Issues in Understanding Exposures to Low Doses of Ionizing Radiation

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Why is studying low dose radiation effects important?

Environmental clean up – Hanford (>$110 Billion to date)

Nuclear Accidents – Fukushima (160,000 evacuated, 20 mGy/yr)

Rad worker exposures

Flight Crews and Astronauts (limits to the Mars mission?)

Potential Terrorist Attacks (dirty bombs, IND) – evacuations?

Security issues (airport backscatter machines)

High natural background exposures – Radon, geographical locations in Karala (India) Yanjing (China)

Medical Diagnostics – >90 million CT scans annually 5-100 mSv each (acute exposure v protracted exposure LDRt)

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So Why Do We Care About Low Dose Radiation Effects?

Approximately 90 million in the USA this year

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CT over exposure to a young patient

Fell from bed and complained of neck pain the following morning

Plain x-rays and then a CT scan of neck ordered by ER

CT table did not index (move) and radiologic technologist manually instituted 151 slices over a period of more than 1 hour

The patient was successfully rescanned by another technician

About 2-3 hours after the first CT attempt he developed a red line around his face at the level of the 151 CT scan slices

Sometimes things do not go as they should!

Hair loss from excessive dose of a CT angiogram

USA TODAY THURSDAY, AUGUST 30, 2012

Laser focus: Webb Simpson, getting scanned by the Lunar iDXA in March in Orlando, says the test results help him pinpoint areas to target in training. "As an athlete, you are always looking for ways to improve, ways to get better," he said.

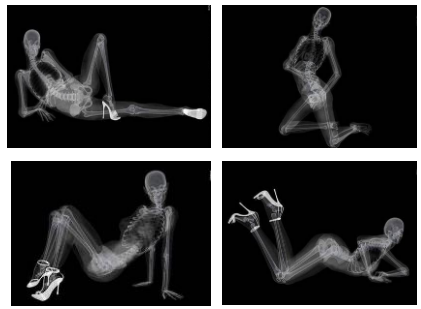
Simpson: Scan is part of plan

Full-body X-ray aids golfers in areas of training, health

http://www.news.com.au/travel/news/naked-scanners-may-increase-cancer-risk

US scientists are warning that radiation from controversial full-body airport scanners has been dangerously underestimated and could lead to an increased risk of skin cancer - particularly in children.

700 million travelers worldwide
Individual dose v collective dose

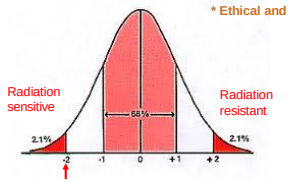


Remember - We All Have Different Perception of Risk

Questions: How to design a system that limits risk?
How do we assign a potential human health risk?

Caveats: This system must take into account :
The most sensitive organ (breast)*?
The most sensitive individual*?

* Ethical and legal questions



Where do you draw this line for regulatory purposes?

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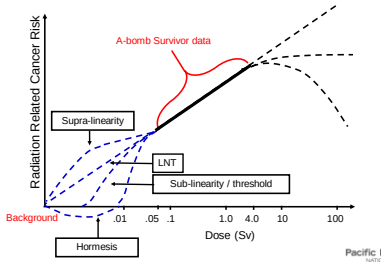
The dilemma for radiation protection: what is the scientific basis for radiation standards to protect the public from exposures to low levels of ionizing radiation (<0 100 mSv) where there are considerable uncertainties in the epidemiological data.



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On one hand - complex biological systems have physiological barriers against damage and disease. Primary damage linear with dose, secondary damage not. Cellular processes block damage propagation to clinical disease.

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Everybody knows radiation causes detrimental effects:

When asked "is a low dose of radiation safe?"
will you say "YES"?
or will you say
"There is always the possibility of a detrimental effect but at low doses it's **very very** small"

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Considerations when integrating molecular, cellular and organismal effects:

- Tissues/organs differentially sensitive
- Risk varies with
  - Age
  - Sex
  - Socio economic status
  - Diet and lifestyle
  - Genetic makeup and race
  - Dose and dose rate
  - Radiation quality

So how do we inform the public about potential radiation risks at low doses?

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Brenner & Hall; "Computed tomography - An increasing source of radiation exposure" NEJM 357, 2277-2284 (2007)

Scott, Sanders, Mitchel & Boreham; "CT scans may reduce rather than increase the risk of cancer" J. Amer. Phys & Surg. 13, 8-11 (2008)

What About in the Low Dose Region?

BEIR VII

Académie des sciences
INSTITUT DE FRANCE

BEIR VII cited 1386 peer reviewed publications

French Academie des Sciences cited 306 publications

Overlap in publications cited = 68

Radiation Protection Considerations

Science is only one input to risk management

What are the other inputs?

Tradition
Not scaring people
Politics
Social values
Economic considerations
Technological considerations

We have a long legacy of mistrust to deal with!

Plus some widely diverging opinions

Hormesis - tolerance - acceptance - total denial

Extrapolation from experimental systems:
Cells → tissues → organs → man

What does *in vitro* cell culture tell us about a response in humans?

What do *in vivo* models tell us about a response in humans - how do you extrapolate from an an animal model to the human population?

Should you?

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A predictive, multi-cellular framework is necessary to understand potential effects of exposure to ionizing radiation

This is our multi-scale, systems-level challenge.

Requires understanding the networks and pathways involved

Developing computational modeling approaches to organize complex biological data

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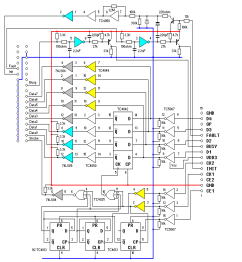
A System is a result of interacting parts:

An "interesting" part is one for which the consequences of interaction is non-trivial

The sum of the system is greater than the sum of the parts.

Biological systems are defined by multiple redundant and interdependent signaling networks and metabolic pathways



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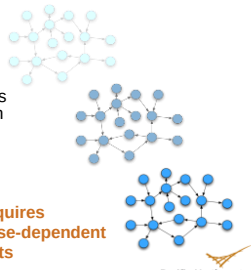
Context cannot be accurately predicted without multiple sources of data

- Well-designed studies with appropriate controls
- Gene expression data does not predict protein abundance
- Protein abundance data does not predict protein function
- Single time points do not provide directionality for correlation to functional outcomes



Network reconstruction requires heterogeneous data for dose-dependent and temporal measurements

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My hypothesis is that a predictive, multi-cellular framework is necessary to understand potential effects of exposure to low dose ionizing radiation

- Requires knowing the networks and pathways involved
- Developing the computational modeling approaches to organize complex biological data
- Interactions essential to develop testable hypotheses
- We plan to utilize resources available at PNNL
- Evolving to include new and old model systems
- Expanding the program to include new, young investigators
- PNNL complements other DOE national laboratories, DOE Low Dose and NOTE / DoReMi / MEODI and EpiRadBio investigators, and would like to work with other systems biology programs to increase the power of these investigations

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What is the rest of the world doing?

20 year program
MELODI* Subprogram, e.g. EpiRadBio CardioRisk Store DoReMi* Members of the EAB**
www.hleg.de/

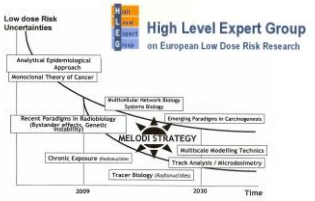

Figure 8: A new holistic approach to accelerate over 20 years the reduction of uncertainties in the understanding of low dose risks.

Japan, India and Korea – vibrant new low dose radiation programs

DOE Low Dose Radiation Research Program had a 10 year head start. Now falling behind technically, competitively and in competence.

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Comments, questions and suggestions

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Morgan & Bair: Issues in low dose radiation biology: The controversy continues. A perspective Radiation Research 179, 501-510 (2013)

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