Linear Non Threshold for Radiation Health Effects

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Objectives

- To review fundamental concepts of ionizing radiation
- To review the basic tenets of radiation biology and health effects
- To describe current radiation risk models
- To describe the attributes of the Linear Non Threshold (LNT) Model
 - What does biology say about LNT
 - Cell death curve characteristics
 - Dose Rate influences
 - Effects of promoters/inhibitors (Synergistic Effects)

What is Radiation?

Radiation = energy in transit

... The transfer of energy by waves or particles

 lonizing radiation has sufficient energy to produce energetic ions in ordinary matter

..."dose" is caused by the absorption of the kinetic energy of these charged particles

Alpha and Beta particles, Gamma- & X-rays, Neutrons

 Non-ionizing radiation does not produce energetic ions

Radio, Microwave, UV, IR, Visible



Penetration of Radiation in Tissue



LET and RBE

- Linear Energy Transfer LET
 - Rate of energy dissipation per unit track length of radiation passing through matter
 - Generalized as low or high LET dependent on type of radiation
 - Low-LET radiations ("sparsely ionizing") gamma, x-ray
 - High-LET radiations ("densely ionizing") alpha, neutron
- Related to radiation "quality" and biological effect
- Relative Biological Effectiveness RBE
 - Customarily based on 250 keV x-rays as the reference radiation
 - RBE is the ratio of the dose of x-rays to that of some other radiation required to produce the same biological effect (in vitro lab results)
 - RBE evolved to become *Radiation Weighting Factors* assigned by ICRP
 specifically applicable to biological effect of interest in radiation
 protection work cancer risk for low-dose exposures

Quantifying/Measuring Dose and Risk

- The radiation weighting factor is used to convert the absorbed dose (energy absorbed per unit mass) from radiations of differing quality into a unit that expresses the exposure normalized to risk – equivalent dose.
- Radiation weighting factor is denoted by W_{R} .
- Absorbed dose (D) is related to equivalent dose (H) through the formula:

$H = D W_R$

The unit of absorbed dose is the gray (Gy)

The unit of equivalent dose is the sievert (Sv)

Thus, $Sv = Gy \times W_R$ (rem = rad $\times W_R$)

Ionizing Radiation Units

Old Units	<u>SI Units</u>	What It Is	
roentgen	C kg-1	Unit of exposure	
1 C kg⁻¹	= 3876 R	Measure of radiatio ability to ionize air (limited to some x-ra gamma rays)	ays or
rad 1 Gy =	Gray 100 rad	Unit of absorbed do Measure of the absorption of all typ radiation in matter	ose X-ray Penetrate Absorbed
rem	Sievert	Unit of dose equiva	alent
1 Sv =	100 rem	Measure of biologic effect from different to and quantities of radiation; multiply the absorbed dose by modifying factors	cal types the

Quantifying/Measuring Dose and Effects

• Exposure (X): Generically, exposure is the condition of being exposed. Exposure is also used to quantify the amount of <u>ionization produced by</u> <u>photons</u> as they pass <u>through air</u>. The unit of exposure in the U.S. is the Roentgen (R). The S.I. unit is C/kg.

1R = 2.58x10-4 C/kg or 1esu/cc (in dry air at STP)

- Absorbed Dose (D): Absorbed dose is the amount of energy deposited in <u>any material</u> by ionizing radiation. The unit of absorbed dose used in the U.S., the rad, is a measure of energy absorbed per gram of material. The S.I. unit is the Gray (Gy). One Gray equals 100 rad.
- Equivalent Dose (H): Equivalent dose is a special concept relating absorbed dose to <u>biological detriment</u>. In the U.S. the unit is the rem. The S.I. unit is the Sievert (Sv). One Sievert equals 100 rem.

Direct Action: critical structures are the targets.



http://jolisfukyu.tokai-sc.jaea.go.jp/fukyu/mirai-en/2008/6_5.html

Indirect Action: water and other noncritical molecules are the targets.

Radiation ionizes H₂O molecule leading to hydrolysis and the creation of very reactive radicals.



Water Hydrolysis

• Radiation ionizes a water molecule

$$H_2O \rightarrow H_2O^+ + e^-$$

• The ion reacts with another water molecule to form a highly reactive hydroxyl radical

$$H_2O^+ + H_2O \rightarrow H_3O^+ + OH^{\bullet}$$

Water Hydrolysis



- Body fluids normally contain H+ and OHions.
- Free radicals may eventually interact with and damage DNA molecules (indirect action).



http://symmetrydirectbuy.com/what-are-free-radicals-and-what-effect-do-antioxidants-have-on-them/

Potential Outcomes of Radiation Damage to Parent Cells



Effects of Radiation on Cells



- 1. Event is not important to cell function no real effect (most likely).
- 2. Damage is repaired- no lasting effect.
- Damage is repaired incorrectlycell may function abnormally (uncontrolled division → cancer could develop).
- 4. Cell is so damaged it dies-only a problem if many cells die at once (acute dose).

Effects of Radiation on Cells



Cellular Sensitivity

- Not all cells are created equal!
- Law of Bergonie & Tribondeau: cell radiosensitivity increases with
 - reproductive rate of cell
 - low morphological/functional differentiation (i.e. specialized cells are LESS sensitive!)
- Other effects on cell sensitivity
 - long mitosis
 - high oxygenation

Radiosensitive Tissues:

- Germinal (reproductive) cells of the ovary and testis (e.g., spermatogonia)
- Hematopoietic (blood forming) tissues: red bone marrow, spleen, lymph nodes, thymus
- Basal cells of the skin
- Epithelium of the gastrointestinal tract (interstitial crypt cells)

Radioresistant Tissues:

- Bone
- Liver
- Kidney
- Cartilage
- → Muscle
 - Nervous tissue

Highly specialized, non-dividing, very

mature

Cellular Sensitivity

- Lymphocytes
- Spermatogonia
- Hematopoietic (Blood Forming)
- Intestinal Epithelium
- Skin
- Nerve Cells
- Muscle Tissue
- Bone
- Collagen

MOST SENSITIVE



Categories of Effects

- Stochastic effect
 - Occurs by chance (random)
 - <u>Risk</u> increases with increasing dose
 - e.g., cancer and genetic mutations
- Deterministic (Non Stochastic) effect
 - Usually does not occur below some threshold dose
 - Occurs as a result of non-random events
 - <u>Severity</u> increases with increasing dose
 - e.g., cataracts, sterility, ARS

Categories of Effects

- Acute (Prompt) Somatic
 - Immediate effects to the organism receiving the dose
 - Due to acute dose
- Delayed (Latent) Somatic
 - Effects that appear years later to organism receiving the dose
 - Cancer is an example
 - Can be caused by low doses
- Genetic (Heritable)
 - Effects that appear in offspring of exposed
 - No evidence seen from human exposures, but clear evidence seen in animal/plant studies
- Teratogenic
 - Effects in embryo/fetus that is directly exposed
 - Cancer, growth abnormalities, death have been seen due to acute doses
 - First 20 weeks of pregnancy are the most sensitive

Biological Effects from Low Doses of Radiation

Biological effects from low doses potentially occur due to chronic exposures. A <u>chronic exposure</u> occurs when a relatively small amount of radiation is absorbed by tissue over a long period of time.

- Under 5 rad of exposure No detectable health effects in exposed individual
- Chronic exposures result in an increased risk in latent adverse health effects
- Health effects could be genetic effects or somatic effects

Latency Period

- Latency period is the time from time of exposure until the effect is exhibited
- n Radiation exposure does not produce cancer in every exposed person
- Effects can be immediate or years later for acute, highlevel exposures



Biological Effects from High Doses of Radiation

Biological effects from high doses occur due to acute exposures. An <u>acute</u> <u>exposure</u> occurs when a relatively large amount of radiation is absorbed by tissue over a short period of time; effects can occur in the short term and long term.

- <u>Hematopoietic Syndrome</u>: (100-200 rad or 1-2 Gray) Early symptoms are anorexia, nausea, and vomiting followed by a phase of bone marrow depression and subsequent susceptibility to infection. After several weeks, death may occur.
- <u>Gastrointestinal Syndrome</u>: (700-1000 rad or 7-10 Gray) Early symptoms are anorexia, nausea, and vomiting followed by fever, diarrhea, and electrolyte imbalance due to ulceration of the intestinal wall. Once GI system ceases to function, death will occur.
- Central Nervous System Syndrome: (2000-5000 rad or 20-50 Gray) Symptoms occur very quickly and the brain and muscles can no longer control bodily functions, including breathing and blood circulation. Death within hours or within several days.

Sources of Radiation



Possible Radiation Dose Response

Curves



- 1. LNT: An increase in dose results in a proportional increase in risk without threshold
- At low doses there is only a slight increase in risk that becomes proportional to dose at higher doses
- 3. There is a threshold for dose response at which lower doses do not result in increased risk
- At low doses there is a higher risk that becomes proportional to dose at higher doses
- 5. Hormesis model (not shown): Low doses of radiation have a positive effect and decrease risk



Effect

What are the Bases for the Models?

- Atomic bomb survivors
- Highly exposed early radiation workers
- Workers/public exposed due to accidents
- Patients undergoing radiation therapy
- Nuclear Medicine misadministrations
- Laboratory animal studies
- In vitro cell studies
- More recent radiation workers
- Background radiation exposures

Knowledge of radiation carcinogenesis has evolved within the larger context of cancer etiology



Epidemiology – Atomic bomb survivors



Kato et al., Health Phys.; 1987



Ozasa et al., Rad Res 177; 2012

Epidemiology – Radium Dial Painters



Epidemiology – Rocketdyne Workers



Boice et al., Rad Res, 2006

Epidemiology – Nuclear Plant Workers

- 15 U.S. Nuclear Facilities
- Occupational Worker cohort for period 1979 1997
- Cohort demonstrated healthy worker effect, i.e. significantly lower cancer and noncancer mortality than general population
- Occupational Worker population routinely exposed to low doses of low-LET whole body ionizing radiation received at low dose rates (i.e. several mSv/yr)
- Excess Relative Risk (EER) estimates for leukemias and solid cancers very similar to EER estimates found in the atomic bomb survivors

Cohort: ~53,000 Mean dose: 30.7 mSv



Risk higher before startup of facilities – Statistically significant?

Jablon et al., JAMA, 1991

What do the Studies Show? Laboratory Studies – Cell Survival



What do the Studies Show? Laboratory Studies – Cell Survival and Dose Rate



CHO (Chinese hamster) cell survival for different dose rates

Width of shoulder and slope of the line beyond the shoulder are affected by the dose rate

Rate effect more dramatic in CHO cells than HeLa cells

Bedford and Mitchell Rad Res, 1973

Laboratory Studies – Cell Survival and Dose Rate



Fu and Phillips Radiology, 1975

Laboratory Studies – Leukemia in Mice



- Effect of dose rate on leukemia
- Highest dose rate exceeds LD₅₀ in humans in 5 minutes
- In occupational exposure setting, the lowest dose rate (240 mrad/h) is considered a "high radiation area"

Upton et al., Rad Res, 1970

Laboratory Studies – Secondary Factors



But Wait, There's More...

What about hormesis?



commentary

Toxicology rethinks its central belief

Hormesis demands a reappraisal of the way risks are assessed.

"As the dose below the standard threshold becomes progressively more dilute, the response becomes more likely to exceed the control value (hormetic-like)."

nature



Nature, 2003

Some Conjecture Based on the Above



A Reasonable Interpretation?

Another way to depict the idea of a variable low-dose outcome becoming definitive at high dose





- Given all the uncertainties, what can we say with any reasonable level of confidence about low-dose radiation?
 - ICRP conclusions:

... the adoption of the LNT model combined with a judged value of a dose and dose rate effectiveness factor (DDREF) provides a prudent basis for the practical purposes of radiological protection, i.e., the management of risks from low-dose radiation exposure.

(ICRP Pub. 103, 2007)

- UNSCEAR:

In general, increases in the incidence of health effects in populations cannot be attributed reliably to chronic exposure to radiation at levels that are typical of the global average background levels of radiation... Therefore, the Scientific Committee does not recommend multiplying very low doses by large numbers of individuals to estimate numbers of radiation-induced health effects within a population exposed to incremental doses at levels equivalent to or lower than natural background levels;

UNSCEAR Sup. 46, 2012

• Health Physics Society:

...the Society has concluded that estimates of risk should be limited to individuals receiving a dose of 50 mSv in one year or a lifetime dose of 100 mSv in addition to natural background...Below these doses...expressions of risk should only be qualitative, that is, a range based on the uncertainties in estimating risk...emphasizing the inability to detect any increased health detriment (that is, zero health effects is a probable outcome).

HPS Position Paper PS010-2, 2010

- Practical inferences
 - LNT can be used to help estimate radiation risks
 - The LNT model probably doesn't under-estimate the risks, and may over-estimate them
 - LNT is useful for "radiation protection"
 - When applied with care, can be used to quantitatively estimate risks for persons with non-trivial doses
 - Useful in making ALARA comparisons and decisions
 - Should not be used for quantitative risk assessments when doses are < 100 mSv
 - Should not be applied to collective doses of low-dose populations (within the range of normal background dose)



Risks in Perspective

- Risk of cancer increases in a generally proportional way with radiation dose. The exact relationship of dose to risk is not known for low doses.
 - About 55% of US citizens get cancer (normal incidence).
 - About 25% of US citizens *die* from cancer (normal mortality).
 - The approximate excess relative risk for radiation is about 40%/Sv.
 - <u>Extrapolating</u> to the lowest level for which quantitative estimates should be considered, gives the following:
- In a population of 100,000 people, all exposed to 100 mSv*, we would predict about 1000 excess cancer deaths
- Studies of people with doses in this range do not show a clearly measurable risk in such populations
- There will be about 25,000 non-radiation cancer deaths in this population

*100 mSv is almost 100 times the normal annual background from cosmic, terrestrial, and internal radiation sources combined.

"The dose makes the poison."

Paracelsus, circa 1520

"All models are wrong, some models are useful."

George Box, industrial statistician, 1979

For More Information on Radiation Protection

Health Physics Society

WEBSITE: <u>http://hps.org</u>

National Council on Radiation Protection and Measurements

WEBSITE: http://www.ncrponline.org/

International Committee on Radiation Protection

WEBSITE: http://www.icrp.org/

United Nations Scientific Committee on the Effects of Atomic Radiation

WEBSITE: http://www.unscear.org/

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• Spare slides

Conditioning Dose



What do the Studies Show? Epidemiology – Mound, Ohio Workers



Boice, submitted 2012

What about non-radiation factors?



Skov, Mutation Res., 1999

Laboratory Studies

THIS IS PLACEHOLDER INFORMATION

•Supralinear behavior is implied by some studies.

•The high-LET curve is exponential at low doses

•The low LET curve often contains a "dip" in the "pseudo-threshold" portion of the curve

•Enhanced RBE at low doses (this is highly technical, and we may not get into this – just putting it here as a placeholder)

•Some epidemiological studies can be interpreted this way

There are different interpretations of these data

Again, almost all are conducted with high dose-rate radiation. Cell studies are perhaps the hardest to apply directly to humans (cell cultures are not living organisms).