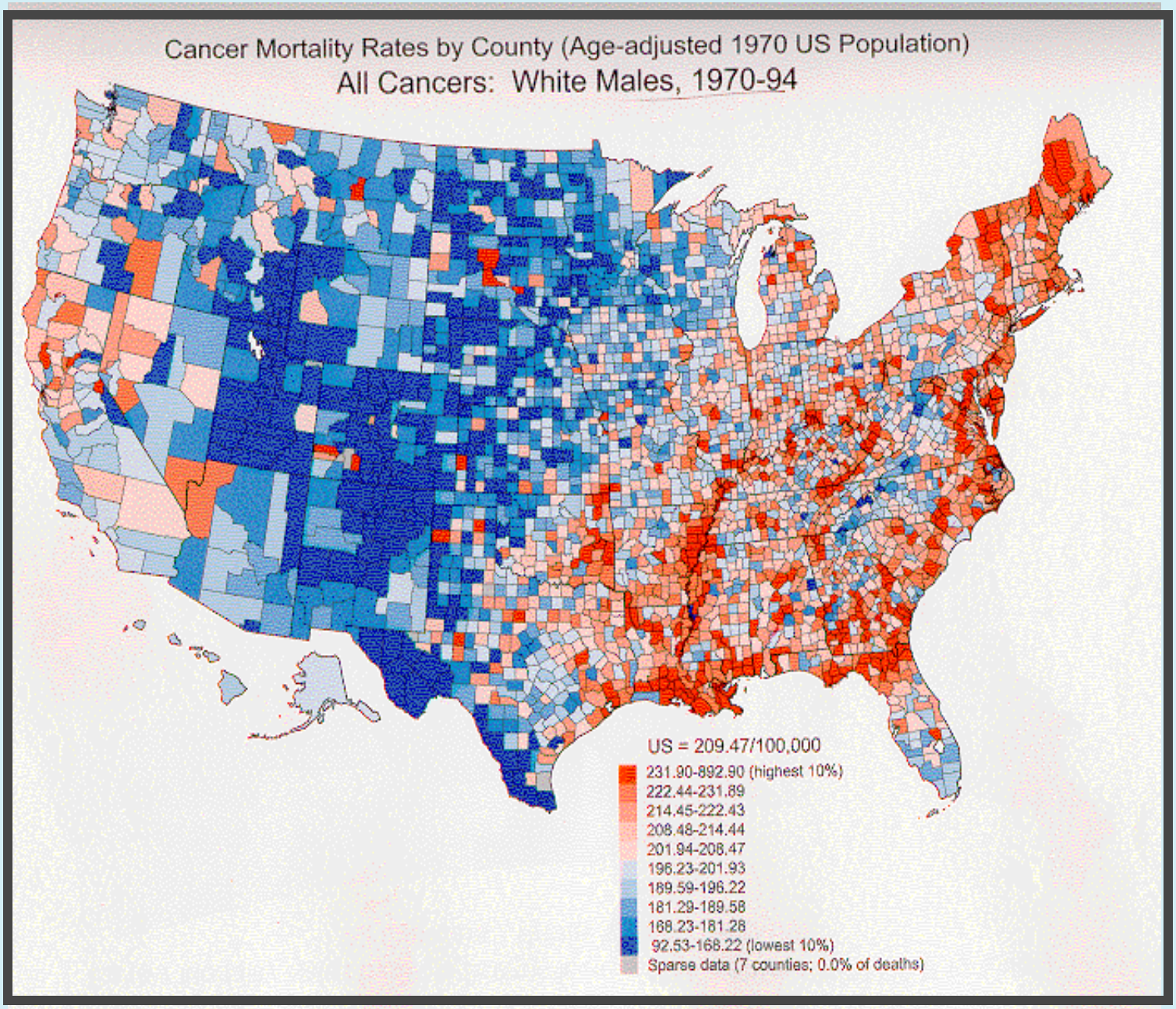
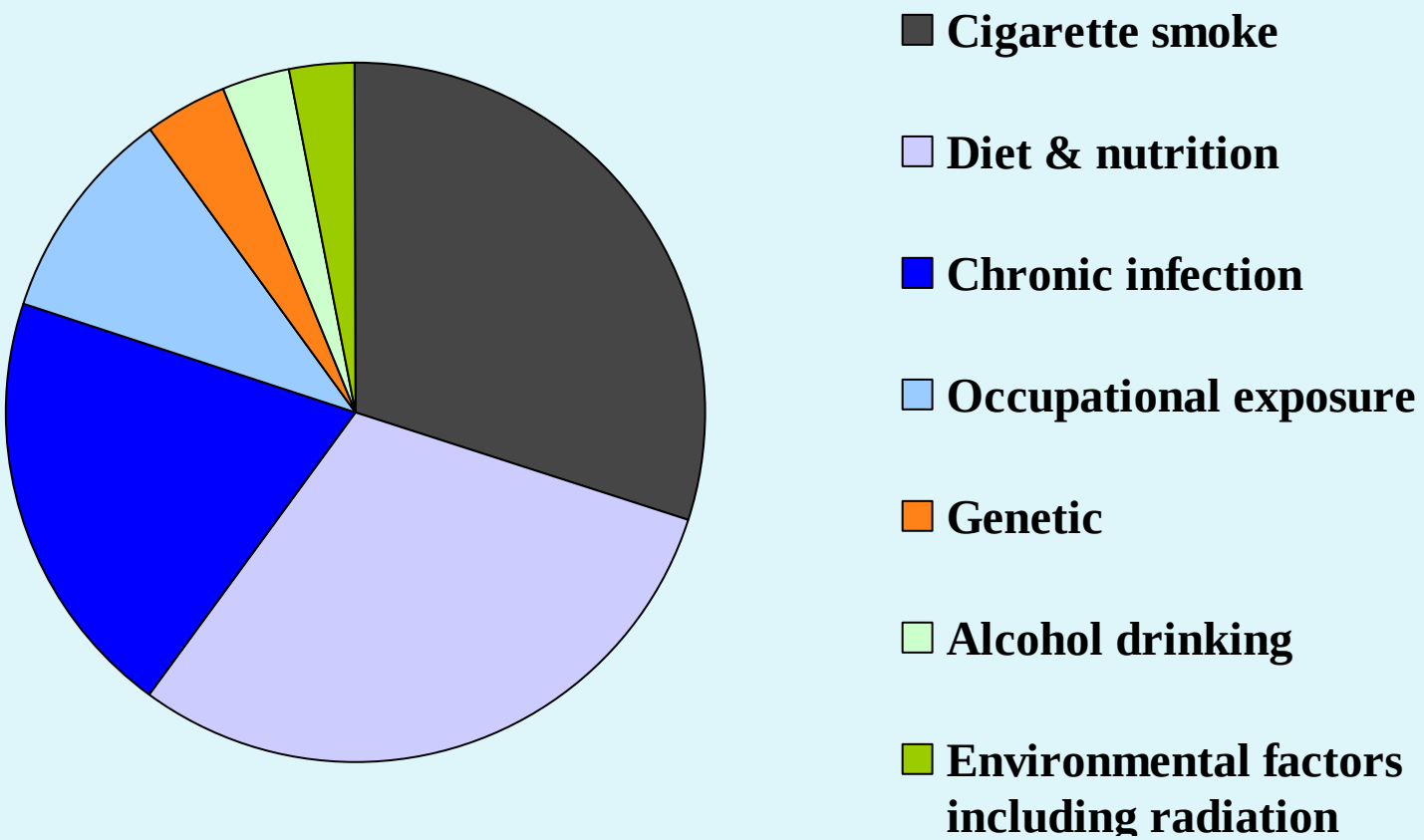


Figure 3.18. Cesium-137 deposition density (Bq/m^2) due to global fallout.


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?



WHO

My answers to major "What ifs..?" of Radiation Biology

- What if fallout has produced a cancer epidemic in Utah?
  (It has Not)

- What if internal emitters are more hazardous than acute external exposure? **(NO)**

- What if Plutonium is the most hazardous substance known to man and a single particle can cause lung cancer? **(NO)**

- What if Radon is a major cause of lung cancer?
  (NO not without Cigarette smoke)

My answers to major "What ifs..?" of Radiation Biology

- What if nuclear power presents a greater health impact than other sources of power production? (NO)
- What if the mechanisms of action following high doses is the same as that following low doses? (NO)
- What if LNT overestimates cancer risk in the low dose region (I think it does)

Summary

- I have enjoyed my career as a radiation biologist. Radiation science has been such a wonderful experience for me, I even named my dog “Sievert” since it is worth 100 of those rems.

Summary

- There have been many “What ifs..”, “Wows!” and “Who Cares?” during my journey.
- What the future holds I cannot predict, but I wish I had another 30+ years to see it play out.
- Thanks to all of you and to my family.