Low Dose Radiation Research: “Radiation Dose is More than a Number”

Radiation Dosimetry Standardization Workshop
NCI / NIAID / NIST

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Noelle Metting, Sc.D.
Program Manager
Low Dose Radiation Research Program
U.S. Department of Energy
History – Low Dose Program initiated in 1999

“The lowest dose at which a statistically significant radiation risk has been shown is ~ 100 mSv (10 rem) of x-rays.”

Bridging Radiation Policy and Science
An international meeting of experts, held at Airlie House Conference Center
1 – 5 December 1999
"The lowest dose at which a statistically significant radiation risk has been shown is ~ 100 mSv (10 rem) of x-rays."

But what do these numbers really mean…??

- What did they mean in the past?
- What do they mean now?

Bridging Radiation Policy and Science
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DOE’s Low Dose Program (1):

• Focused on very low dose exposures that are encountered by workers in energy production and environmental cleanup
  • Less than 0.1 Gy (10 rads)
  • Mostly low LET (x- and gamma-ray)
  • Higher doses, then titrate down to lower doses
  • Low dose rates
  • High dose rates

• For low dose exposures, the dosimetry is critically important (spatial and temporal)
DOE’s Low Dose Program (2):

• Biological models include
  • Molecular endpoints within single cells (microbeams)
  • Cell culture models (yeast, rodent, human)
  • 3-D tissue models
    • Rat trachea
    • Matek skin model
    • Ductal mammary epithelia
  • Animal subjects
    • rat
    • mouse
    • Medaka and zebrafish

• Re-analysis of archived tissues and data
  • Mega-mouse studies
  • Beagle dog studies
  • Conducted in the second half of the 20th century
DOE’s Low Dose Program (3):

- Research to enable mechanism-based models that incorporate both radiobiology and epidemiology
  - From cellular and molecular actions within tissues
  - To the evolution of cancer as a multi-cellular disease
  - ... in human populations

- Clear understanding of both the biological assumptions and the dosimetry underlying epidemiological analysis in low dose range
The Underlying Assumption for (Low Dose) Dosimetry:

“If the spatial and temporal distribution of energy deposition events were clearly described, it would improve the understanding of biological mechanisms leading to radiation-induced effects.”

Hans-Georg Menzel, 2010 (paraphrased)
End
**Classic Paradigm of Radiation Injury** (High Dose)

- **Ionizing Radiation**
  - Excitations
  - Heat

- **Chemical Changes**
  - Chemical "Repair" (ions recombine)

- **DNA Damage**
  - Damaged non-DNA molecules replaced
  - Enzymatic DNA Repair

- **Unrepaired, Misrepaired DNA**

- **Cell Deaths - many**

- **Mutant Cells**
  - Germ line
  - Somatic

- **Early Effects**
  - Radiation Sickness (ARS)

- **Late Effects**
  - Developmental Effects (fetal)

- **Heritable Genetic Effects**

- **Cancer**

**Time Frames**
- < 1 Second
- Min - Hours
- Days - Decades
**Classic Paradigm of Radiation Injury** *(High Dose)*

- **Ionizing Radiation**
- **Heat**
- **Ionizations** = **Chemical changes** *(Free radical formation, etc)*
- **DNA Damage**
- **Enzymatic DNA Repair**
- **Damaged non-DNA molecules replaced**
- **Unrepaired, Misrepaired DNA**
- **Cell Deaths—many**
- **Early Effects**
  - Radiation Sickness (ARS)
- **Late Effects of Radiation Damage**
- **Heritable Genetic Effects**
- **Cancer**
- **Mutant Cells**
  - Germ line
  - Somatic *(Malignant Transformation)*

**Time Frames**
- **< 1 Second**
- **Min - Hours**
- **Days - Decades**
Low Doses show other pathways....

Ionizing Radiation

Ionizations = Chemical changes (Free radical formation, etc)

Chemical "Repair" (ions recombine)

Damaged non-DNA molecules replaced

DNA Damage

Enzymatic DNA Repair

Enhanced DNA Repair

Unrepaired, Misrepaired DNA

DNA Damage

Altered antioxidant status

Molecular sensors trigger altered activity

DNA Damage

Altered DNA Repair

Enhanced DNA Repair

Enzymatic DNA Repair

Cell repopulation

Cell Deaths - few

Tissue remains healthy

Developmental Effects (fetal)

Late Effects of Radiation Damage

Early Effects Radiation Sickness (ARS)

Heritable Genetic Effects

Cancer

Mutant Cell

Germ line

Somatic

(Malignant Transformation)

Immune suppression of cancer phenotype?

Enhanced DNA Repair

Altered DNA Repair

Tissue Microenvironment

(Protects multi-cellular organism at low doses)

<1 Second

Min - Hours

Days - Decades
**Time Factors:**

- **Dose Rates**
  - The biology is clearly different (dose rate effects…)
  - Gamma irradiators change over time (half-lives calculated…)
  - Calibrated radiation-generating machines can drift…

- **Timing of the Experimental Protocol**
  - Dose Fractionation
  - The periods before, between, after each step

- **Daytime, Nighttime**
  - The biology is clearly different (diurnal/nocturnal effects…)
  - The physics

- **Historical Time**
  - The definitions of quantities change
  - New measurement techniques allow improved precision, accuracy
  - Annotation, curation of the literature…
Spatial Factors:

• Microdosimetry
  • (Les Braby)
  • Energy distributions
  • Monte Carlo track structure simulations

• Partial vs. Full
  • Body of animal subject
  • Cell/tissue culture dish
  • Single cell (intra-, inter-, extra-)

• Uniform radiation field
  • To encompass entire subject

• Background radiation matters
  • Gamma-rays (soil)
  • Radon
  • Cosmic rays
  • (manmade)
Background Radiation:


Dose Rates from Natural Background USGS

U.S. average annual dose = 310 mrem/yr, including radon

Dose Rates from Natural Background USGS

Terrestrial Gamma-Ray Exposure at 1m above ground


Dose Rates from Natural Background USGS

U.S. average annual dose = 310 mrem/yr, including radon
Ionizing Radiation

Dose Ranges

( Rem )

Whole body, acute: G-I destruction; lung damage; cognitive dysfunction (death certain in 5 to 12 days)*

Life Span Study (A-bomb survivor epidemiology)

Total Body Irradiation (TBI) Therapy

Acute Radiation Syndromes

Whole body, acute: circulating blood cell death; moderate G-I damage (death probable 2-3 wks)*

Human LD50 range acute exposure with medical intervention*

Charge particle event (Solar flare) dose on moon, no shielding

Estimated dose for 3-yr Mars mission (current shielding)

DHS emergency guideline to save a life: 25 rem

Typical missions on International Space Station (ISS)

Ramsar, Iran high natural bkg/yr

DOE Low Dose Program

Guarapari, Brazil high natural bkg/yr

DOE, NRC dose limit for workers: 5 rem/yr (50 mSv/yr)

Medical Diagnostics (A-O)

see chart >>

Medical Diagnostics rads

(Estimated maximum organ dose)

X-ray films

A - Chest (PA & Lat) 0.014
B - Dental Panoramic 0.07
C - Lumbar-Sacral Spine 0.2 - 0.3
D - Mammogram 0.2 - 0.4

Radiotracer Imaging

E - Heart Stress (Tc-99m) 0.6 - 1.2
F - Bone (Tc-99m) 0.4 - 1.5
G - Dual Isotope Stress Test 4.0 - 4.5
H - PET: F-18 FDG (bladder) 5.5 - 8

CT Scans (X-ray)

(multiple scan average dose)

E - Chest 2 - 3
J - Head 3 - 5
K - Abdominal 2 - 6
L - Full Body 5 - 10

Fluoroscopy/Procedures

M - Barium Contrast G.I. 1.2 - 2.2
N - Cardiac Catheterization 1.2 - 4
O - TIPS Procedure 40 - 140

Regulations & Guidelines

DOE facility releases

Natural background, USA average ≈ 310 mrem/yr (includes radon)

Yangjiang, China high natural bkg/yr

EPA dose limit from release in air: 10 mrem/yr

EPA dose limit public drinking water systems: 4 mrem/yr

NRC cleanup criteria for site decommissioning/unrestricted use: 25 mrem/yr

DOE, NRC dose limit for the public: 100 mrem/yr (1 mSv/yr) (ICRP, NCRP)

LD50 = Lethal Dose to 50% (whole body dose that results in lethality to 50% of exposed individuals in 30-60 days)

Dose Equivalent: 100 rem = 1 Sievert (absorbed dose x radiation quality)

Absorbed Dose: 100 rad = 1 Gray

Chart compiled by NF Meeting, Office of Science, DOE/BER. "Orders of Magnitude" revised June 2010

1 rem ≈ 1 rad for X- and gamma-rays

http://www.lowdose.energy.gov/

*Note: Whole body acute dose.

Medical intervention (G-I = gastrointestinal)
Ionizing Radiation
Dose Ranges (Sievert)

Cancer Radiotherapy
Total doses to tumor

- Whole body, acute: cerebral/vascular breakdown (death in 0-5 days)*
- Whole body, acute: G-I damage (death certain in 5 to 12 days)*

Acute Radiation Syndromes

- Human LD_{50} range acute exposure no medical intervention*
- Human LD_{50} range acute exposure with medical intervention (G-I = gastrointestinal)

Evidence for small increases in human cancer above 100 mSv acute exposure or 200 mSv chronic exposure

Typical mission doses on International Space Station (ISS)

Keral coast, India high natural bkg/yr

Typical added annual dose for commercial airline flight crews

Airport x-ray whole body scanner: 0.00007 mSv/scan (Limit = 0.25 mSv/yr = 4000 scans/yr)

Natural background, USA average = 3.1 mSv/yr (includes radon)

DHS emergency guideline for public relocation: 20 mSv/yr (2 rem/yr)

Guarapari, Brazil high natural bkg/yr

DHS emergency guideline to save a life = 250 mSv

DOE Low Dose Program

DOE, NRC dose limit for workers: 50 mSv/yr (5 rem/yr)

Medical Diagnostics (A-O) see chart >>

Medical Diagnostics mGy (Estimated maximum organ dose)

- X-ray films
  - A: Chest (PA & Lat) 0.14
  - B: Dental Panoramic 0.7
  - C: Lumbar-Sacral Spine 2 - 3
  - D: Mammogram 2 - 4

- Radiotracer Imaging
  - E: Heart Stress (Tc-99m) 6 - 12
  - F: Bone (Tc-99m) 4 - 15
  - G: Dual Isotope Stress Test 40 - 45
  - H: PET: F-18 FDG (bladder) 55 - 80

- CT Scans (X-ray) (multiple scan average dose)
  - I: Chest CT 20 - 30
  - J: Head CT 30 - 50
  - K: Abdominal CT 22 - 60
  - L: Full Body CT 50 - 100

- Fluoroscopy/Procedures
  - M: Barium Contrast G.I. 10 - 22
  - N: Cardiac Catheterization 12 - 40
  - O: TIPS Procedure 400 - 1400

Regulations & Guidelines

LD_{50} = Lethal Dose to 50% (whole body dose that results in lethality to 50% of exposed individuals in 30-60 days)

Dose Equivalent: 1 Sievert = 100 rem

- Radiation Protection Program (NSC = National Science Council)
- Radiation Protection Program (DOE/BER)
- Radiation Protection Program (TIPS: Translational Imaging Prostate)