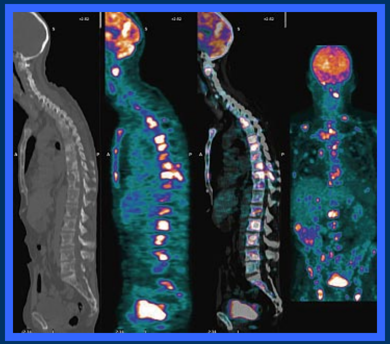
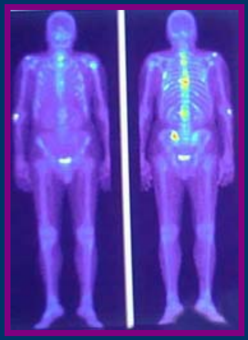
AAPM Summer School 2012

Biological Effects of Radiation

-an overview





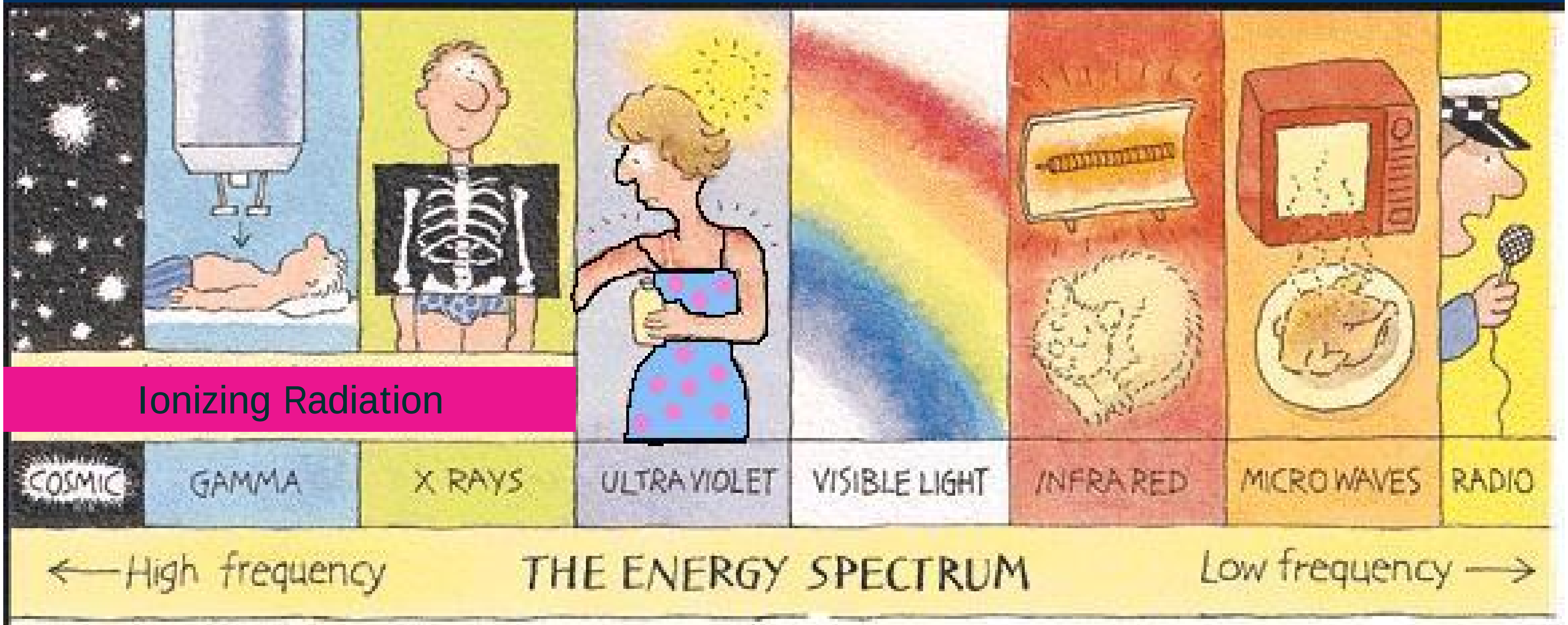
Lawrence T. Dauer, PhD, CHP
Assistant Attending Health Physicist
Departments of Medical Physics & Radiology

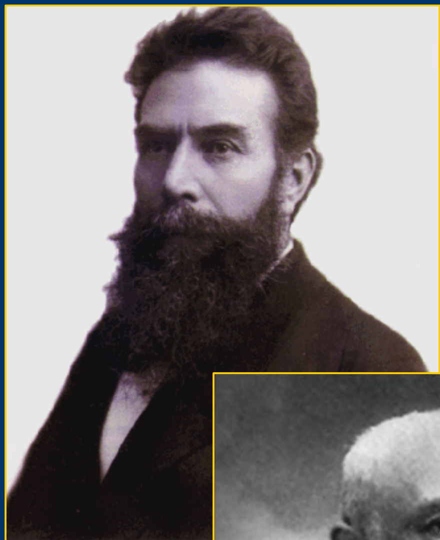
AAPM Summer School 2012

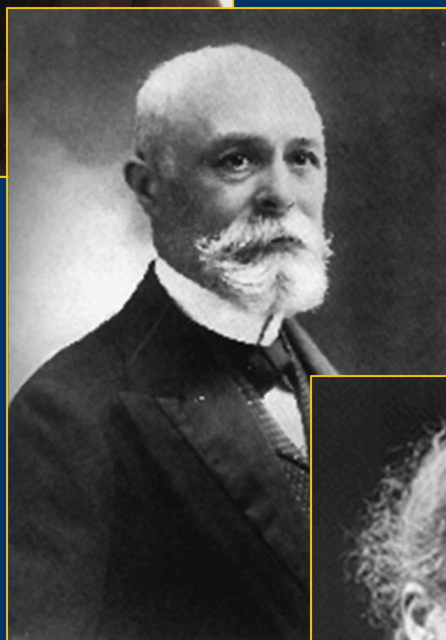
Topics Covered

- Ionizing Radiation
- Mechanisms of Damage/Repair
- Dose Effect
- Modulators
- Cancer and Non-Cancer Effects
- Low Dose Effects – Paradigm shift?
- From Effects to Risks
- Research Needed
- References for More Information

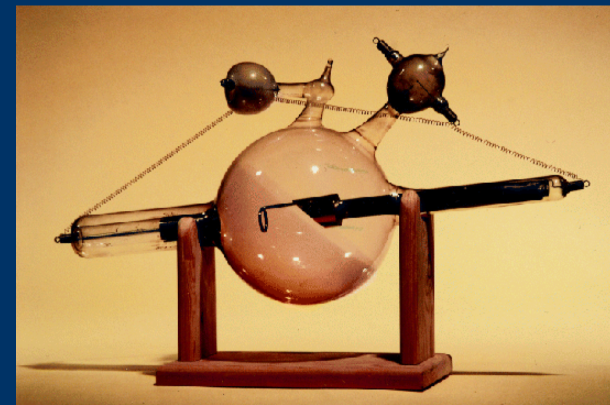
Ionizing radiation

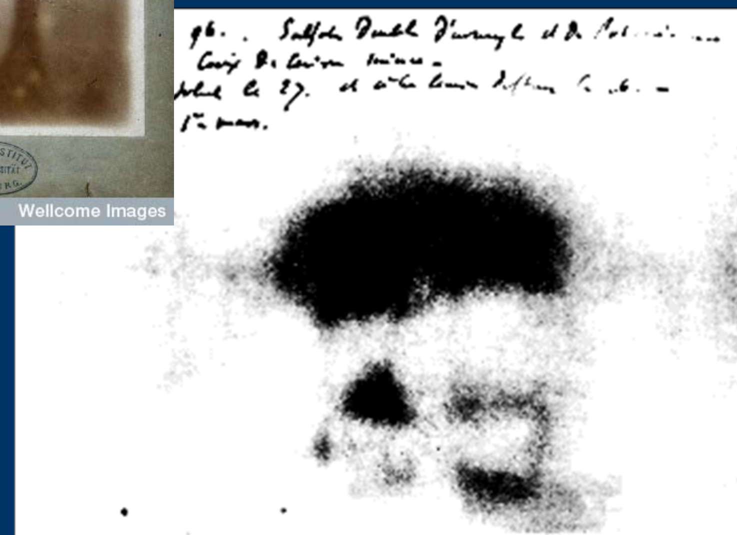


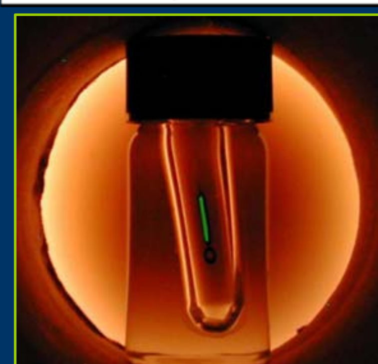





Hand mit Ringen
Wellcome Images

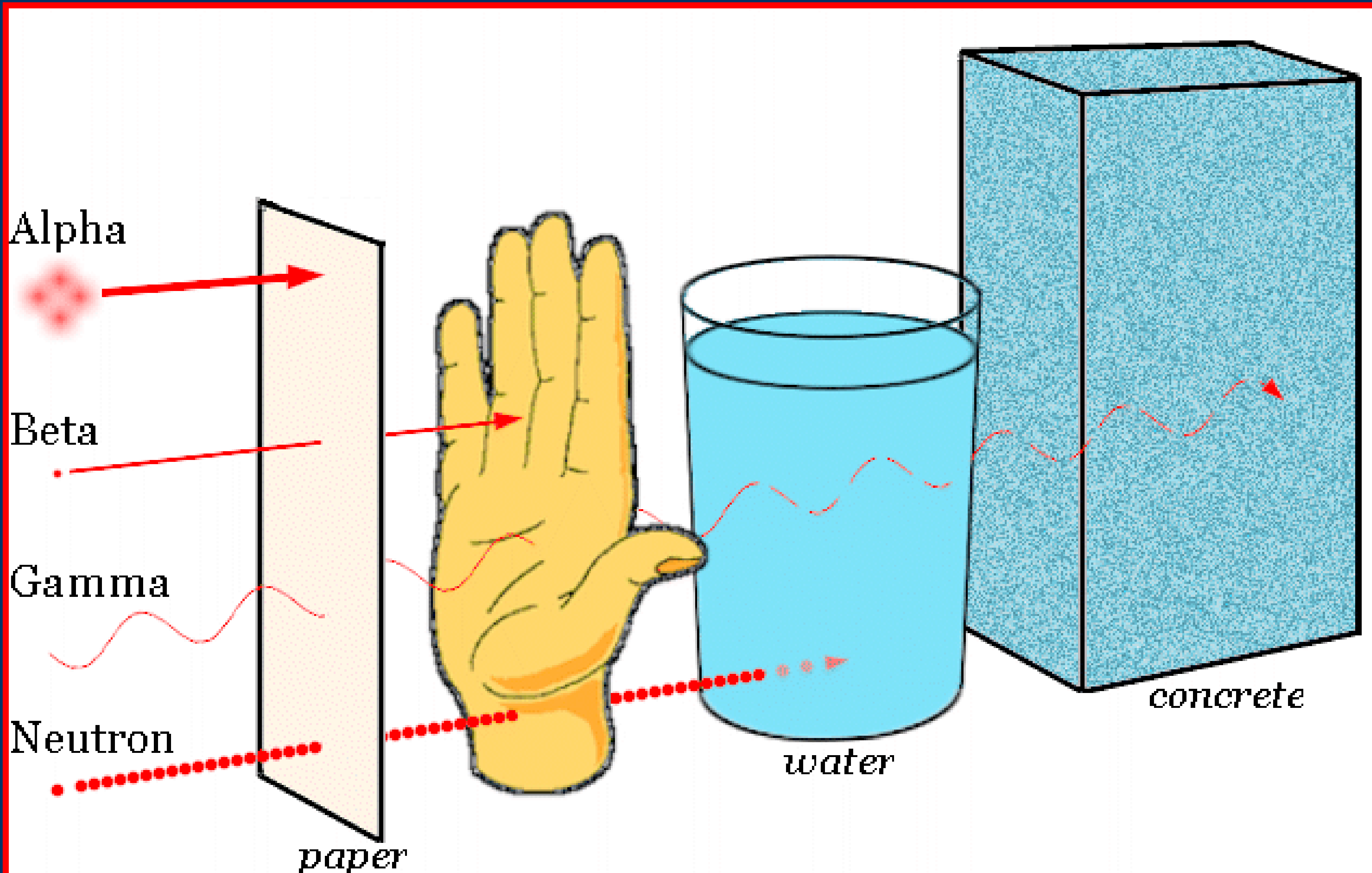






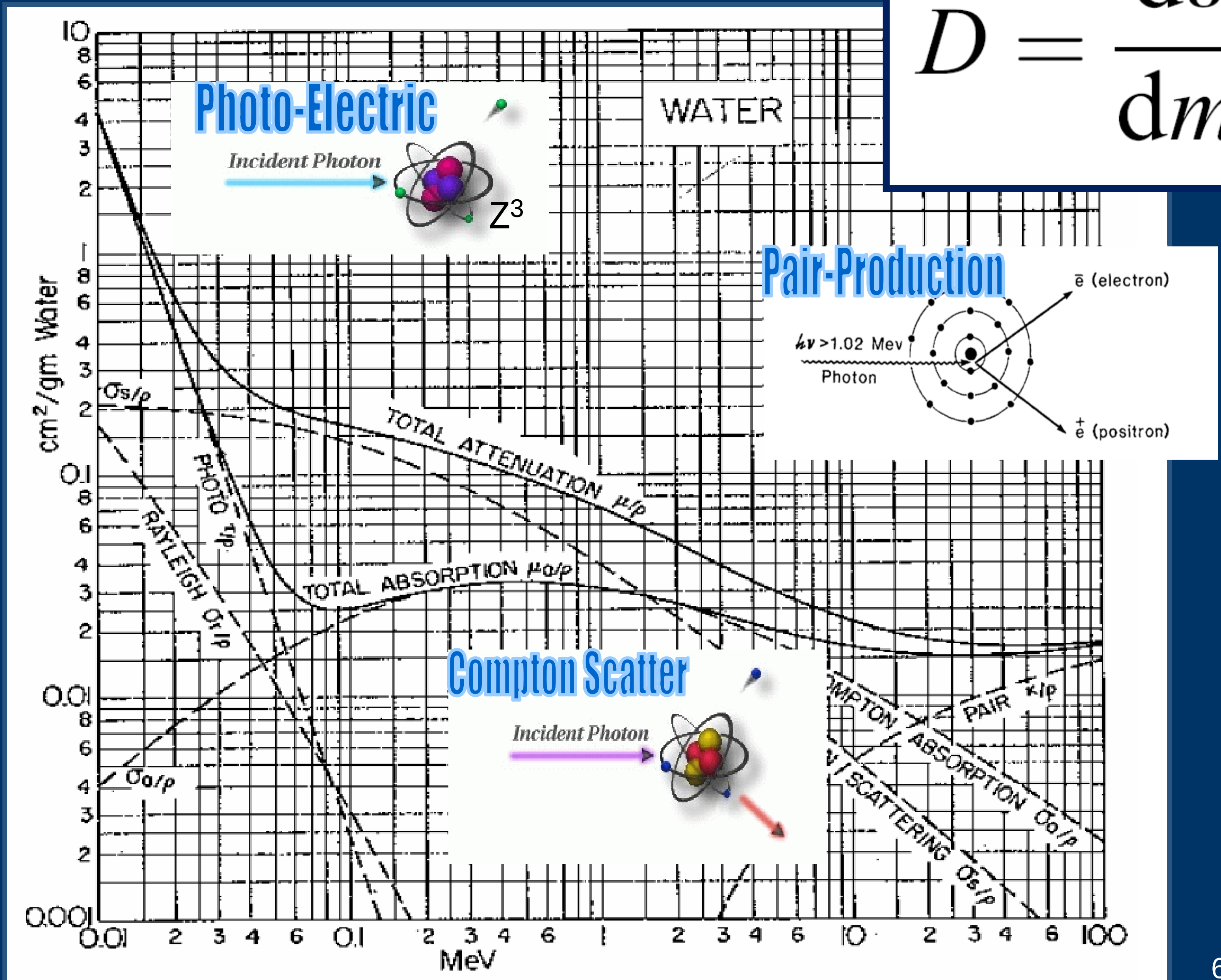

Ra 88
RADIUM
(226) 5.0
700 1140

Types of Ionizing Radiation



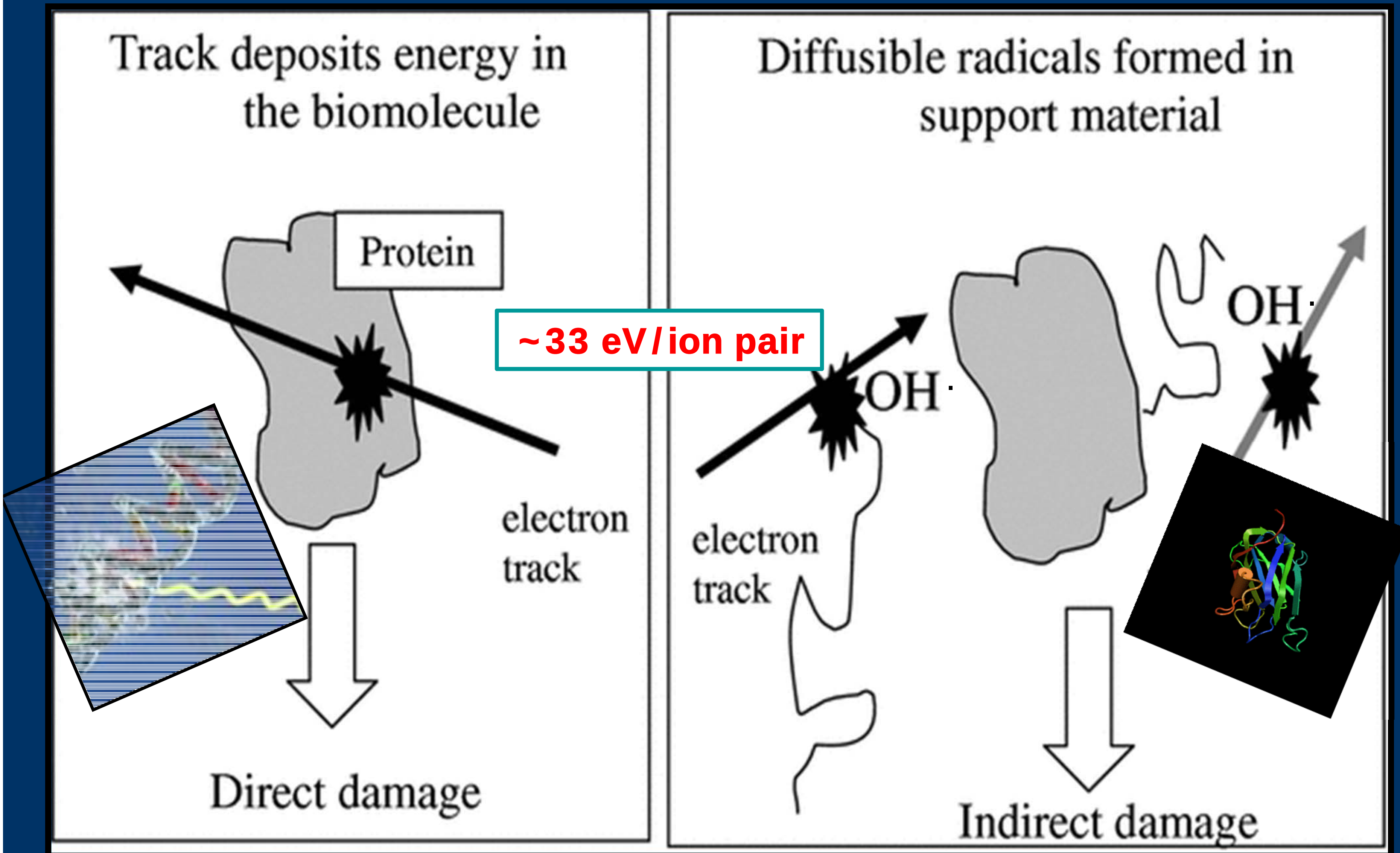
X-Ray Interactions

$$D = \frac{d\bar{\varepsilon}}{dm}$$



Mechanisms of Damage/Repair

Direct and Indirect Damage



2/3 of damage

Damage Process

Incident Photon

↓

Fast electron, e⁻

↓

Ion Radical

↓

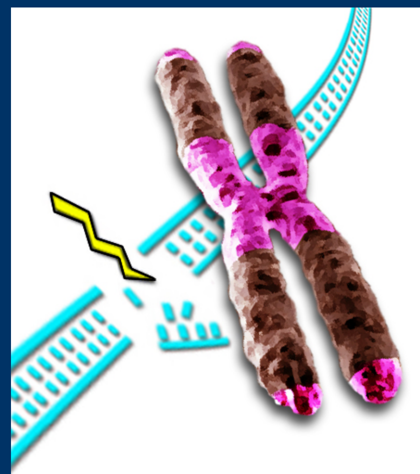
Free Radical

↓

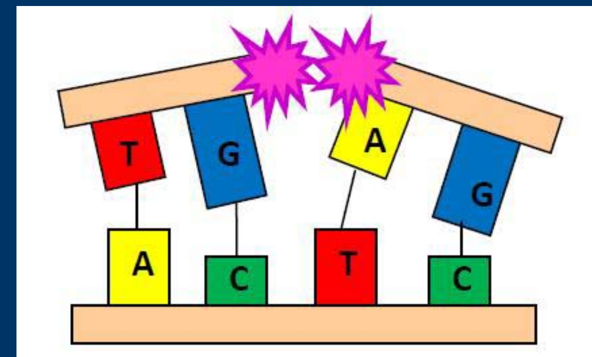
Chemical Changes From Bond Breaks

↓

Biological Effects



DSB
~40/cell/Gy
related to cell killing



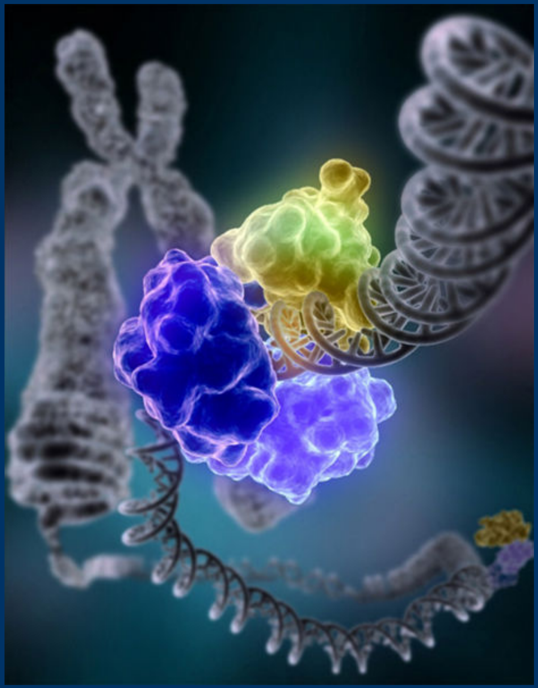
SSB
~1000/cell/Gy

DNA Protein Crosslinks

Locally Multiply Damaged Sites
> 50% of total DNA damage

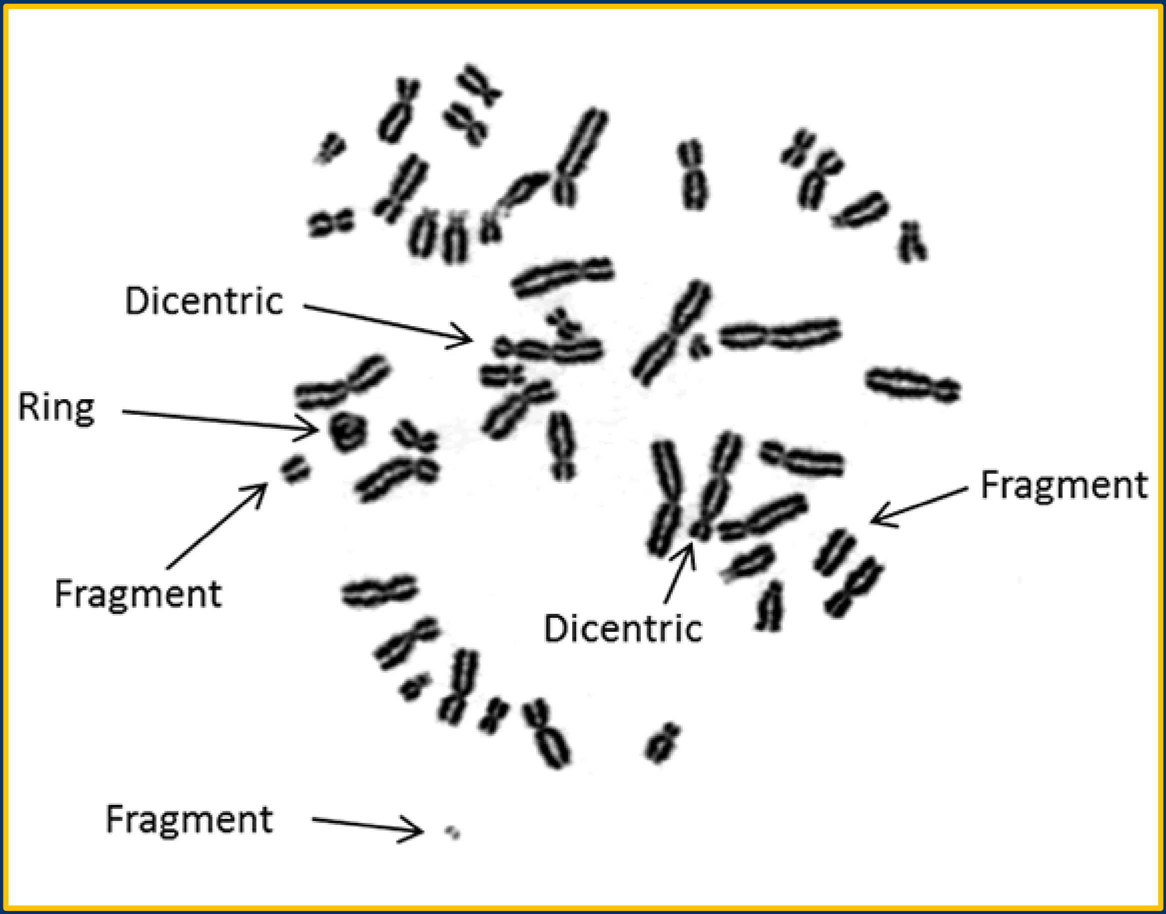
Mechanisms of Repair

- $T_{1/2}$ repair ~ 1-2 h and some slower
- Base Excision Repair
- Nucleotide Excision Repair
- DSB – Nonhomologous End-Joining
- DSB – Homologous Recombination Repair
- Crosslink Repair
- Mismatch Repair

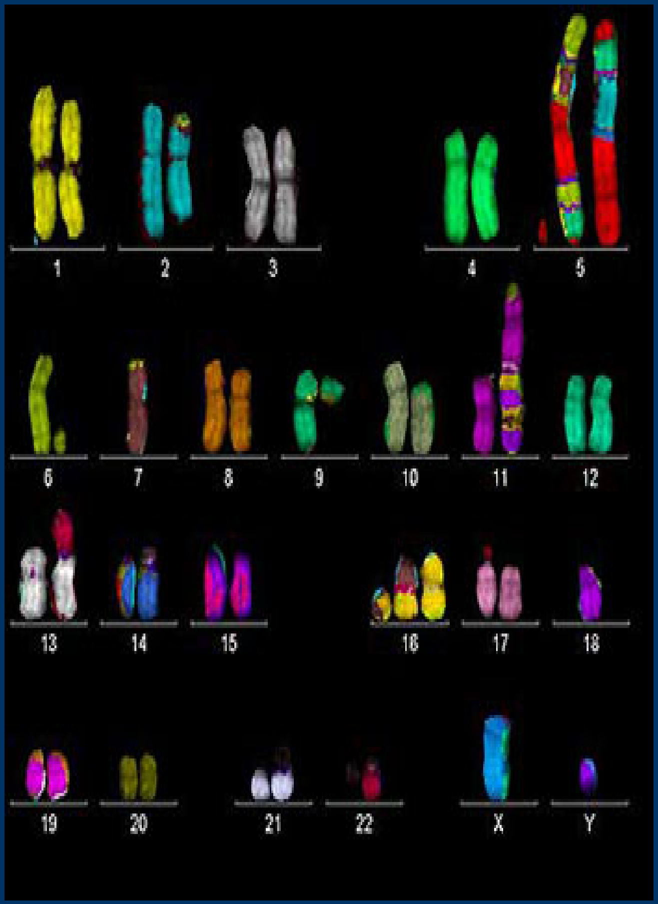


DNA Ligase

Chromosome Aberrations

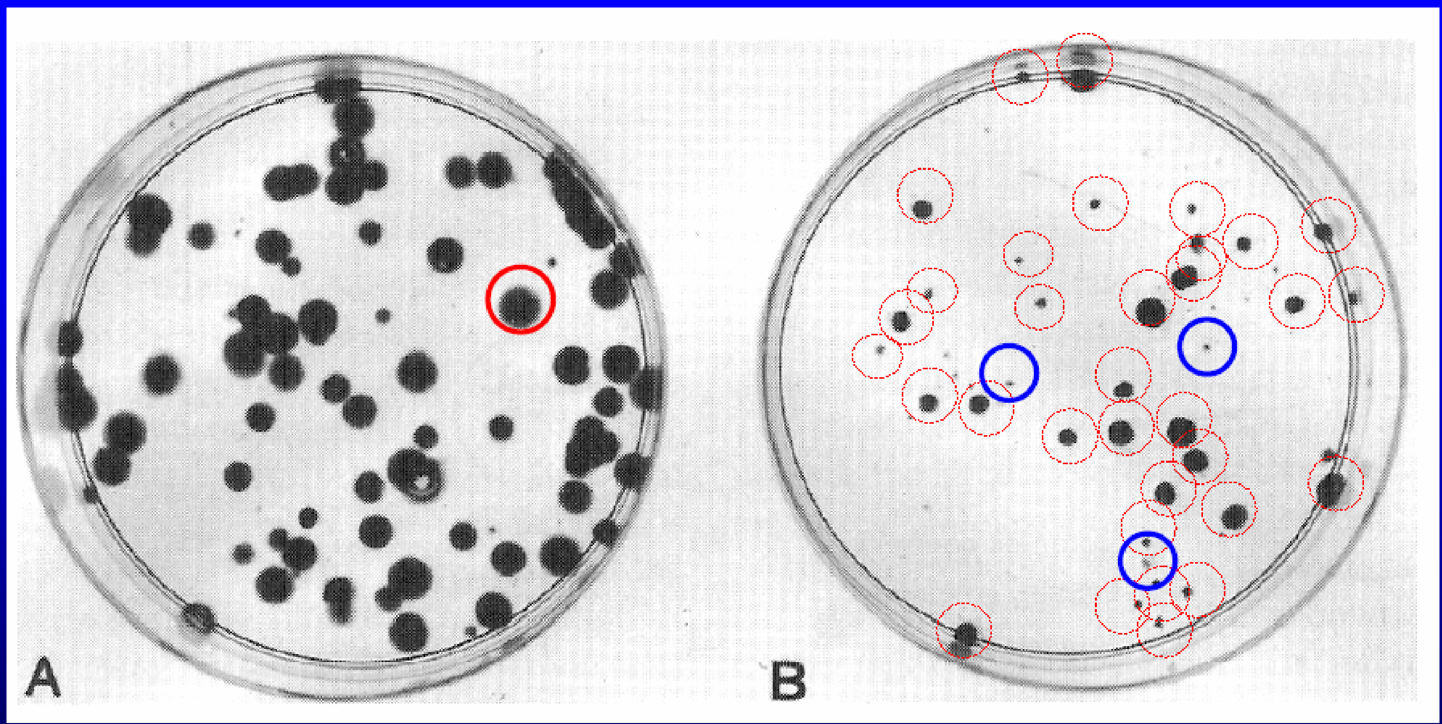


http://www.nirs.go.jp



Human Chromosomes Showing Translocations From Radiation
Massey University

Dose Effect



Control: 70 colonies

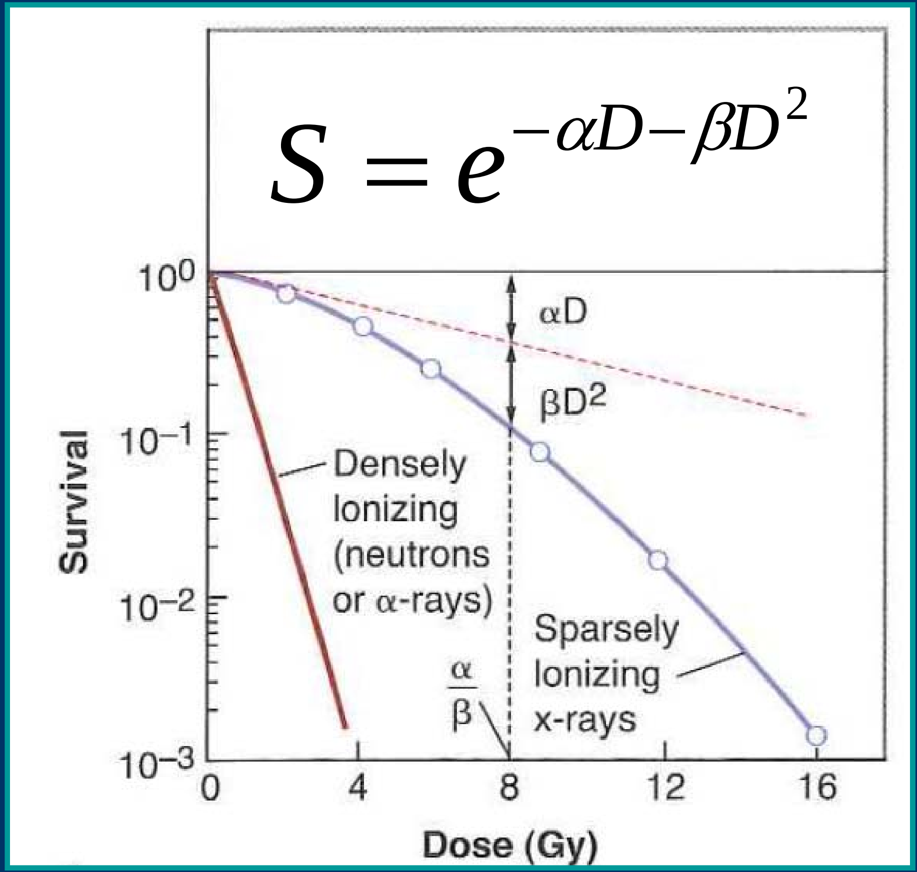
8 Gy: 32 colonies

Linear-Quadratic Relationship

- Linear and quadratic contributions are equal at:

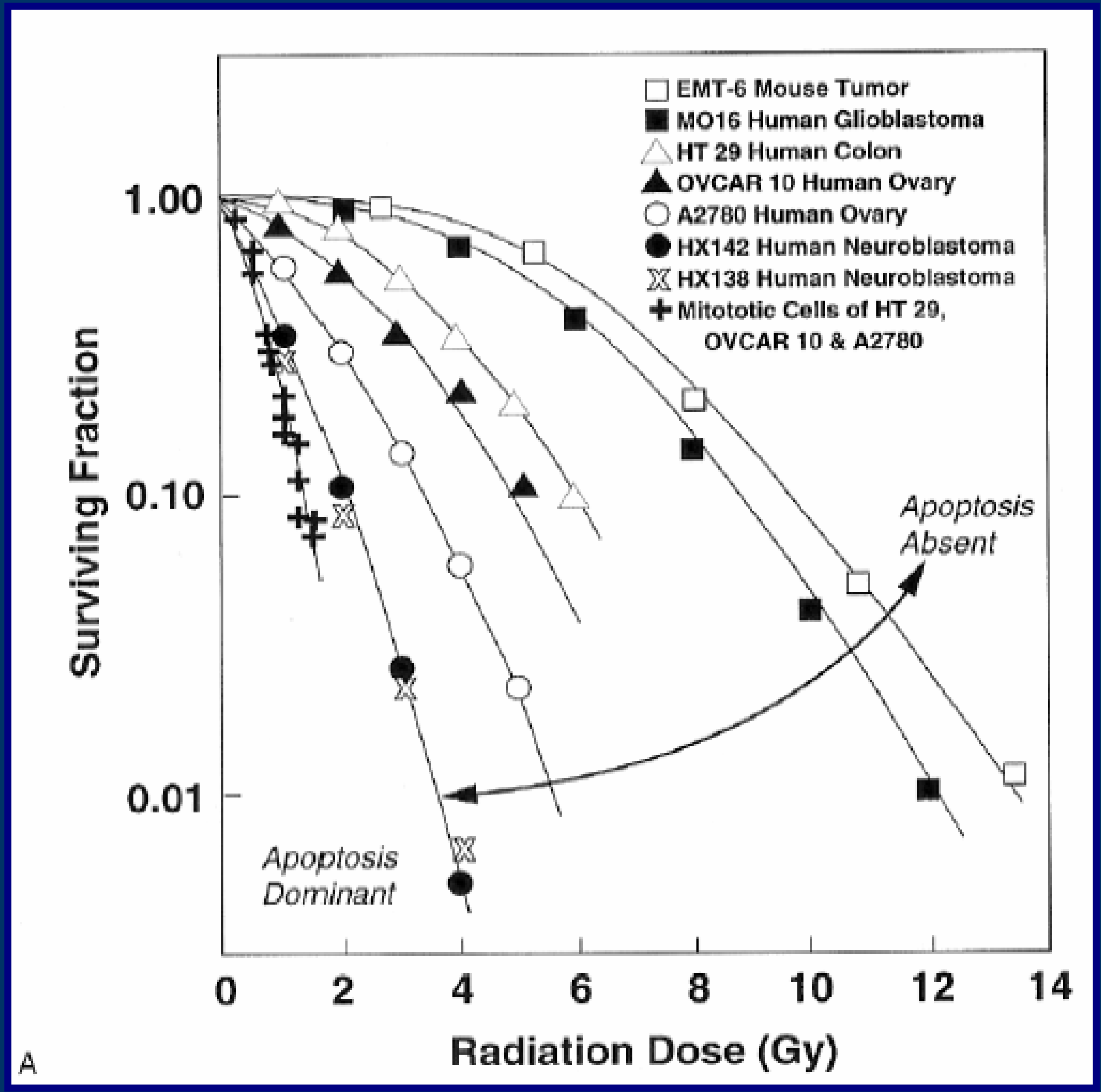
  $D=\alpha/\beta$

- Nucleus (DNA) as target
- Bystander effect?



Hall & Giaccia,
Radiobiology for the Radiologist
7th Ed, 2012

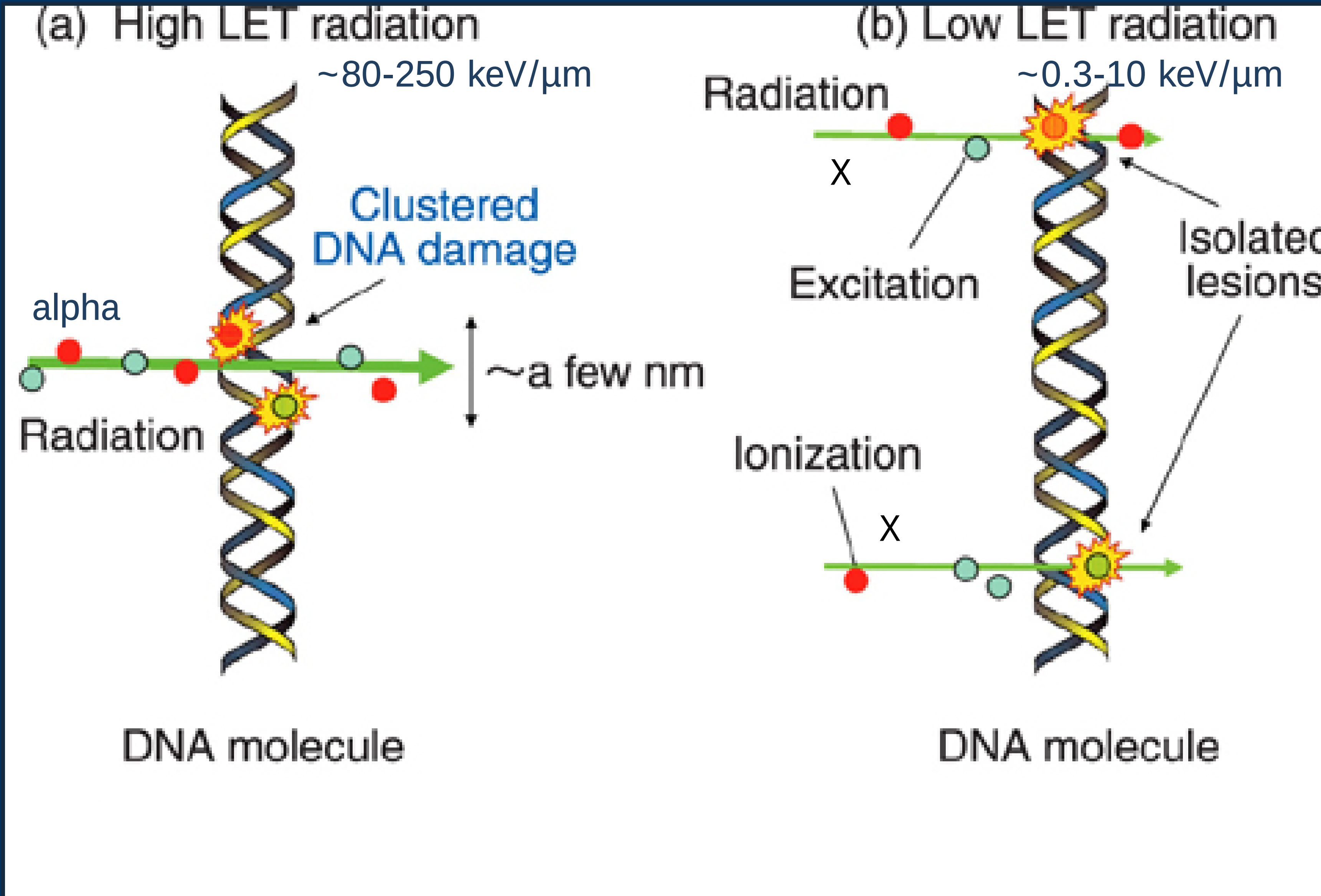
Dose Effect - Cell Survival Curves



Hall & Giaccia, Radiobiology for the Radiologist

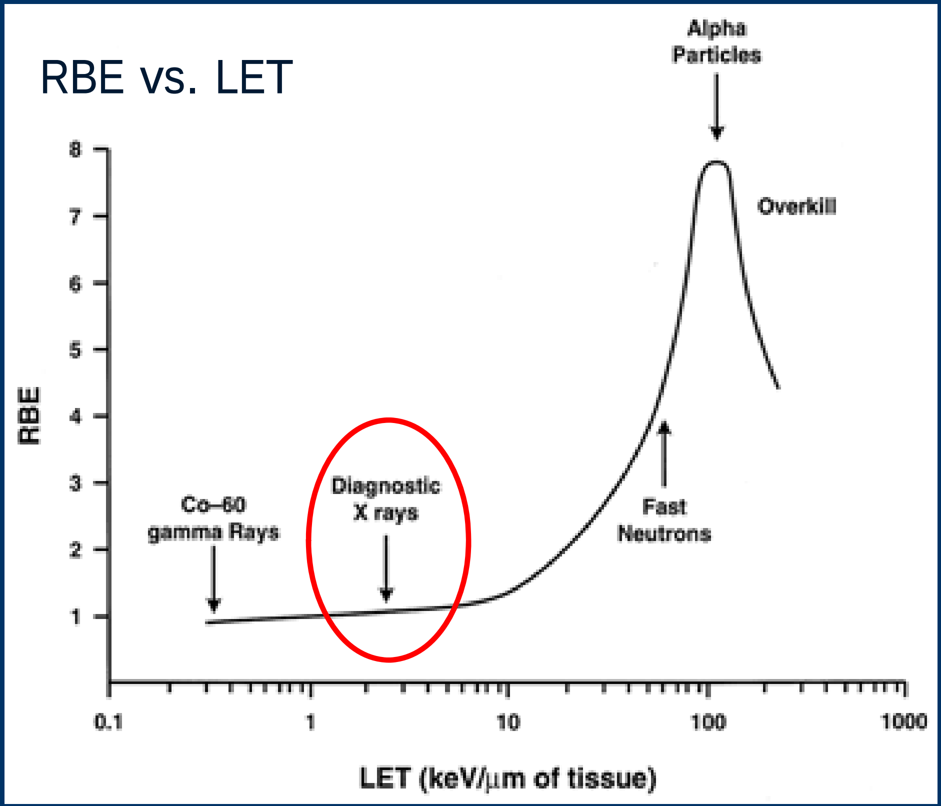
Modulators

Linear Energy Transfer L= dE/dl

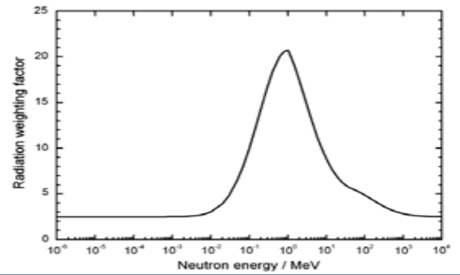


Relative Biological Effectiveness

- For the same biological endpoint...
- $RBE = D_{ref}/D_{test}$ $\quad RBE \sim QF \sim w_R$



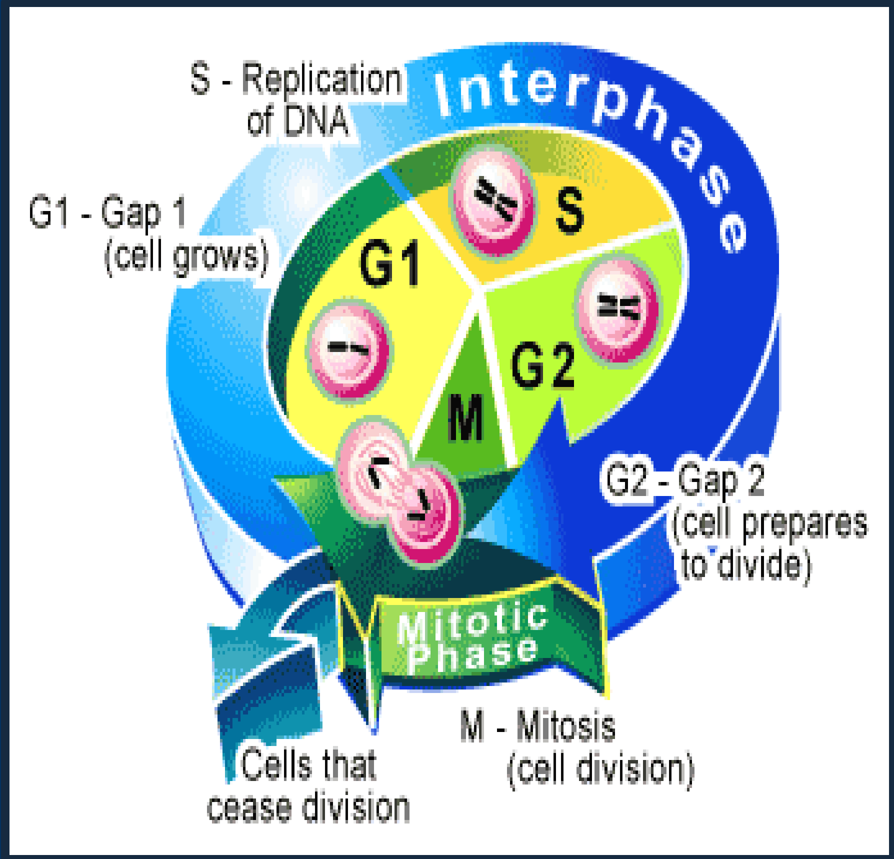
Radiation type	Radiation weighting factor, w_R
Photons	1
Electrons[a] and muons	1
Protons and charged pions	2
Alpha particles, fission fragments, heavy ions	20
Neutrons	



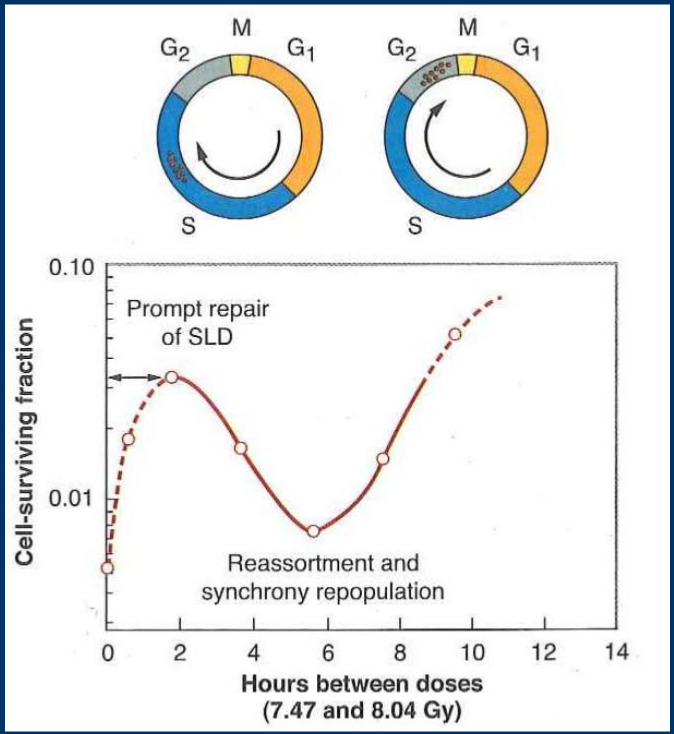
ICRP-103

Mitotic Cell Cycle

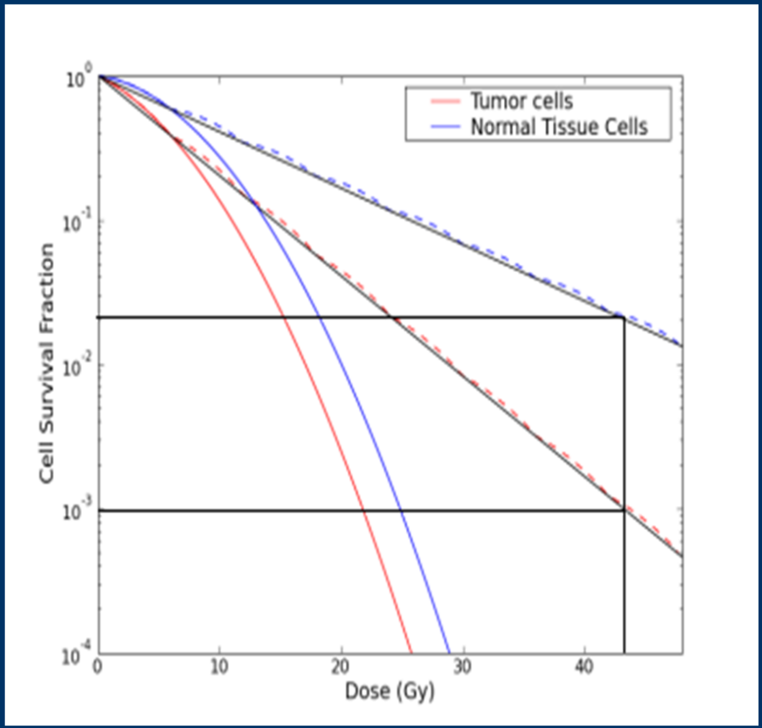
- Most Radiosensitive:
  - M and G2 Phase
  - DSB Nonhomologous end joining
- Most Resistant
  - Late S Phase
  - DSB Homologous repair
- Molecular Checkpoints



Fractionated Radiation



Hall & Giaccia, Radiobiology for the Radiologist 7th Ed, 2012

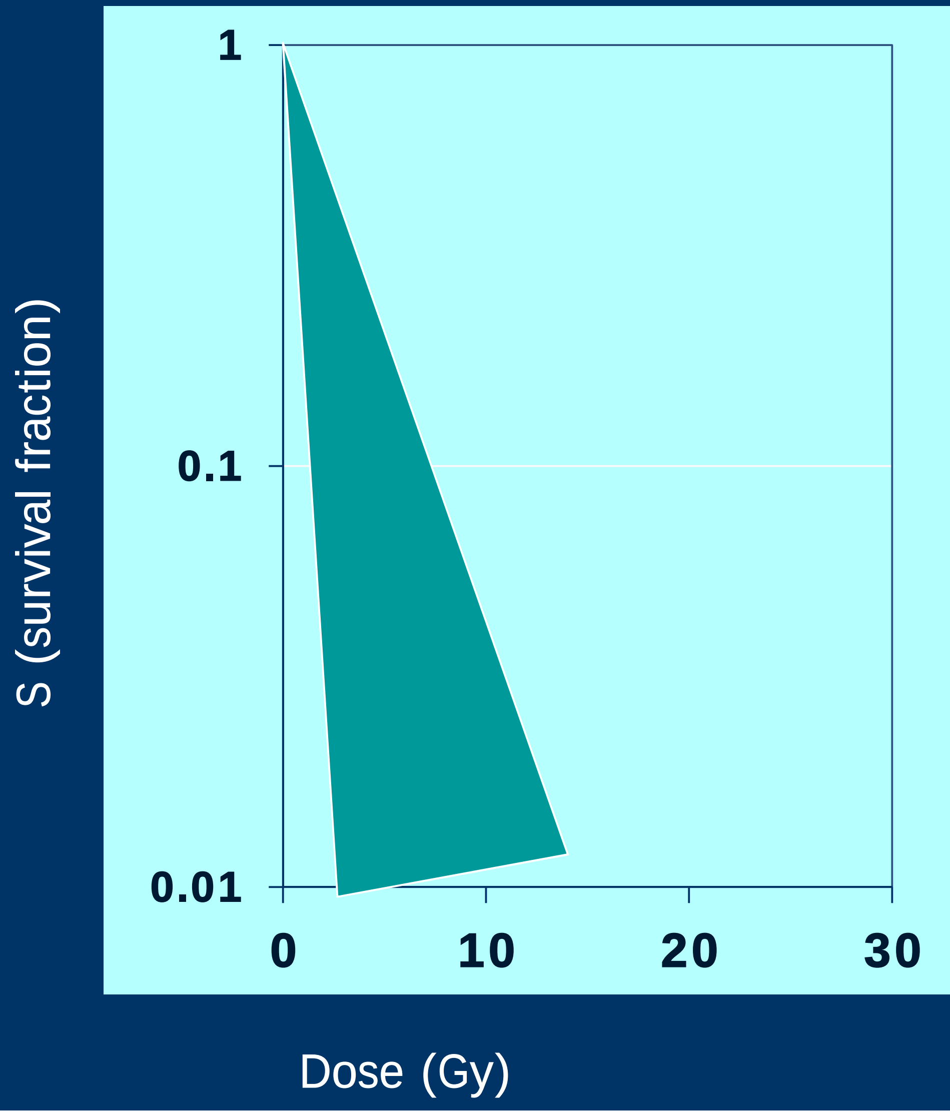


http://www.drflounder.com/archives/59

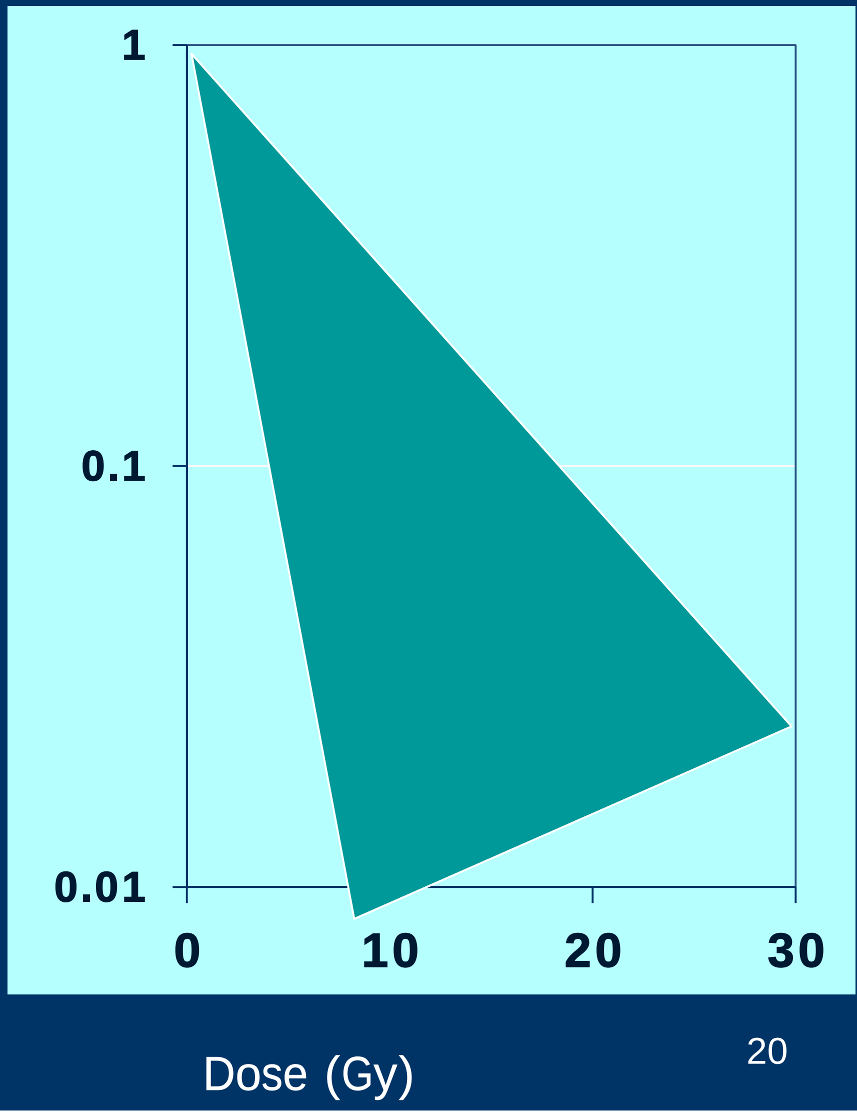
- Repair - sublethal damages repaired before they interact to form lethal aberrations
- Re-assortment - may cause sensitization
- Repopulation - cell division if long interval

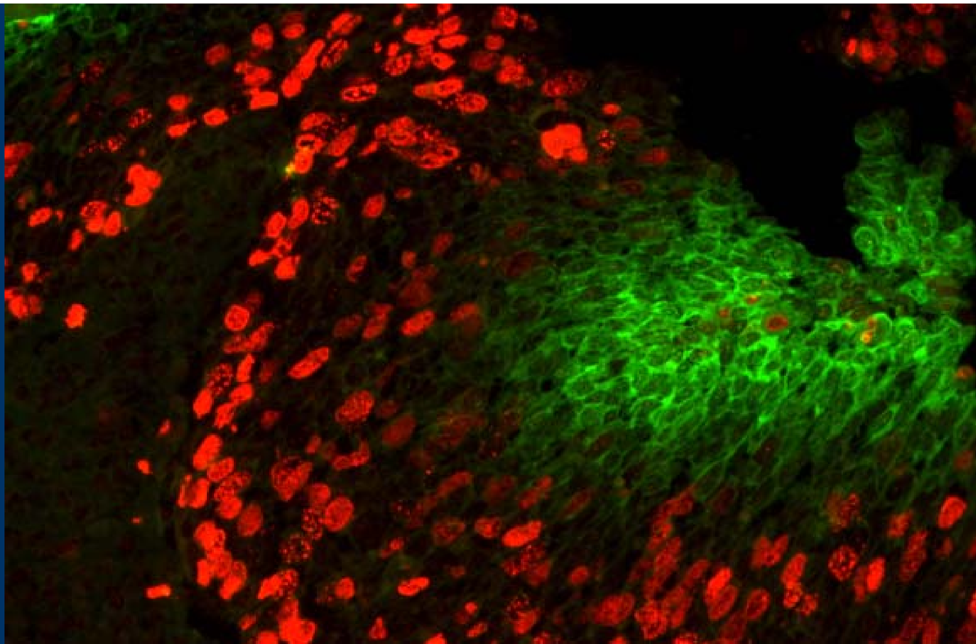
Dose-Rate

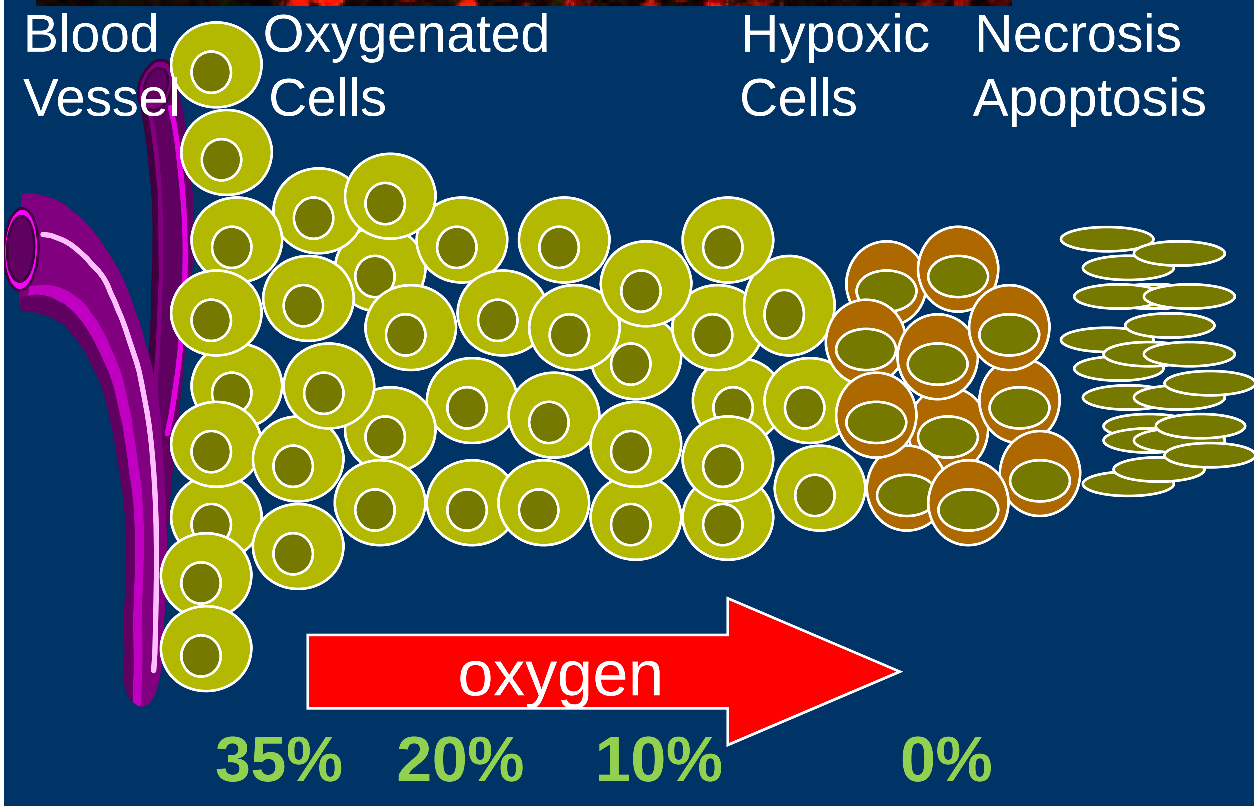
High Dose Rate



Low Dose Rate



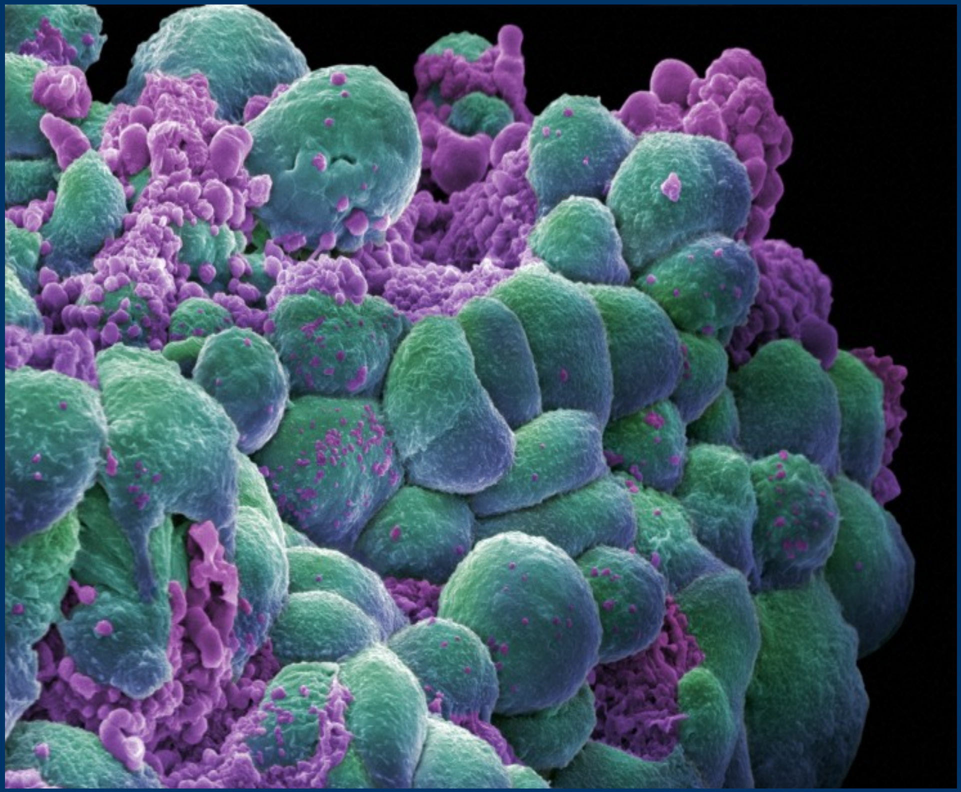




Oxygen Effect

- O^2 increases effect
- OER ~3.5 high D
- OER ~2.5 low D
- Oxygen makes ‘permanent’ the damage produced by free radicals.
- Low LET have Higher OER.

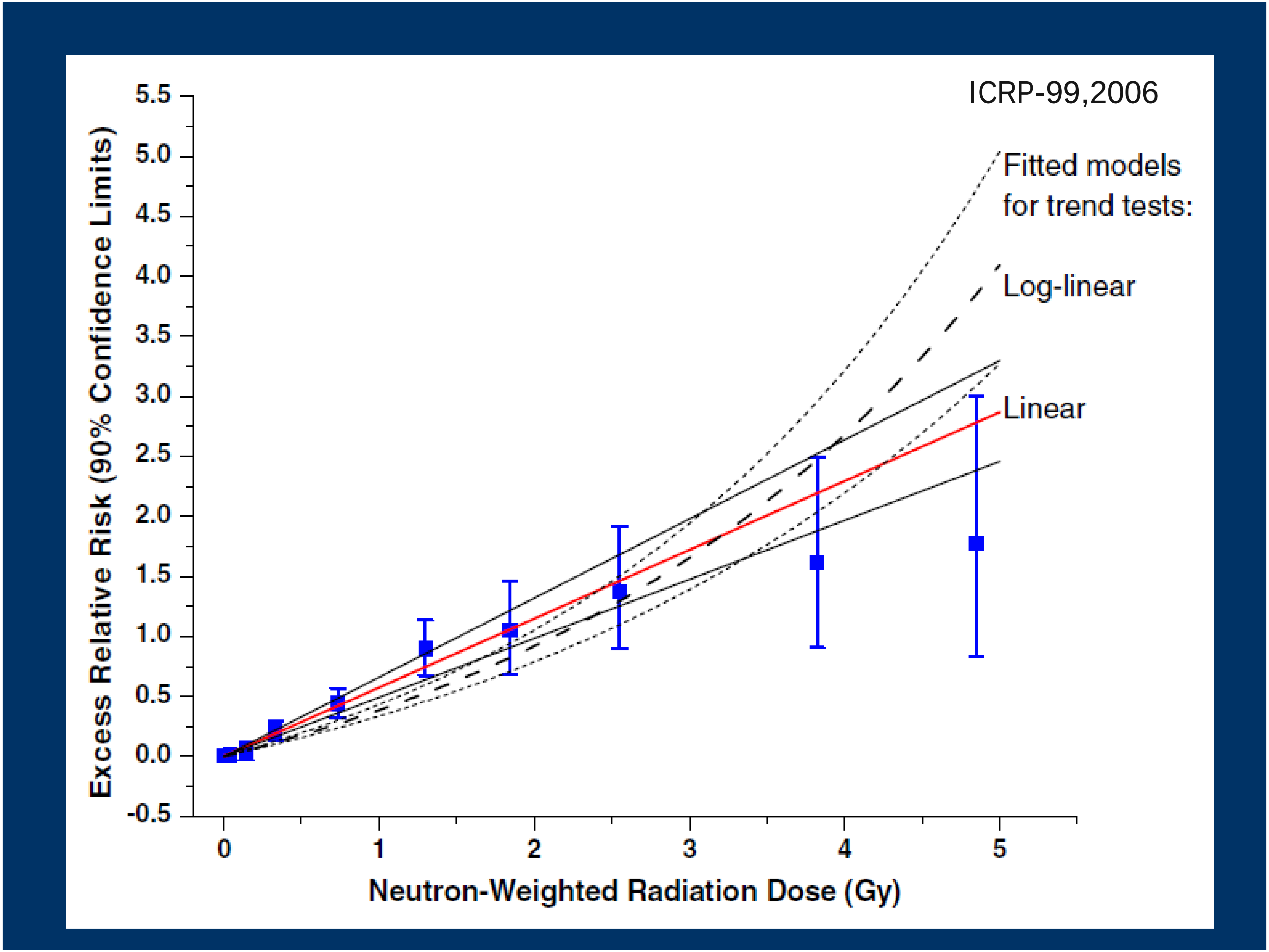
Cancer & Non-Cancer Effects



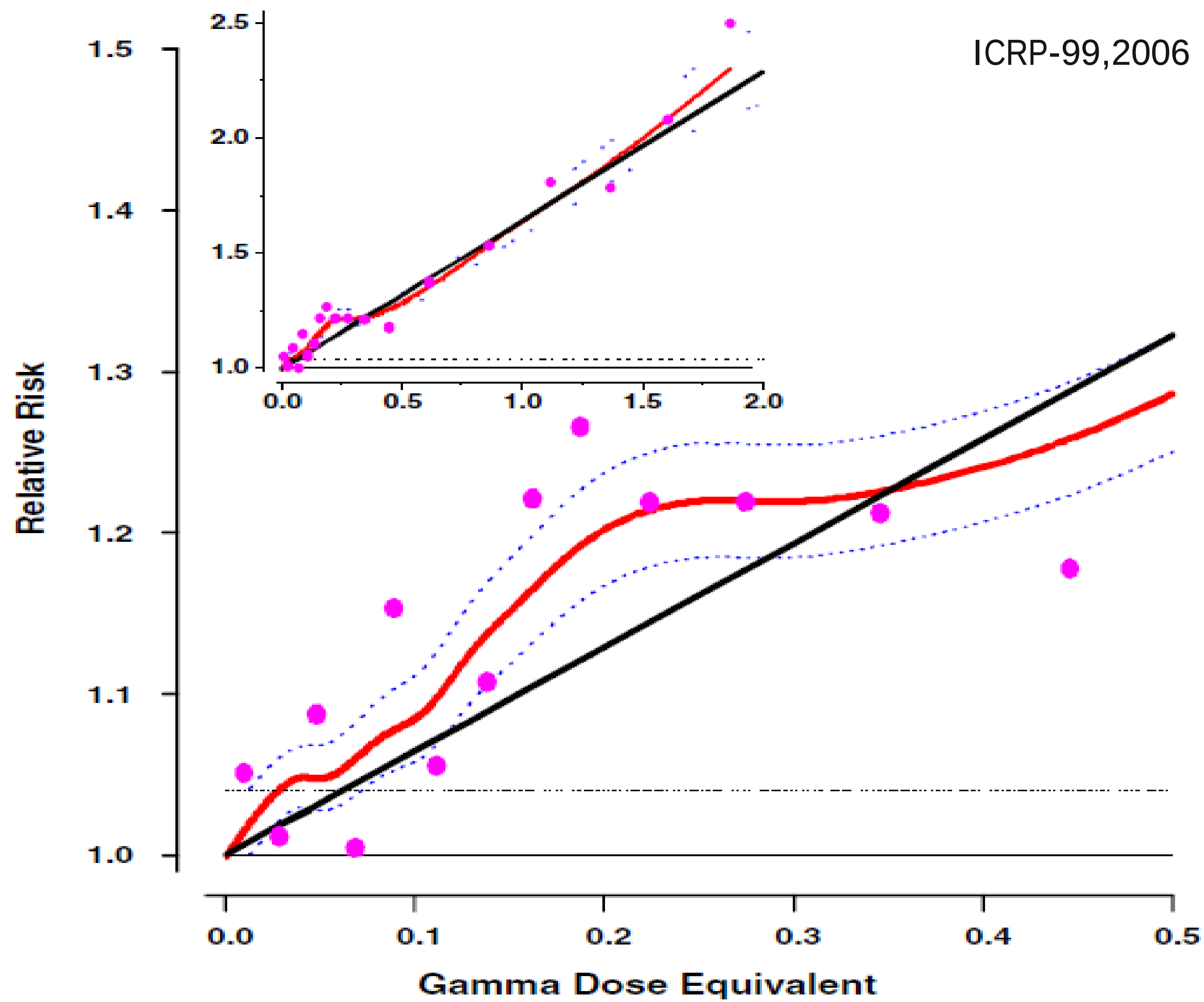
www.fda.gov

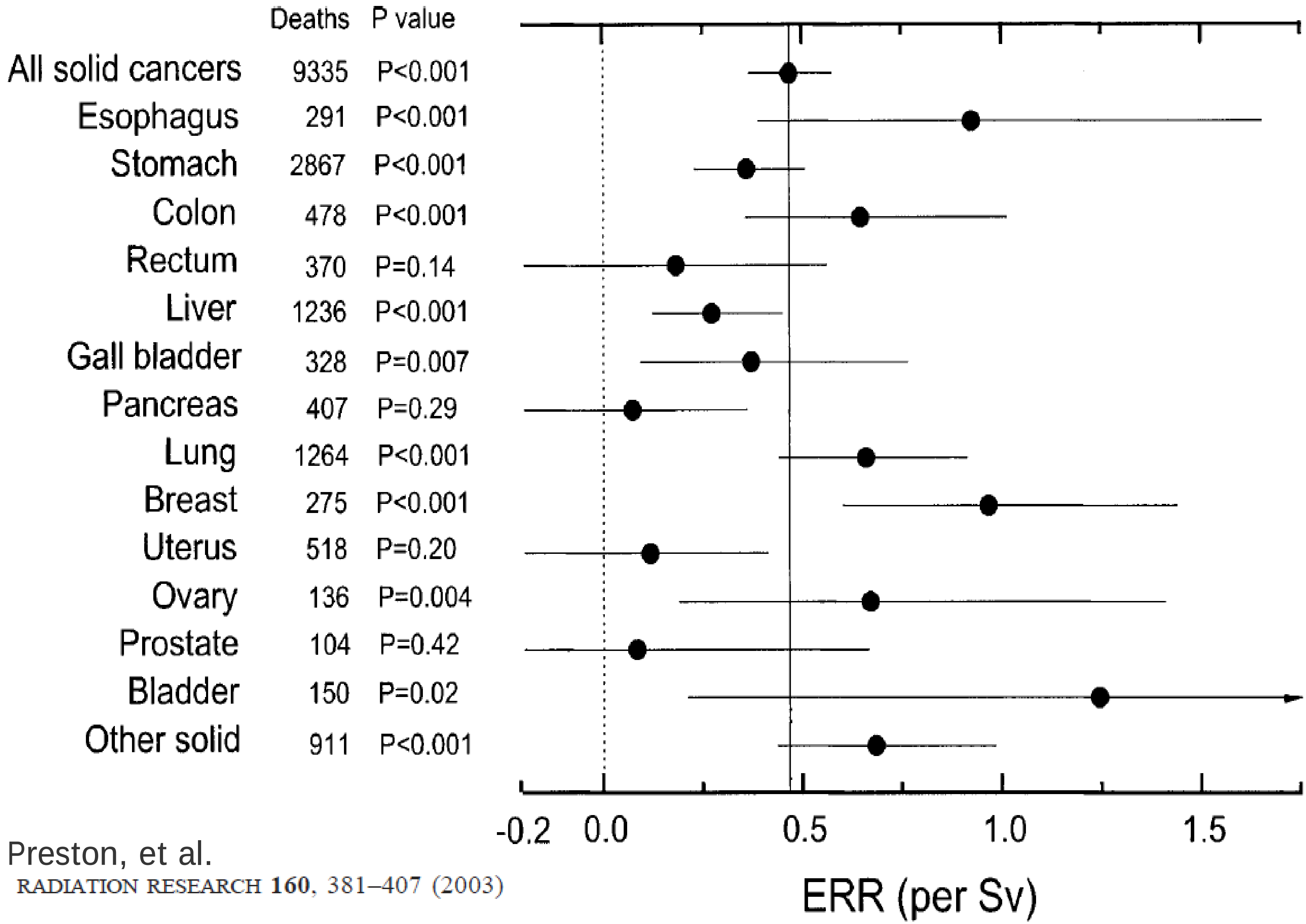
Radiation Carcinogenesis

- Radiation has been shown to be carcinogenic, especially at high doses and dose-rates.
- Reasonably good epidemiological basis for acute exposures above ~.2-5 Gy.
- Inversely correlated with age at exposure.
- Females generally more risk than Males.
- Min latent periods vary ~3 y leukemia, ~4 y bone, ~5 y thyroid, ~10 y solid.
- Mean latent periods of about 20-30 y.



ICRP-99,2006
Fitted models for trend tests:
Log-linear
Linear
Excess Relative Risk (90% Confidence Limits)
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
0
1
2
3
4
5
Neutron-Weighted Radiation Dose (Gy)


ICRP-99,2006
Relative Risk
1.5
1.4
1.3
1.2
1.1
1.0
0.0
0.1
0.2
0.3
0.4
0.5
Gamma Dose Equivalent
2.5
2.0
1.5
1.0
0.0
0.5
1.0
1.5
2.0



Preston, et al.
RADIATION RESEARCH **160**, 381–407 (2003)

ICRP-103 Tissue Weighting w_T

Table B.2. Tissue weighting factors, w_T, in the 2007 Recommendations.

Organ/Tissue	Number of tissues	w_T	Total Contribution
Lung, stomach, colon, bone marrow, breast, remainder	6	0.12	0.72
Gonads	1	0.08	0.08
Thyroid, oesophagus, bladder, liver	4	0.04	0.16
Bone surface, skin, brain, salivary glands	4	0.01	0.04

Remainder = adrenals, extrathoracic tissue (ET), gall bladder, heart, kidneys, lymphatic nodes, muscle, oral mucosa, pancreas, prostate (♂), small intestine (SI), spleen, thymus, uterus/cervix (♀).

Heritable Effects

- Animal data shows that radiation does cause genetic changes, but they are much less common than spontaneous mutations.
- Acute radiation at moderate doses results in a negligible adverse effect on subsequent generation.
- No direct evidence of human effects. If any, are submerged in the background and can’t be demonstrated.
- At 10 mGy, estimated Risk of heritable effects assumed to be only ~0.004-0.009% of baseline.

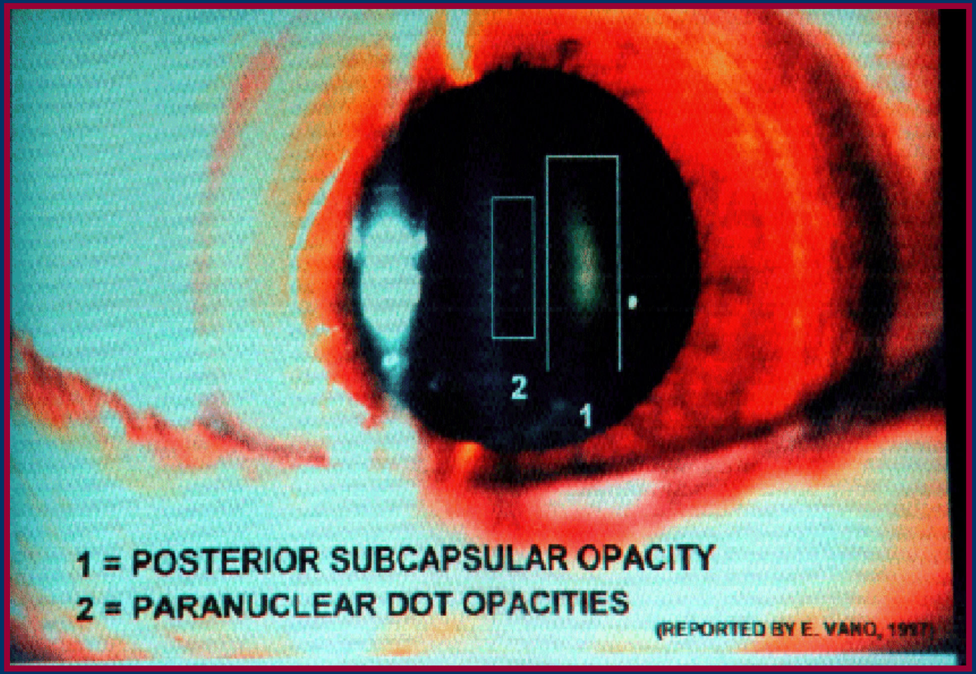
In Utero Radiation Risk

- Most Risk – 1st Trimester
- No Malformations <100 mGy
- No Malformations 100-1000 mGy 3rd Trimester
- Termination of pregnancy at <50 mGy is NOT justified based upon radiation risk
- Take care - especially during multiple pelvic CTs, long fluoro, or radiotherapy

Wagner, ICRP, IAEA, ACOG

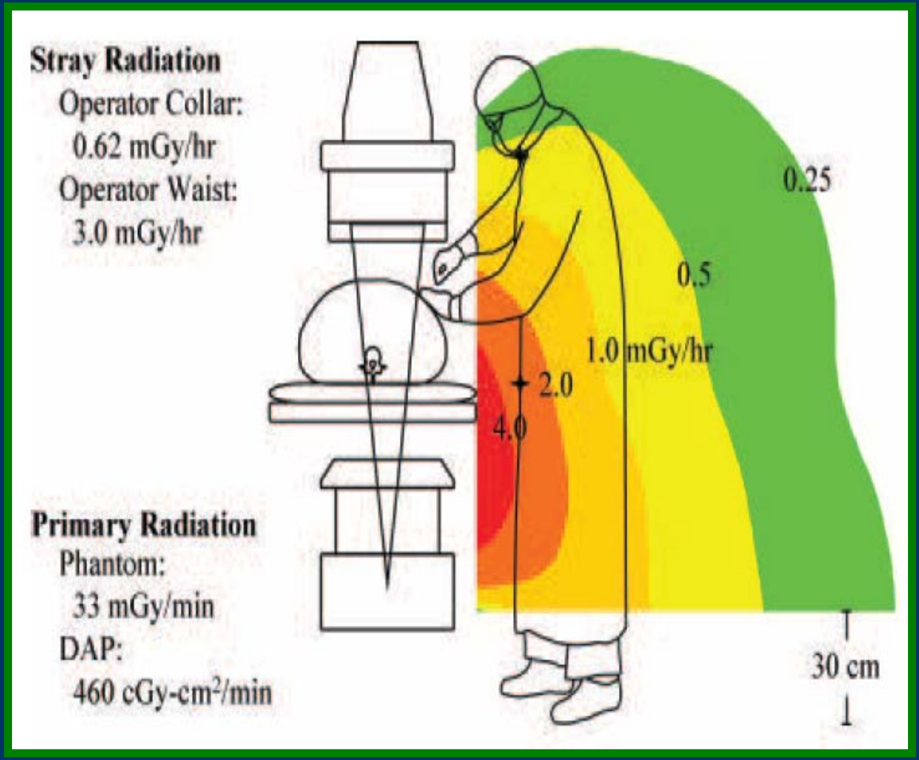
Most risk → Less → Least

Radiation Induced Cataracts



Interventional Radiologists

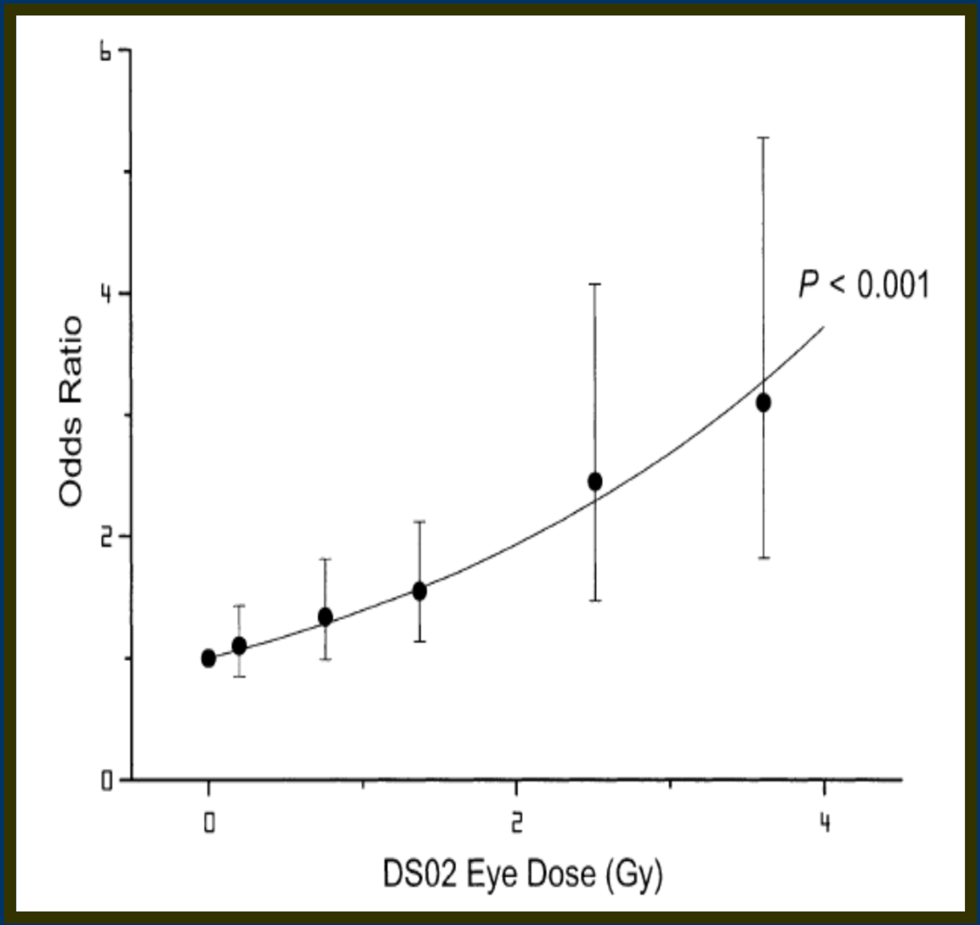
- Haskal & Worgul, RSNA News 2004:14
  - 8% (5/59) posterior subcapsular cataracts
  - 37% (22/59) small dot-like opacities (early sign of radiation damage)
  - 2% (1/59) had undergone cataract surgery in one eye
- IAEA RELID studies.



Schueller et al, Radiographics 2006

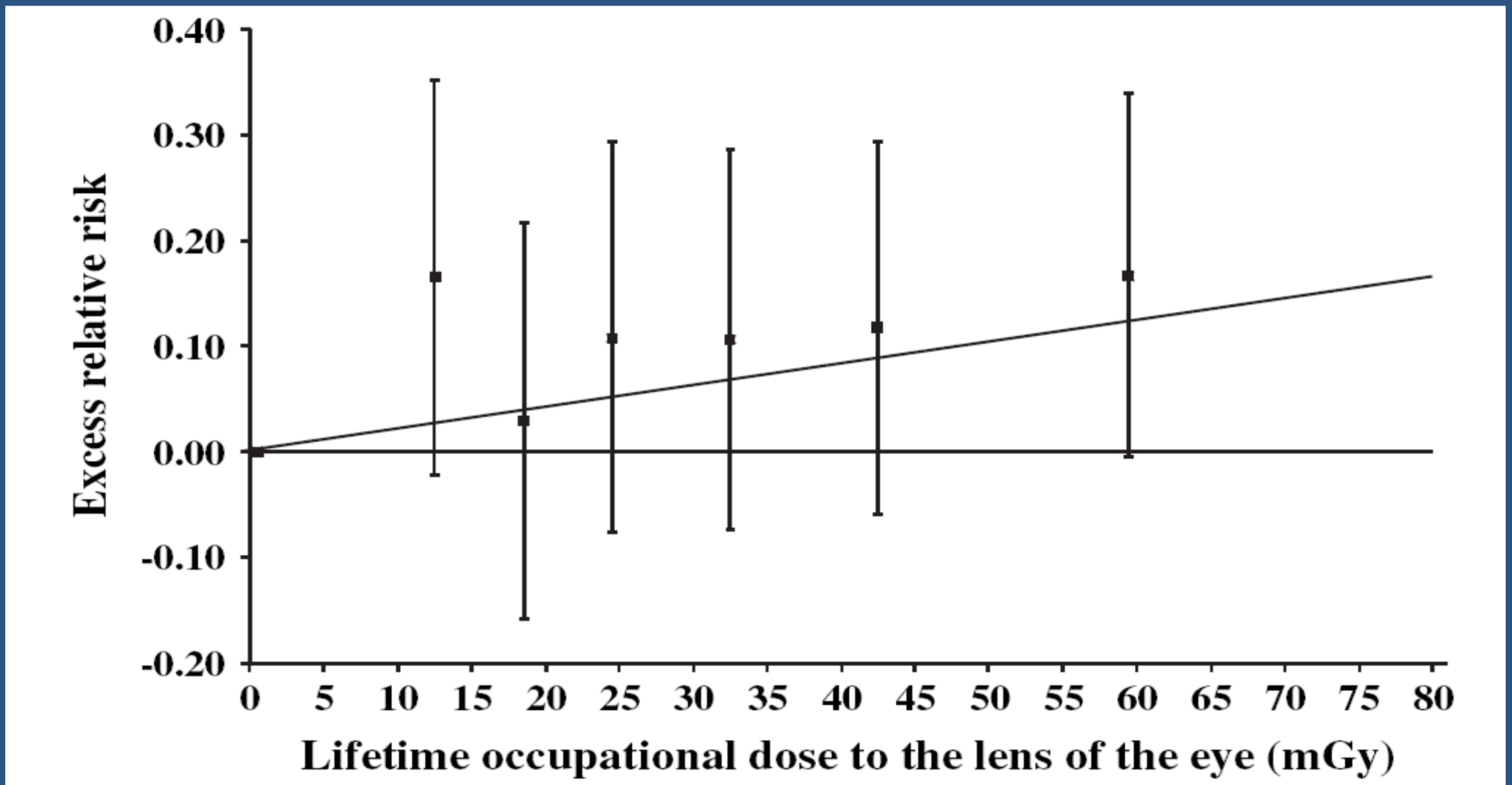
A-Bomb Survivors

- Neriishi et al, Rad Research 168:2007
- Minamoto et al, Int. J Rad Biol 80(5):2004
- Operative Cataract odds ratio of ~**1.4 at 1 Gy**
- Dose threshold seen at **0.1 Gy** (upper bound of 0.8 Gy).



US Radiologic Technologists Study

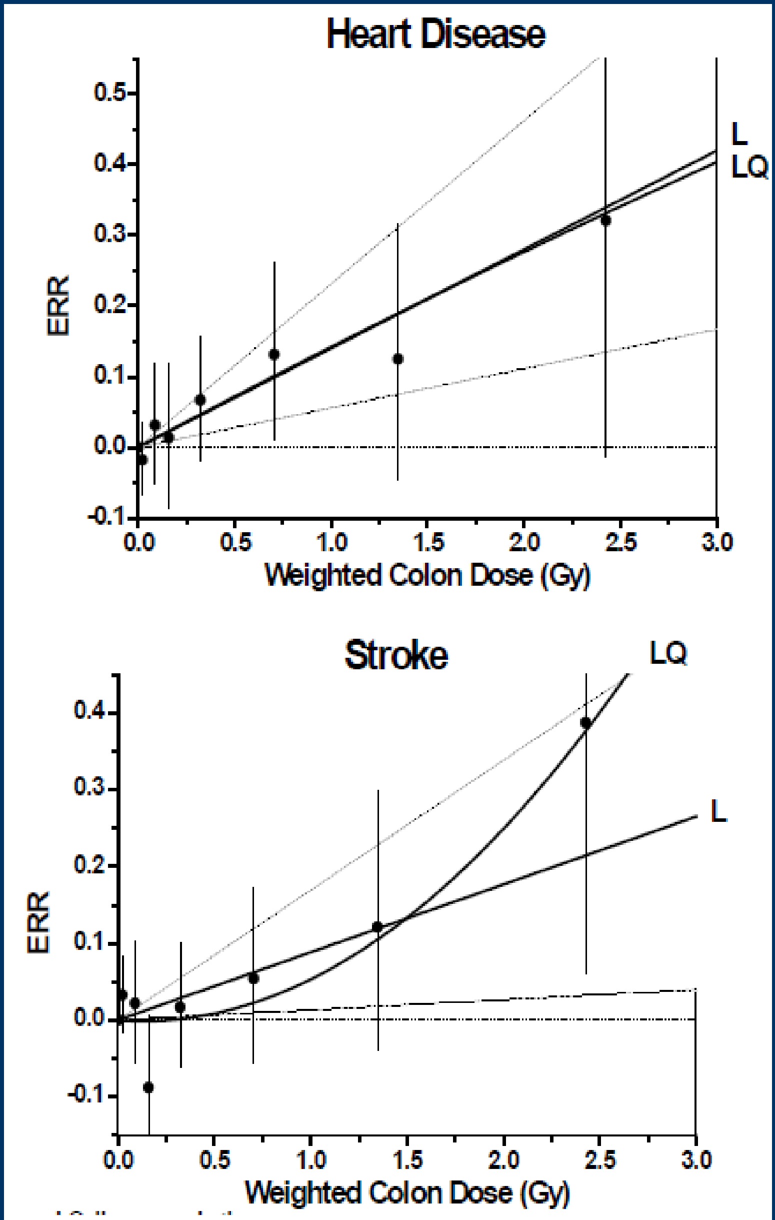
- Chodick et al, Am J Epidemiol 2008:168
  - 20 year prospective with 35,705 technologists
  - Linear Excess Relative Risk of **2.0 / Gy**



Cardiovascular Effects

Shimizu 2010

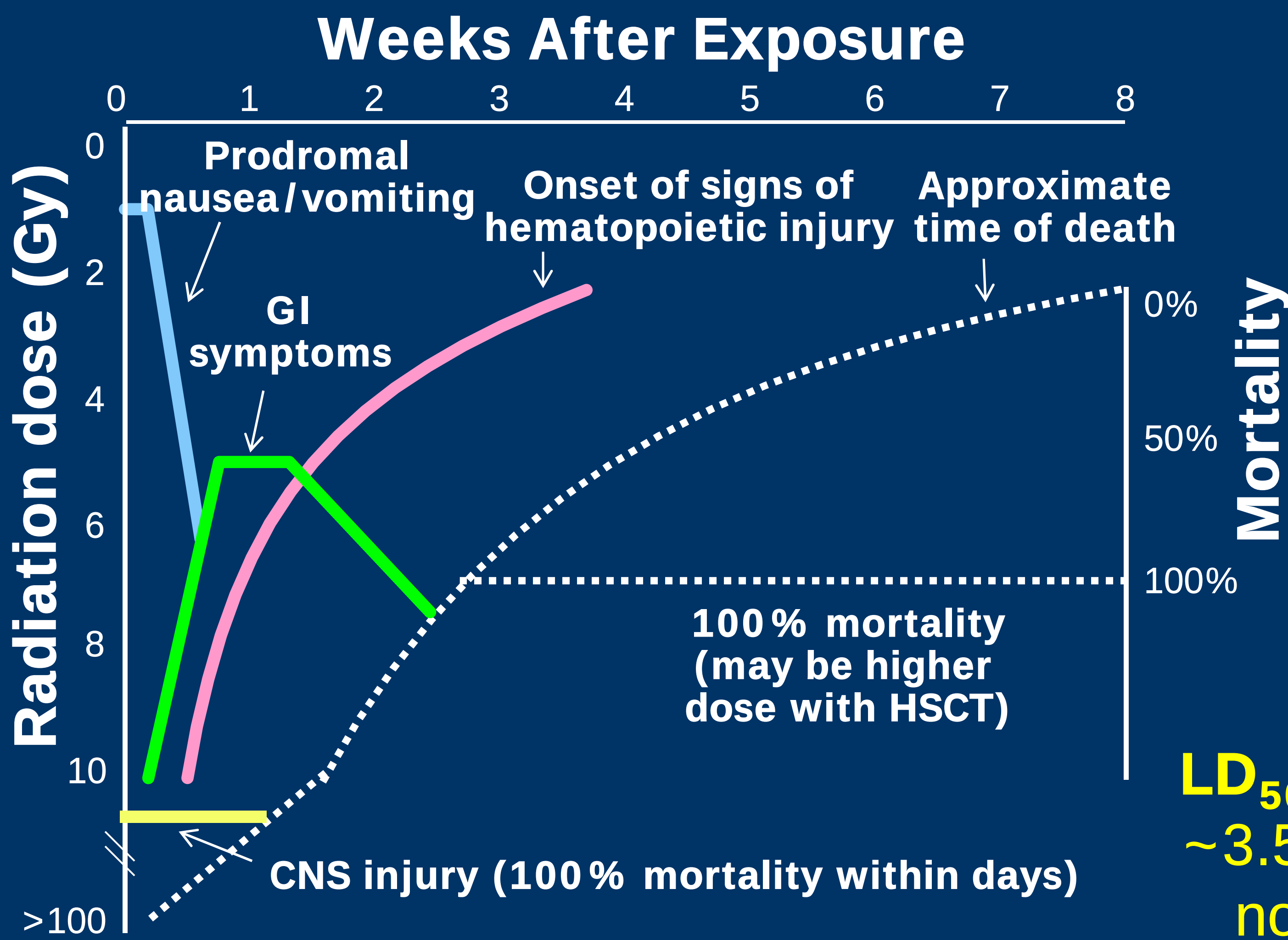
- LSS shows ERR 0.14/Gy for heart disease.
- LSS shows ERR 0.09/Gy for cerebrovascular.
- Radiotherapy patients given 1-2 Gy show risk 10-20 y later.
- Radiation induced heart disease – microvascular damage to myocardium leads to atherosclerosis.



ICRP 2011 Statement on Tissue Reactions

- Recent epidemiological evidence suggests some tissue reaction effects with lower thresholds than previously considered.
- Lens of eye threshold is now considered to be 0.5 Gy. (therefore limit to 20 mSv/y averaged over 5 y, no single year > 50 mSv.
- Circulatory disease threshold is now considered to be 0.5 Gy to heart or brain.

Acute Radiation Syndrome



$LD_{50/60}$

~3.5-4 Gy no care

~4.5-7 Gy with care

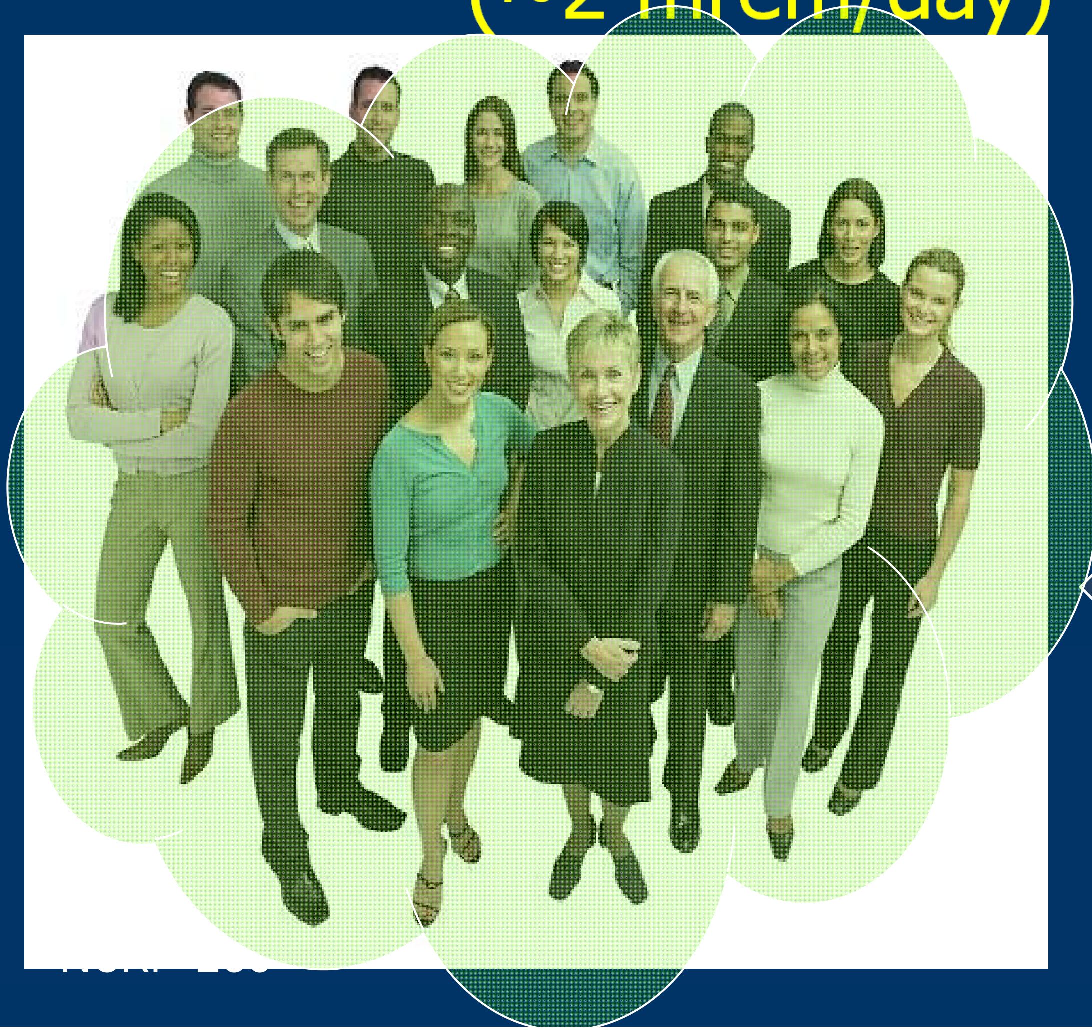
Tissue and Organ Sensitivities

No Functional Impairment	**<100 mGy**
Temporary Sterilization (Men)	**150 mGy**
Temporary blood count change	**250 mGy**
Cataract or Cardiovascular	**~500 mGy**
Permanent Sterilization (Women)	**2500 mGy**
Skin Erythema (reddening)	**>2000-3000 mGy**

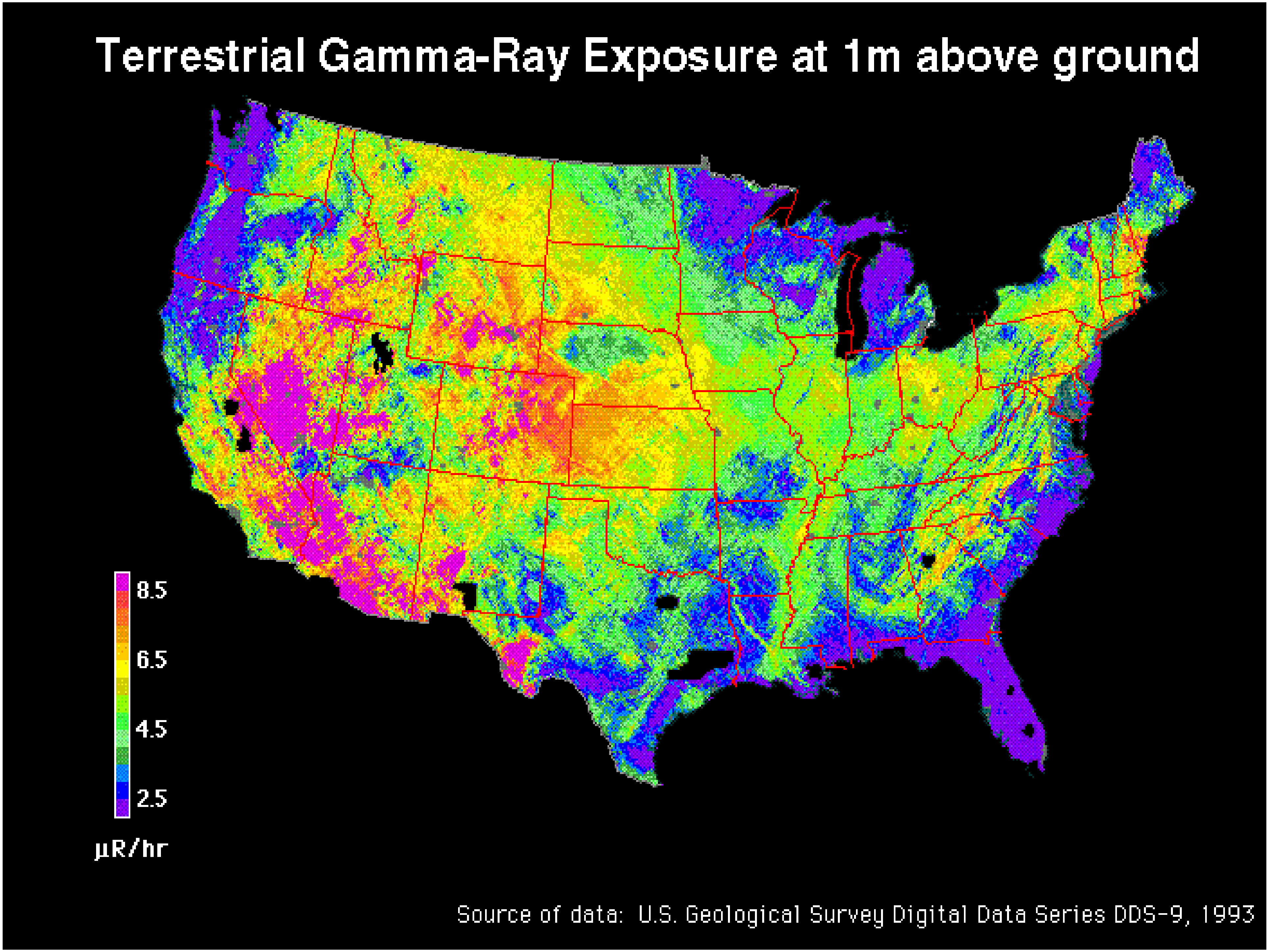
Low Dose Effects

Background Radiation in U.S.

~6.3 mSv/yr
~0.02 mSv/day
(~2 mrem/day)

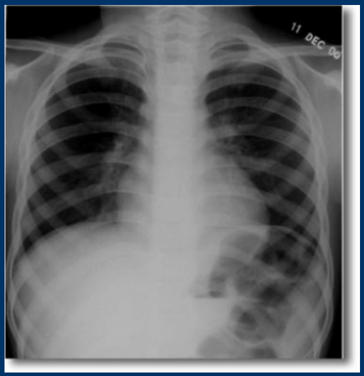


- Medical 3.2
- Radon 2.0
- Cosmic 0.3
- Earth 0.3
- Internal 0.4
- Cons Prod 0.1
- Occup 0.002



Terrestrial Gamma-Ray Exposure at 1m above ground
8.5
6.5
4.5
2.5
µR/hr
Source of data: U.S. Geological Survey Digital Data Series DDS-9, 1993

Typical Radiation Doses - General Radiology



Examination	Effective Dose mSv
Dental	0.05 (0.02-0.09)
Chest	0.1 (0.02-0.81)
Head	0.1 (0.1-0.22)
Mammography	0.7 (1-3 gland)
Abdomen/Pelvis	1.2 (0.7-1.2)

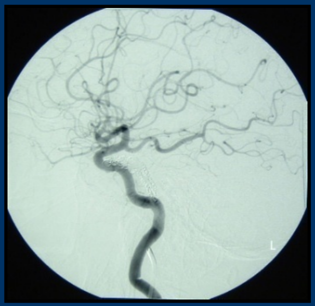
Typical Radiation Doses - Computed Tomography

Examination	Effective Dose mSv
PET Attenuation (CT Only)	0.72
Head	2 (0.8-5)
Chest	7 (4.6-20.5)
Abdomen or Pelvis	10 (6-27.4)
CT Angiography	13 (4.6-15.8)

Typical Radiation Doses - Nuclear Medicine

Examination	Effective Dose mSv
F-18 FDG 15mCi (Nuclear Med only)	9
I-131 MIBG 1mCi	7.5
Tc-99m pertech.	5
Tc-99m stress	6
I-131 therapy	270

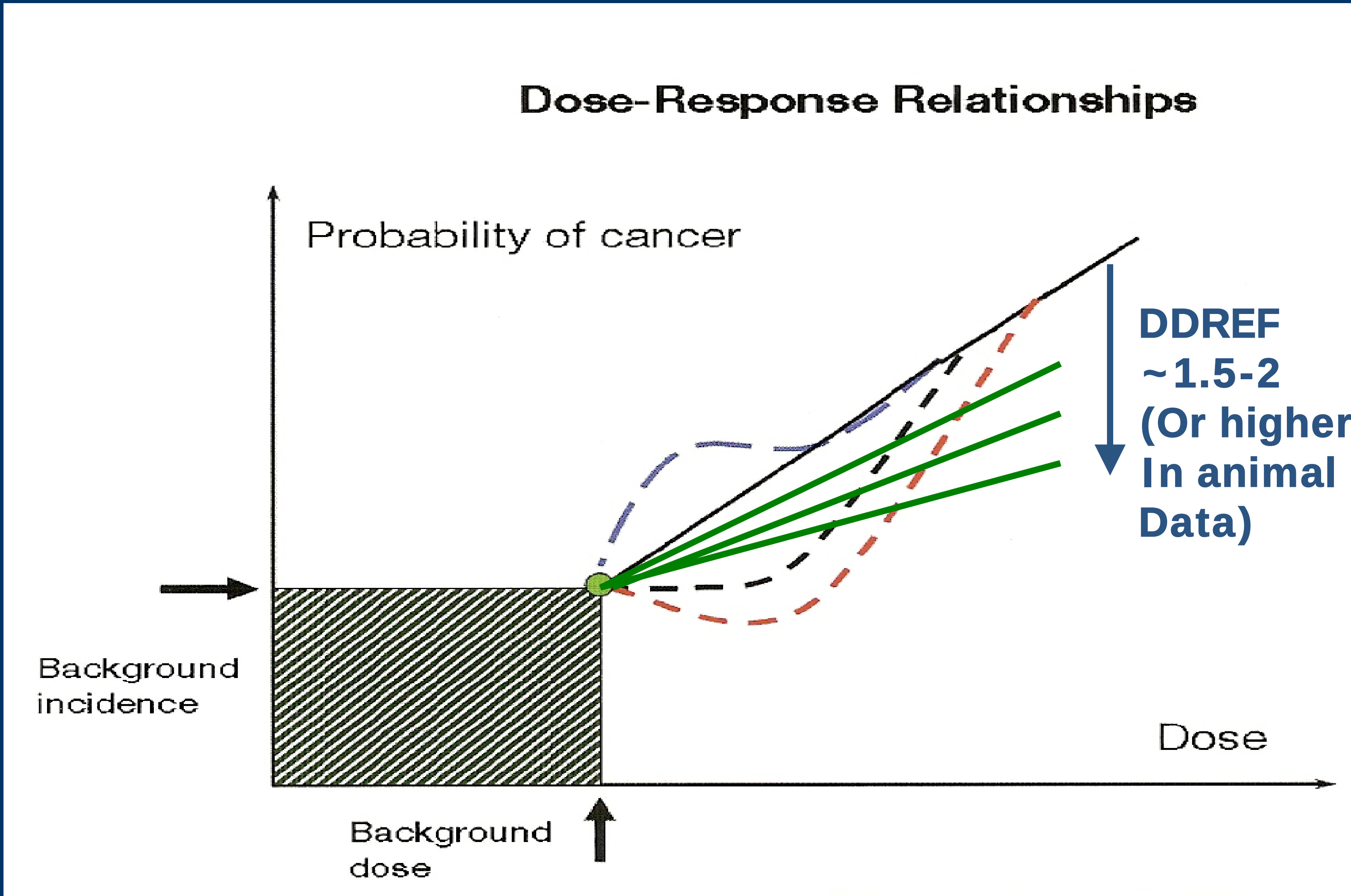
Typical Radiation Doses
Fluoroscopy Entrance Skin Dose



Dauer, Thornton, JVIR 2009

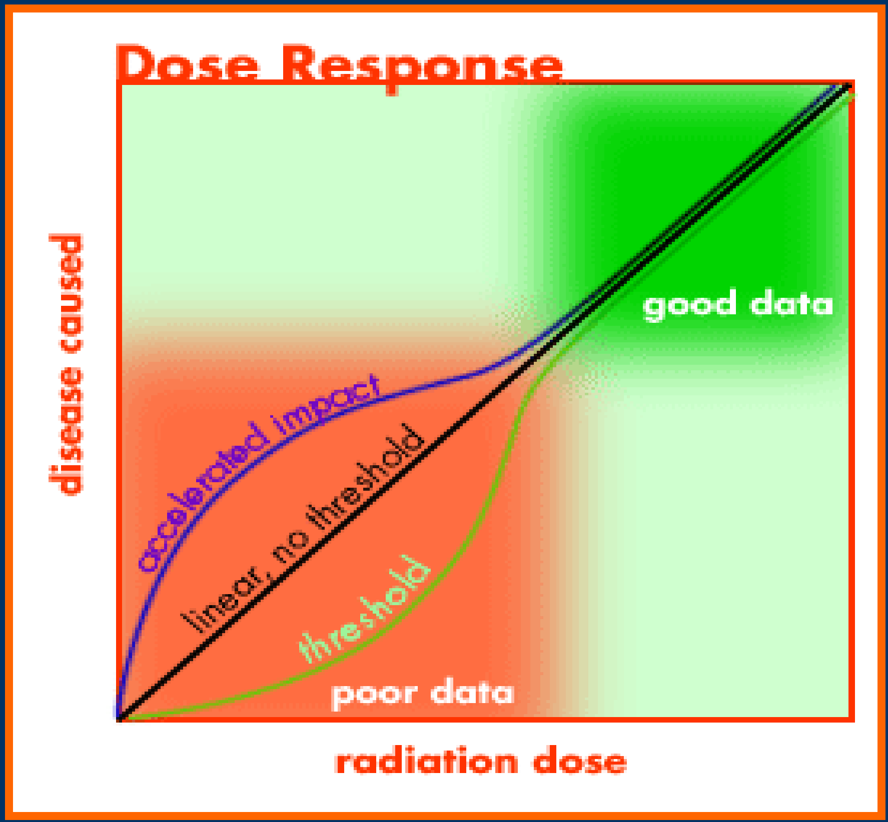
Examination	Skin Dose mGy
Hepatic Embolization	2000 (1251-9500)
Arterial Embolization	3000 (1761-8073) E~60 mSv
Biliary Drainage	660 (401-3569)
IVC Filter	260 (162-2686)
Mediport – Chest	12 (8-620)

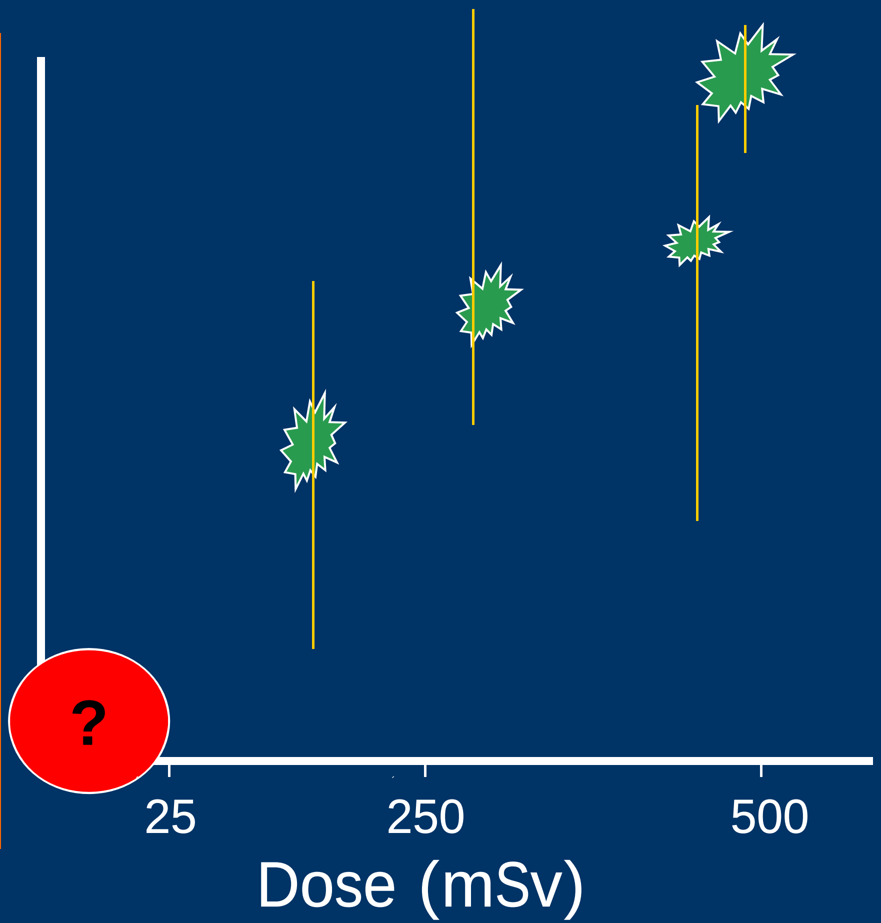
Low Dose Effects ?



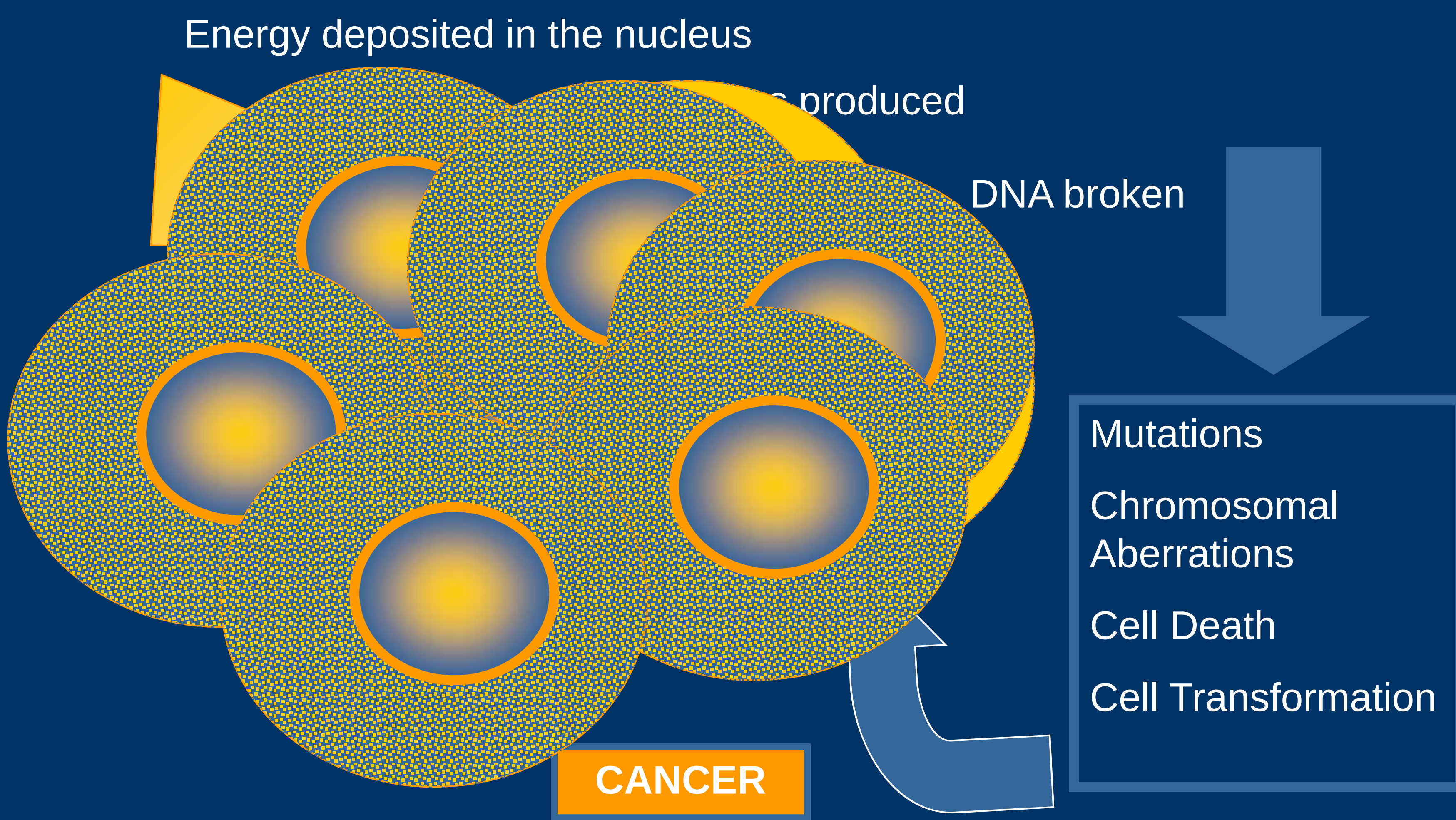
Can We Predict Effects at Low Doses?

While moderate/high doses cause well-documented effects, we cannot measure significant effects at the doses where typical diagnostic or regulated doses occur.



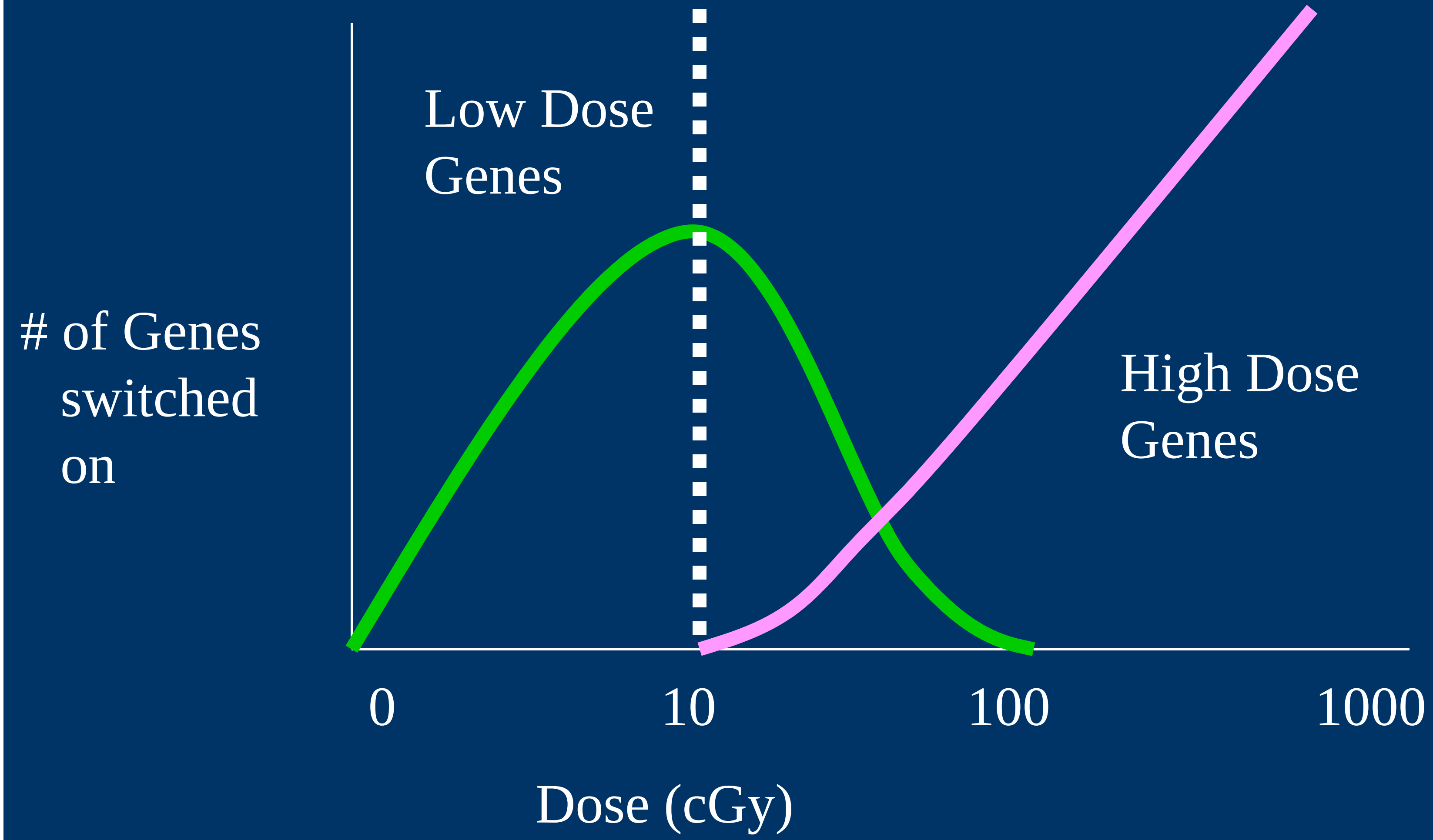


Classic Paradigm: Target Theory



Non-Linear Radiation-induced Changes in Gene Expression Shown by Microarrays

Wyrobek Radiat. Res.164, 369–382 (2005).



Expanded Paradigm

GENETIC SENSITIVITY

Energy deposited in the nucleus OR cytoplasm

Ionizations produced

DNA may be broken, or other molecules may be damaged

Epigenetic factors

Adaptive Response

DNA Damage

Genomic Instability

CANCER

Other Proteins

PCNA, RPA and APE

TISSUE RESPONSE

Oxidative Status

Up regulation of antioxidant enzymes

Inhibition of superoxide anions

???

Bystander

Modifies GENE AND PROTEIN EXPRESSION

Triggers biological processes

SIGNALING

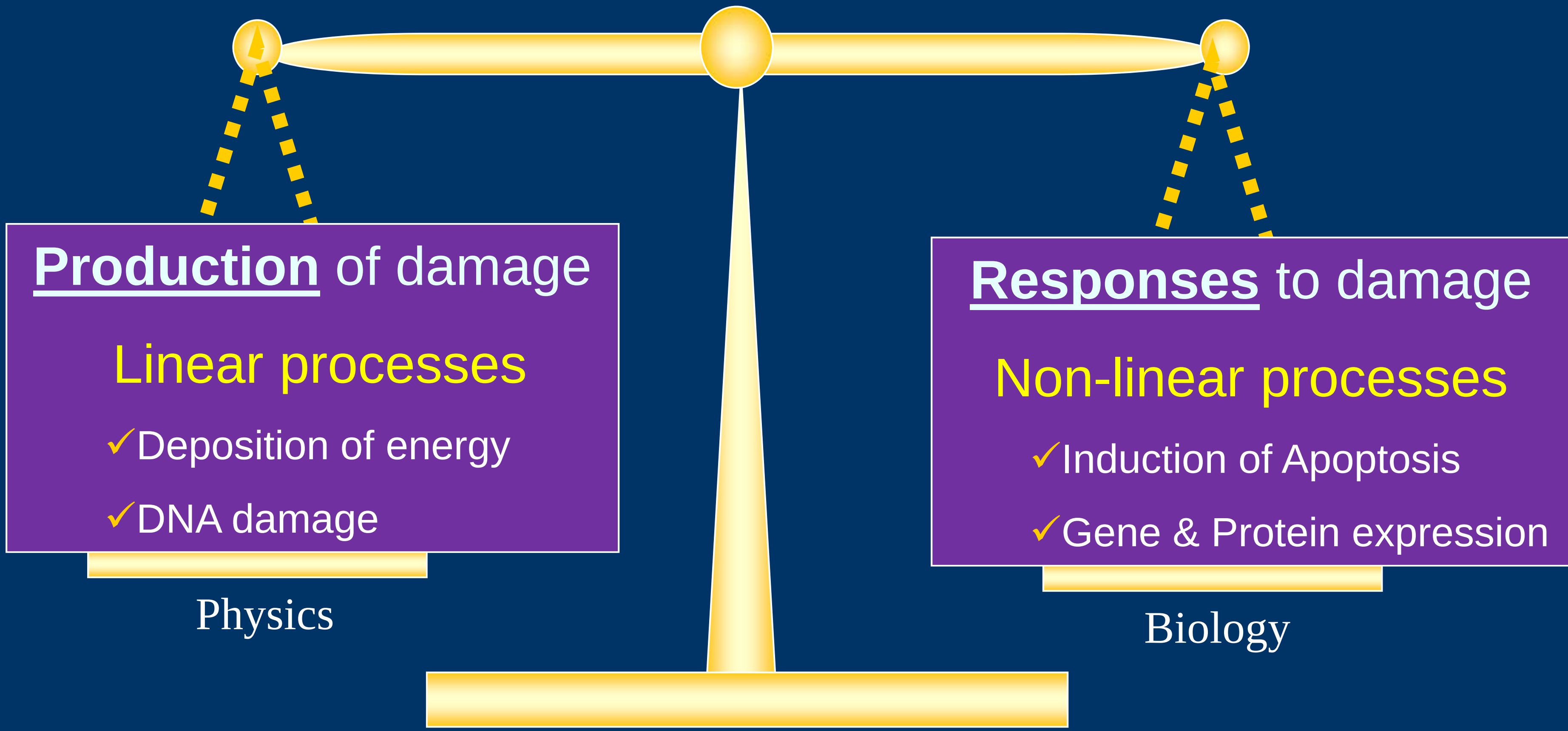
Direct Cell-cell

Indirect –secreted or shed

Signaling molecules

$^{++}$Ca DNA-PKc's TGF-B

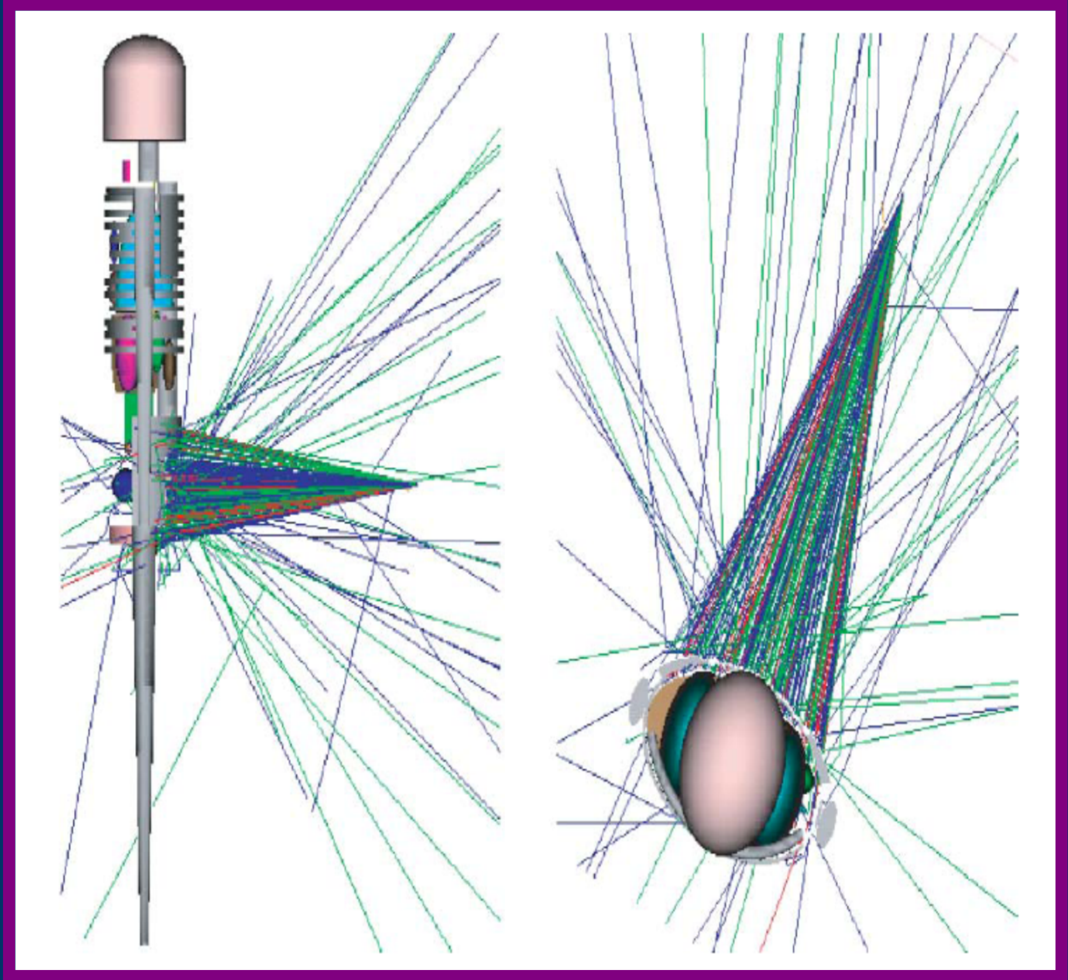
Expanded Paradigm:



From Effects to Risk

Risk Evaluations

- Monte-Carlo transport and energy deposition
- J/kg
- Equivalent Dose
- Age-Adjusted
- Gender-Adjusted
- Organ risk factors



Internal Radionuclide Radiation Dosimetry
MIRD Formalism
(Medical Internal Radionuclide Dosimetry)

Absorbed fractions and S factors from reference anatomic phantoms

Energy Emitted per Decay
Equilibrium Dose Constant

Fraction of energy emitted in Source Region r_h absorbed in Target Region r_k
Absorbed Fraction

Number of decays in Source Region r_h
Cumulated Activity

$$D\,(r_k \leftarrow r_h) = \frac{\tilde{A}_h \sum_i \Delta_i\, \phi_i(r_k \leftarrow r_h)}{M_k}$$

$$S\,(r_k \leftarrow r_h)$$

Absorbed Dose from Source Region r_h to Target Region r_k

Mass of Target Region r_k

Effective Dose

$$E = \sum_T w_T H_T = \sum_T w_T \sum_R w_R D_{T,R}$$

Tissue	w_T	$\sum w_T$
Bone-marrow (red), Colon, Lung, Stomach, Breast, Remainder tissues*	0.12	0.72
Gonads	0.08	0.08
Bladder, Oesophagus, Liver, Thyroid	0.04	0.16
Bone surface, Brain, Salivary glands, Skin	0.01	0.04
	Total	1.00

* Remainder tissues: Adrenals, Extrathoracic (ET) region, Gall bladder, Heart, Kidneys, Lymphatic nodes, Muscle, Oral mucosa, Pancreas, Prostate (♂), Small intestine, Spleen, Thymus, Uterus/cervix (♀).

ICRP-103 (2007)

Low Dose - Linear Risk Assumption (% per Sv)

ICRP-103 for cancer and heredity effects

Exposed Population	Cancer	Heredity Effects	Total
Whole	**5.5**	0.2	5.7
Adult	4.1	0.1	4.2

A statistically significant increase in cancer has not been detected in populations exposed as adults to doses of less than ~0.2 Sv.

No hereditary effects in atomic bomb survivor offspring.

ICRP-103 on Individual Risks

"it remains the policy of the Commission that its recommended nominal risk coefficients should be applied to whole populations and not to individuals...[and] believes that this policy provides for a general system of protection that is simple and sufficiently robust" (p.55)

HEALTH PHYSICS SOCIETY

RADIATION RISK IN PERSPECTIVE

POSITION STATEMENT OF THE HEALTH PHYSICS SOCIETY*

Adopted: January 1996
Reaffirmed: March 2001
Revised: August 2004

If dose is < 100 mSv …Take Care When Attempting to Assign Quantitative Risk to Individuals

Radiogenic Health Effects Have Not Been Consistently Demonstrated Below 10 Rem

Radiogenic health effects (primarily cancer) have been demonstrated in humans through epidemiological studies only at doses exceeding 5–10 rem delivered at high dose rates. Below this dose, estimation of adverse health effect remains speculative. Risk estimates that are used to predict health effects in exposed individuals or populations are based on epidemiological studies of well-defined populations (for example, the Japanese survivors of the atomic bombings in 1945 and medical patients) exposed to relatively high doses delivered at high dose rates. Epidemiological studies have not demonstrated adverse health effects in individuals exposed to small doses (less than 10 rem) delivered in a period of many years.

Limit Quantitative Risk Assessment to Doses at or Above 5 Rem per Year or 10 Rem Lifetime

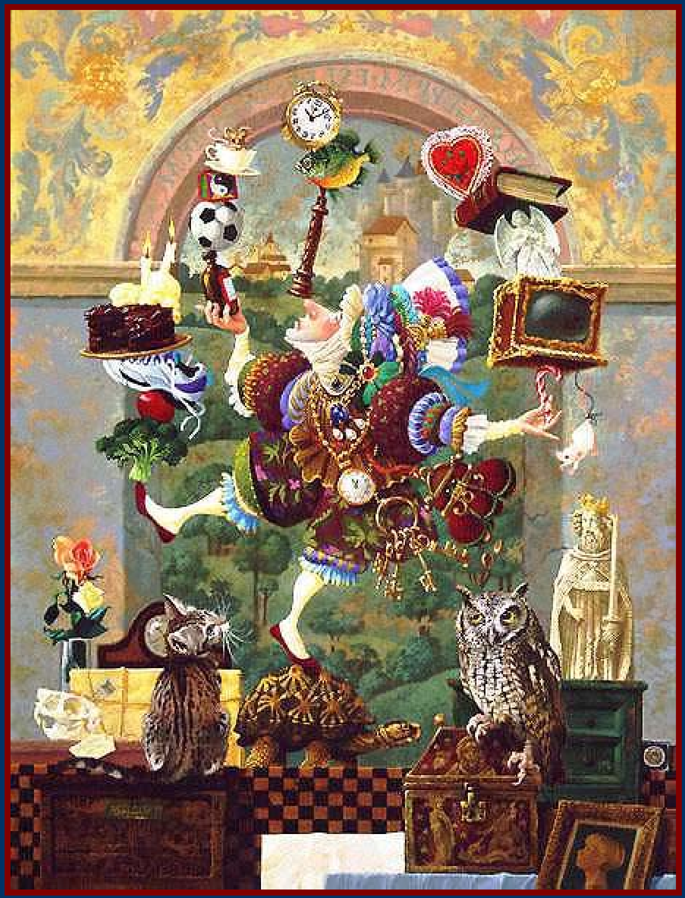
In view of the above, the Society has concluded that estimates of risk should be limited to individuals receiving a dose of 5 rem in one year or a lifetime dose of 10 rem in addition to natural background. In making risk estimates, specific organ doses and age-adjusted and gender-adjusted organ risk factors should be used. Below these doses, risk estimates should not be used. Expressions of risk should only be qualitative, that is, a range based on the uncertainties in estimating risk (NCRP 1997) emphasizing the inability to detect any increased health detriment (that is, zero health effects is a probable outcome).

AAPM Position Statement PP-25A

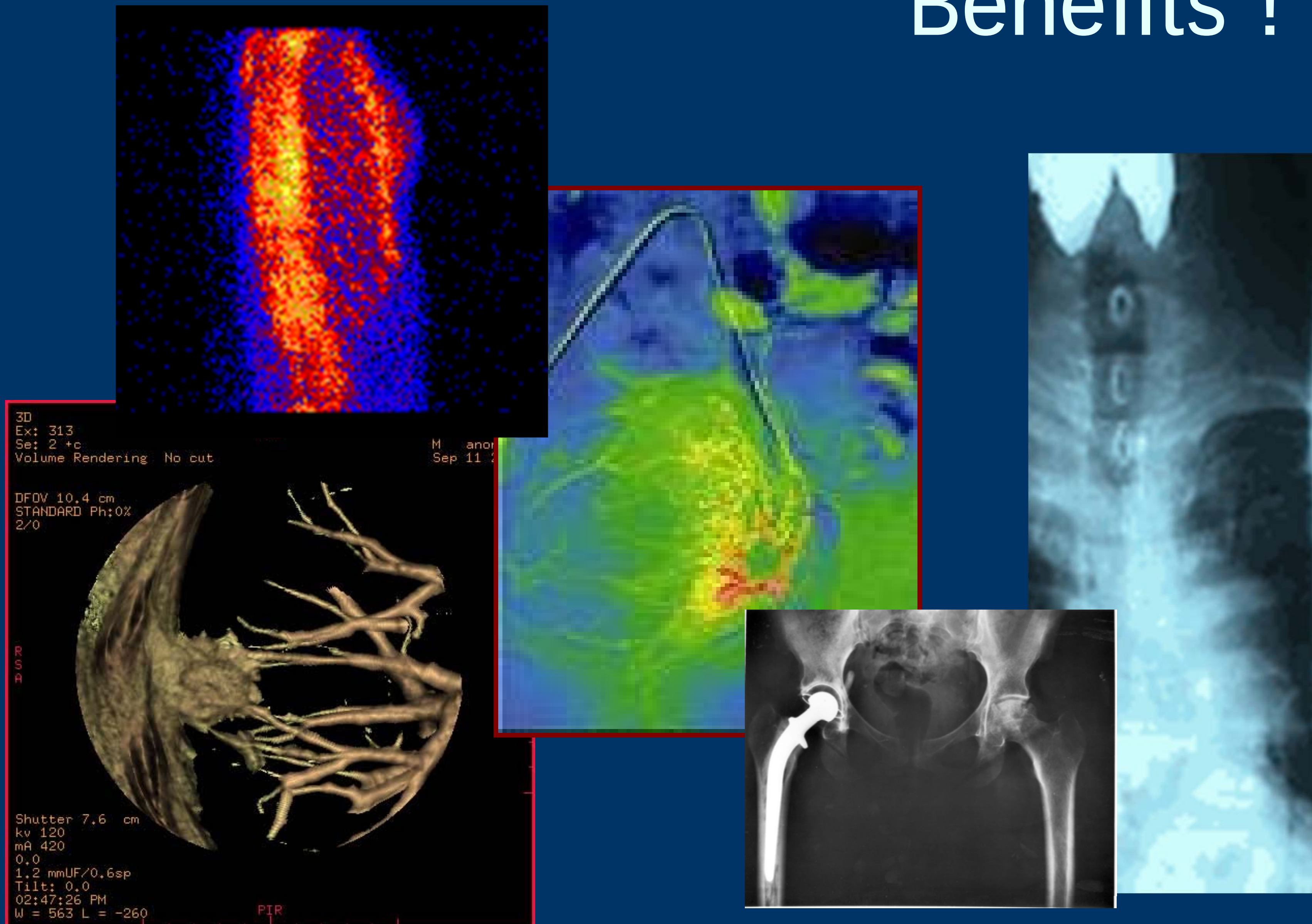
- Justify and Optimize procedures.
- Discuss Benefit & Risk with patients.
- Risks at E< 50 mSv for single procedures or E<100 mSv for multiple procedures over short time periods are too low to be detectable and may be nonexistent.
- Predictions of risks at such low doses are highly speculative and should be discouraged.
- Such predictions are harmful.

Principles of Radiation Safety

- Justification
  - Benefit greater than risk
- Optimization
  - Benefit AHARA
  - Risk ALARA
- Limitation
  - Occupational doses based on risk of safe industries



Benefits !


3D
Ex: 313
Se: 2 +c
Volume Rendering No cut
DFOV 10.4 cm
STANDARD Ph:0%
2/0
R
S
A
Shutter 7.6 cm
kv 120
mA 420
0.0
1.2 mmUF/0.6sp
Tilt: 0.0
02:47:26 PM
W = 563 L = -260
PIR

Research Challenges

Some Questions Still Need Answers...

- Molecular markers of DNA damage at low doses?
- DNA repair fidelity and capacity for double and multiple strand breaks at low doses?
- Adaptation, hypersensitivity, bystander effects, hormesis, and genomic instability for radiation carcinogenesis?
- How to best communicate risk with patients?
- Benefits?

Research Challenges
What Data are still Needed?

- Prospective cohort and nested case-control studies of moderate-dose medical exposures.
- Epidemiological study consortia for medically exposed populations (CTs, Pediatrics, IR).
- Occupational low-dose studies.
- Exposed Population studies.
- Current Policies justified and optimized themselves?

References For Additional Info

- Hall E, Giaccia A. Radiobiology for the Radiologist, 7th Ed. Wolters Kluwer, 2012.
- Mettler F, Upton A. Medical Effects of Ionizing Radiation, 3rd Ed. Saunders, 2008.
- BEIR. Health Risks from Exposure to Low Levels of Ionizing Radiation: BEIR VII. NAS, 2006.
- UNSCEAR. Effects of ionizing radiation, 2006.
- ICRP-103, 2007 Recommendations and Associated Annex on Biology and Epidemiology.
- Dauer LT, et al. Evaluation of updated research on the health effects and risks associated with low dose ionizing radiation. *Rad Prot Dos* 2010;140(2):103-136.
- U.S. EPA Radiogenic Cancer Risk Models and Projections for the U.S. Population, 2011.

Which of the following tissues does the ICRP currently give the highest weighting factors?

0%	1.	Gonads
0%	2.	Bone surface, skin, brain, salivary
0%	3.	Thyroid, esophagus, bladder, liver
0%	4.	Lung, stomach, colon, marrow, breast
0%	5.	Skin

10

Countdown

Which of the following tissues does the ICRP currently give the highest weighting factors?

1. Gonads
2. Bone surface, skin, brain, salivary
3. Thyroid, esophagus, bladder, liver
4. Lung, stomach, colon, marrow, breast
5. Skin

Ref: "The 2007 Recommendations of the International Commission on Radiological Protection, ICRP Publication 103". Annals of the ICRP 37(2), p. 65.

Which of the following can be concluded from the human heritable effects studies?

0%	1.	They are clearly larger than in animals
0%	2.	No clear evidence in humans
0%	3.	It is the most significant effect on kids
0%	4.	Higher than spontaneous mutations
0%	5.	Heritable radiation effects are additive.

10

Countdown

Which of the following can be concluded from the human heritable effects studies?

1. They are clearly larger than in animals
2. No clear evidence in humans
3. It is the most significant effect on kids
4. Higher than spontaneous mutations
5. Heritable radiation effects are additive.

Ref: “The 2007 Recommendations of the International Commission on Radiological Protection, ICRP Publication 103”. Annals of the ICRP 37(2), p. 54.

ICRP considers the dose threshold for the lens of the eye and circulatory disease to now be?

0%	1.	5 Gy
0%	2.	5 mGy
0%	3.	500 mGy
0%	4.	100 mGy
0%	5.	1 Gy

10

Countdown

ICRP considers the dose threshold for the lens of the eye and circulatory disease to now be?

1. 5 Gy
2. 5 mGy
3. 500 mGy
4. 100 mGy
5. 1 Gy

Ref: "Statement on Tissue Reactions", International Commission on Radiological Protection, April 21, 2011, p. 1-2.

What ratio does the ICRP utilize when assessing low dose radiogenic cancer risks to the whole population?

0%	1.	10% / Sv
0%	2.	1% / Sv
0%	3.	0.55% / Sv
0%	4.	0.25% / Sv
0%	5.	5.5% / Sv

10

Countdown

What ratio does the ICRP utilize when assessing low dose radiogenic cancer risks to the whole population?

1. 10% / Sv
2. 1% / Sv
3. 0.55% / Sv
4. 0.25% / Sv
5. 5.5% / Sv

Ref: "The 2007 Recommendations of the International Commission on Radiological Protection, ICRP Publication 103". Annals of the ICRP 37(2), p. 53.

What is AAPM's position on predicting hypothetical cancer in patients exposed to < 50 mSv for single procedure?

0%	1.	It should be discouraged, and is harmful.
0%	2.	It is essentially predictable.
0%	3.	It will lead to improved medicine.
0%	4.	It should only be performed by epidemiology.
0%	5.	It is only relevant when combined w surgery.

10

Countdown

What is AAPM's position on predicting hypothetical cancer in patients exposed to < 50 mSv for single procedure?

1. It should be discouraged, and is harmful.
2. It is essentially predictable.
3. It will lead to improved medicine.
4. It should only be performed by epidemiology.
5. It is only relevant when combined w surgery.

Ref: "AAPM Position Statement on Radiation Risks from Medical Imaging Procedures" PP 25-A, December 13, 2011.

The $LD_{50/60}$ for acute exposure without care is?

0%	1.	1-2 Gy
0%	2.	3.5-4 Gy
0%	3.	5-10 Gy
0%	4.	10-20 Gy
0%	5.	10-20 mGy

10
Countdown

The $LD_{50/60}$ for acute exposure without care is?

1. 1-2 Gy
2. 3.5-4 Gy
3. 5-10 Gy
4. 10-20 Gy
5. 10-20 mGy

Ref: "Medical Effects of Ionizing Radiation, 3rd ed." Mettler and Upton, 2008, p. 354.

Memorial Sloan-Kettering Cancer Center

The Best Cancer Care. Anywhere.

Lawrence T. Dauer, PhD, CHP
Assistant Attending Health Physicist
Departments of Medical Physics & Radiology
dauerl@mskcc.org

ICRP INTERNATIONAL COMMISSION ON RADIOLOGICAL PROTECTION

HPS Health Physics Society
Specialists in Radiation Safety • Founded 1956 • http://hps.org

American Association of Physicists in Medicine

NCRP National Council on Radiation Protection & Measurements

RSNA Promoting and developing the highest standards of radiology and related sciences through education and research

image gently[SM] The Alliance for Radiation Safety in Pediatric Imaging

Society of Interventional Radiology
Enhanced care through advanced technology

EPRI Electric Power Research Institute