Environmental factors

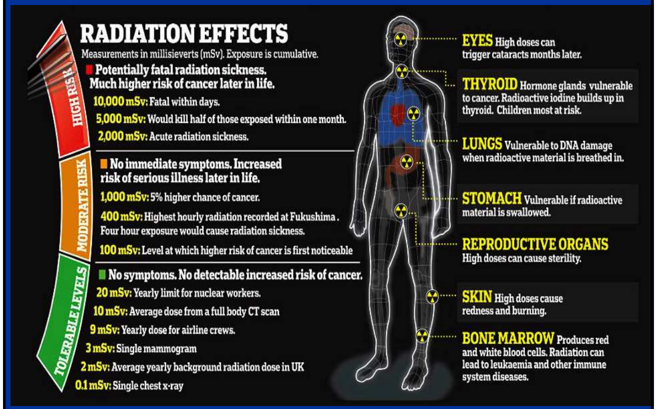
- CHEMICALS
- **RADIATION**
- NATURAL TOXINS
- VIRUSES

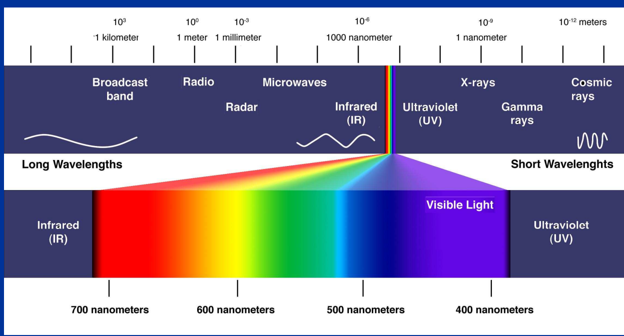
Radiation-induced Carcinogenesis

Radiations contain energies greater than that in chemical bonds. Therefore, chemical bonds can be broken by radiation.

Energy release from various radiations:

Atomic particles > X-rays
> ultraviolet (UV) light
> visible light





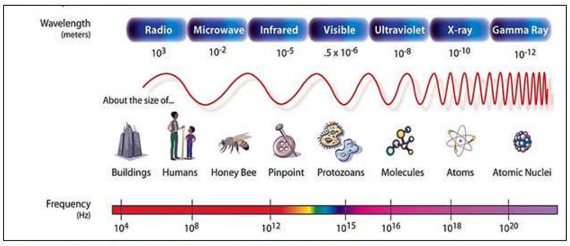
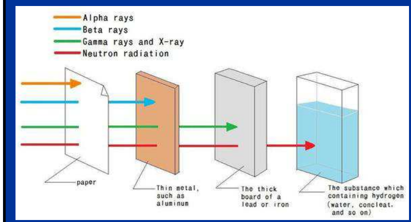
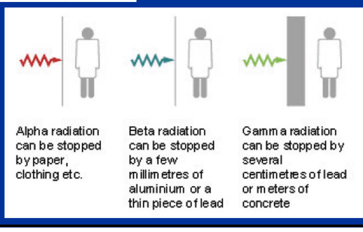


Figure 1: Characteristics of the electromagnetic spectrum. (Public domain image from Wikimedia Commons at: http://commons.wikimedia.org/wiki/File:EM_Spectrum3-new.jpg)

The penetrating power of different rays



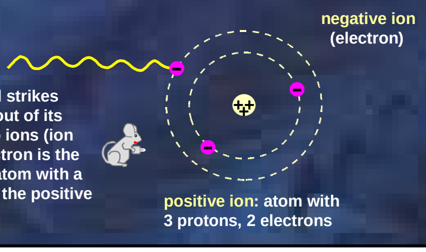


Ionization

Ionization is the process of removing an electron from an electrically neutral atom to produce an ion pair. An ion is an atom or subatomic particle with a positive or negative charge.

Ionization

X-ray enters atom and strikes electron, knocking it out of its orbit and creating two ions (ion pair). The ejected electron is the negative ion and the atom with a net positive charge is the positive ion.



Ionizing Radiation

The two types of ionizing radiation are electromagnetic and particulate.

Electromagnetic: Electromagnetic radiation has both electrical and magnetic properties. It includes x-rays and gamma rays. X-rays are produced by a machine and gamma rays are produced when radioactive materials decay. Neither one has any mass.

Particulate: Particulate radiation consists of particles that have mass and travel at high speeds. Included are alpha particles (helium nuclei), electrons (beta particles; also called beta rays), protons and neutrons.

LET (linear energy transfer) indicates the relative amount of energy (in KeV) that the radiation transfers to the atoms while traversing the material (of lenght X= microMeter).

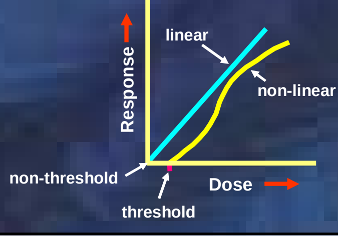
Note that DNA is 2nm and chromosome is of 840 nm.

Electromagnetic X e γ rays have low LET: they do not give way ionizing energy while traversing the material and therefore can penetrate the body in depth.

Alpha and beta particles are radiation with high LET: they produce ionization while traversing the material thus loosing very soon their energy, and therefore they do not penetrate much in depth the tissues.

Dose-Response Curves

Dose-Response curves represent the relationship between the dose of radiation a person receives and the cellular response to that exposure. These responses may be linear or non-linear and may, or may not, have a threshold dose; the responses (effects) may be stochastic or deterministic. (See next two slides for definitions of these terms).



Stochastic effect: occurs by chance, usually without a threshold level of dose. The probability of a stochastic effect is increased with increasing doses, but the severity of the response is not proportional to the dose (e.g., two people may get the same dose of radiation, but the response will not be the same in both people). Genetic mutations and cancer are the two main stochastic effects.

Deterministic effect: health effects that increase in severity with increasing dose above a threshold level. Usually associated with a relatively high dose delivered over a short period of time. Skin erythema (reddening) and cataract formation from radiation are two examples of deterministic effects.

DNA

Radiation effects at the cellular level result from changes in a critical or “target” molecule. This target molecule is DNA (deoxyribonucleic acid), which regulates cellular activity and contains genetic information needed for cell replication. The DNA molecule is called a chromosome. Permanent changes in this molecule will alter cell function and may result in cell death.

Direct vs. Indirect Effect

If an x-ray or some type of particulate radiation interacts with the DNA molecule, this is considered a direct effect. Particulate radiation, because of its mass, is more apt to cause damage to the DNA by this direct effect. Other molecules that contribute to cell function, such as RNA, proteins, and enzymes, may also be affected by the direct effect.

DNA = Direct effect

x-ray or particulate radiation

Direct vs. Indirect Effect

Most of the damage to DNA molecules from x-rays is accomplished through the indirect effect. When x-rays enter a cell, they are much more likely to hit a water molecule because there are a large number of water molecules in each cell. When the x-ray ionizes the water molecule, ions and free radicals are produced which in turn bond with a DNA molecule, changing its structure. Since the x-ray interacted with the water molecule before the DNA was involved, this is considered an indirect effect.

H_2O → ions and free radicals → DNA = Indirect effect

x-ray or particulate radiation

Free Radical

A free radical is an atom or molecule that has an unpaired electron in the valence shell, making it highly reactive. These free radicals aggressively join with the DNA molecule to produce damage. In the presence of oxygen, the hydroperoxyl free radical is formed; this is one of the most damaging free radicals that can be produced. Free radicals are the primary mediator of the indirect effects on DNA.

Cellular Effects

Cells undamaged: ionization alters the structure of the cells but has no overall negative effect.

Sublethal injury: cells are damaged by ionization but the damage is repaired.

Mutation: cell injury may be incorrectly repaired, and cell function is altered or the cell may reproduce at an uncontrolled rate (cancer).

Cell death: the cell damage is so extensive that the cell is no longer able to reproduce.

Sublethal Injury: Cellular Repair

1. Ionization causes damage to DNA (single-strand break of DNA).
2. Cellular enzymes recognize the damage and coordinate the removal of the damaged section.
3. Additional cell enzymes organize replacement of the damaged section with new material.

Radiosensitive Cells

Cells that are more easily damaged by radiation are radiosensitive. The characteristics of radiosensitive cells are:

1. High reproductive rate (many mitoses)
2. Undifferentiated (immature)
3. High metabolic rate

Lymphocytes, germ cells, basal cells of skin and mucosa, and erythroblasts are examples of radiosensitive cells.

Radioresistant Cells

Cells that are not as susceptible to damage from radiation are radioresistant. The characteristics of radioresistant cells are:

1. Low reproductive rate (few mitoses)
2. Well differentiated (mature)
3. Low metabolic rate

Nerve and muscle cells are examples of radioresistant cells.

Radiation Effect Modifiers (continued)

- Oxygen Effect: Radiation effects are more pronounced in the presence of oxygen. Oxygen is required for the formation of the hydroperoxyl free radical, which is the most damaging free radical formed following ionization.

Units of Radiation Measurement

Traditional Units	SI* Units
Roentgen (R)	Coulombs per kilogram
rad	Gray
rem	Sievert

* SI = International System of Units; used worldwide

Roentgen

The Roentgen (R) is the traditional unit of measuring radiation exposure. This measures the ionization of air. (The exact definition of Roentgen is complicated and not worth remembering). The Roentgen measures radiation quantity before the radiation enters the body. There is no exact SI unit comparable to the Roentgen, but in keeping with the metric system it is measured in coulombs per kilogram.

rad/Gray

The rad (radiation absorbed dose) is the traditional unit used to measure the energy absorbed by the body. The SI unit is the Gray (Gy). 1 Gray = 100 rads; 1 cGy (centiGray) = .01 Gray = 1 rad.

rem/Sievert

The rem (roentgen equivalent man) is the traditional unit used for comparing the effects of different types of ionizing radiation (electromagnetic and particulate). The dose (in rads) is multiplied by a quality (weighting) factor. The quality factor for x-rays is 1. Therefore the dose in rems (dose equivalent) is the same as the dose in rads. For alpha particles the quality factor is 20. Therefore the dose in rems (dose equivalent) would be 20 times the dose in rads for alpha particles. The higher the LET, the higher the qualifying factor.
The SI unit is the Sievert (Sv). 1 Sievert = 100 rems; 1cSv (.01 Sievert) = 1 rem.

Conversions*

1 R = 1 rad = 1 rem

1 Gray = 1 Sievert = 100 rads = 100 rems

c (centi) = .01   m (milli) = .001   μ (micro) = .000001

1000 mrem = 1 rem = 1 cSv

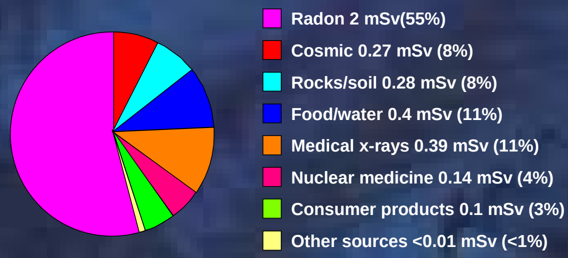
100 mrem = 1 mSv = 1000 μSv

1 Sv = 100 cSv = 1,000 mSv = 1,000,000 μSv

* For x-rays, not particulate radiation

Annual Radiation Exposure

Each year, people are exposed to various types of ionizing radiation (listed below) and receive an average dose of 3.6 mSv (360 mrem) per year. The actual dose depends on the degree of exposure to the ionizing radiation sources.



Natural (Background) Radiation

Environmental radiation that we are exposed to daily is called natural or background radiation. It is composed of both external and internal sources. Background radiation averages 3.0 mSv (300 mrem) per year.

External Sources:

Cosmic (8%*): Ionizing radiation from space. Increased exposure at higher altitudes and during airline travel.

Terrestrial (8%*): Results from radioactive materials in soil and rocks. May be incorporated into some building materials. (See next slide).

* Percent of average annual radiation exposure

Natural (Background) Radiation
(continued)

Internal Sources:

Radon (55%*): Radon and its decay products enter our homes via the atmosphere and water. Inhalation of these products contributes more than half of our average annual radiation exposure.

Food/Water (11%*): Some of the food and water we ingest contains radioactive materials.

* Percent of average annual radiation exposure, both natural and artificial

Artificial (Man-made) Radiation

Artificial radiation results in an annual exposure of about 0.6 mSv (60 mrem). Included are:

Medical X-rays (11%*): Diagnostic medical x-rays are the major component of artificial radiation. Therapeutic x-rays contribute a small portion. Dental x-rays account for only 0.1% of the total annual exposure.

Nuclear medicine (4%*): Diagnostic and therapeutic

Consumer Products (3%*): Dental porcelain, smoke alarms, televisions, airport inspections, etc..

Other Sources (<1%*): Primarily nuclear fallout

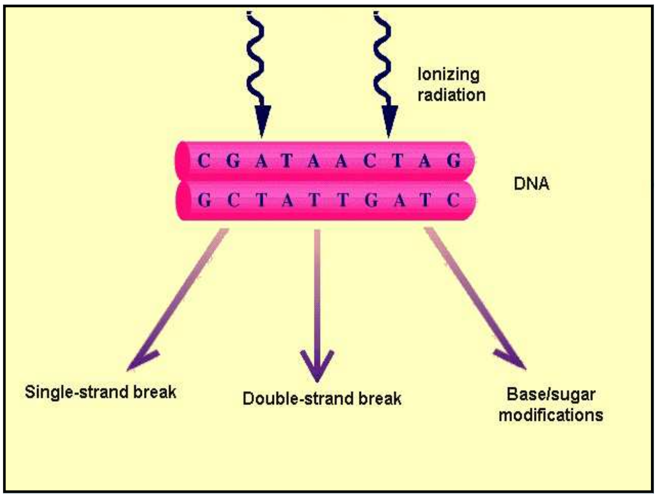
* Percent of average annual radiation exposure, both natural and artificial

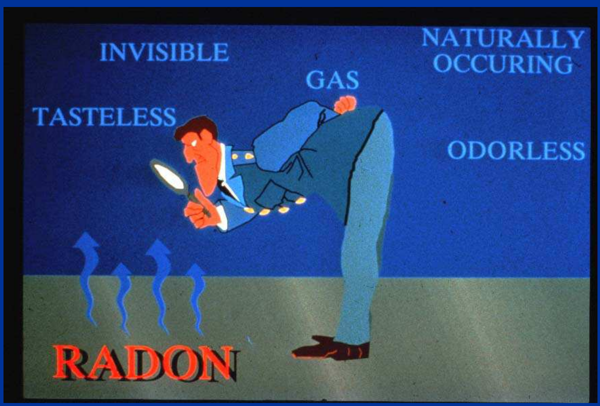
Ionizing Radiation

- Ionizing radiation includes: **X-rays, gamma rays**, as well as particulate radiation; **alpha, beta, protons, neutrons and primary cosmic radiation**. All forms are carcinogenic with special sensitivity in:
  - **Bone Marrow**: Acute leukemia occurs before other radiation-induced neoplasia (Seven year latent period in atomic bomb survivors).
  - **Thyroid**: Carcinoma occurs in 9 % of those exposed during infancy or childhood.
  - **Lung**: Increased frequency of lung cancer in miners exposed to Radon gas (an alpha particle emitter).

Ionizing Radiation

- The oncogenic properties of ionizing radiation are related to its mutagenic effects; it causes chromosome breakage, translocations, and, less frequently, point mutations.
- Double-stranded DNA breaks seem to be the most important form of DNA damage caused by radiation.
- There is also some evidence that non-lethal doses of radiation may induce genomic instability, favoring carcinogenesis

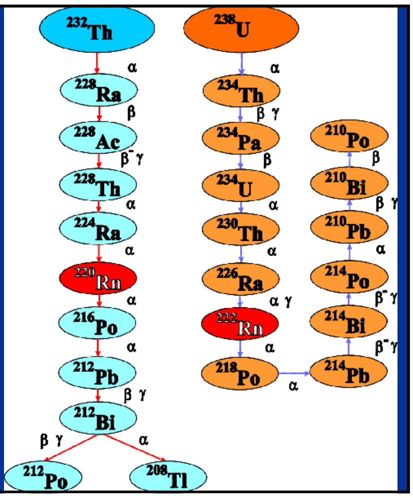




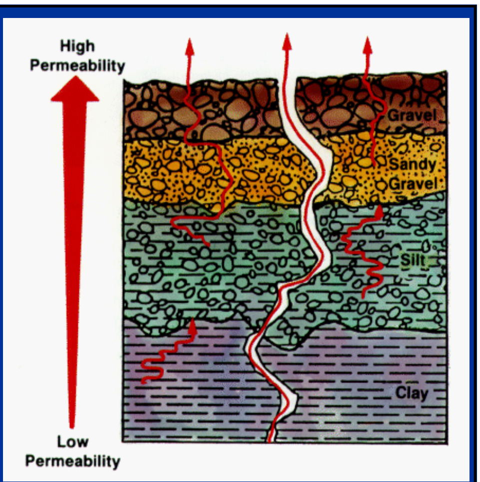
RADON arises from THORIO and URANIUM

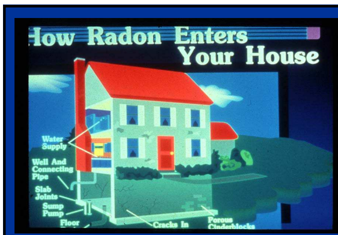
Radon emits alpha-radiation

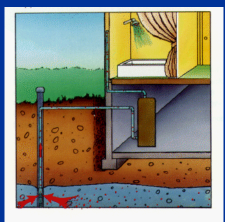
(half-life is 3.82 days)

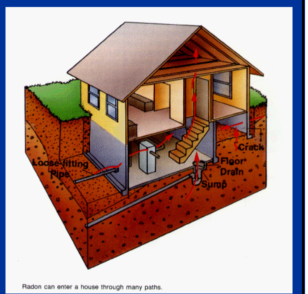


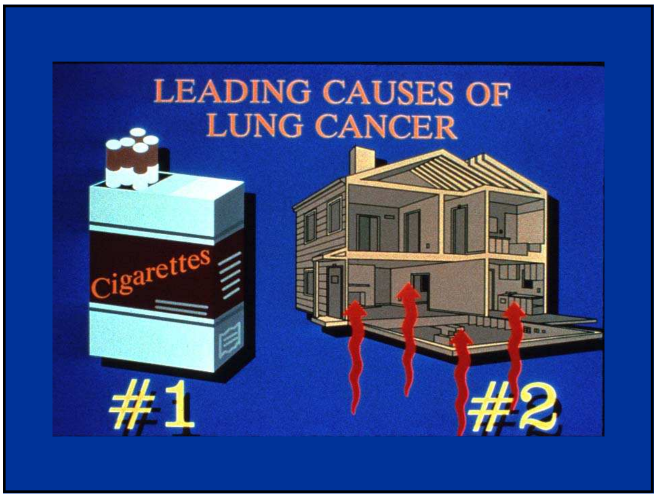
Radons diffuses

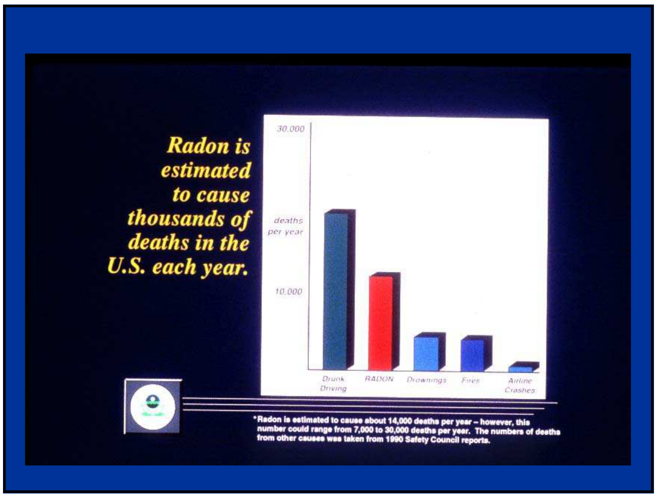


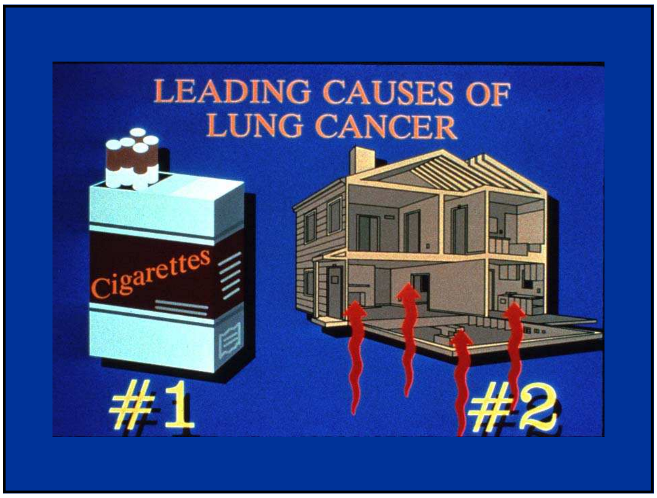


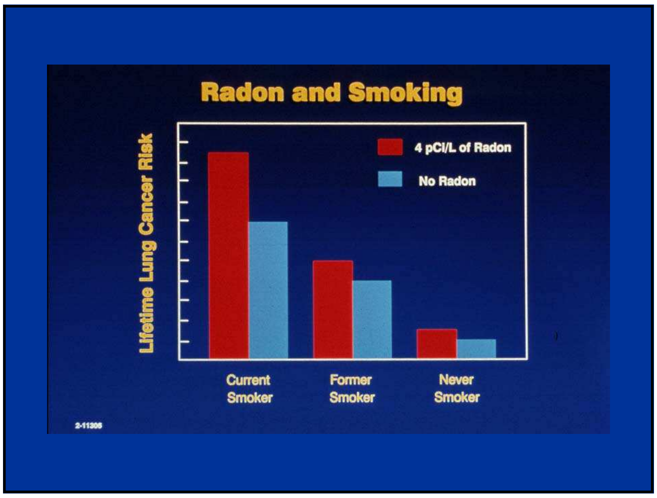


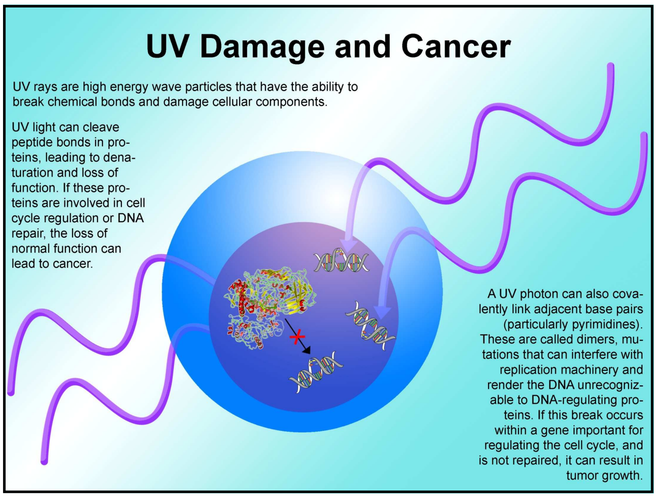






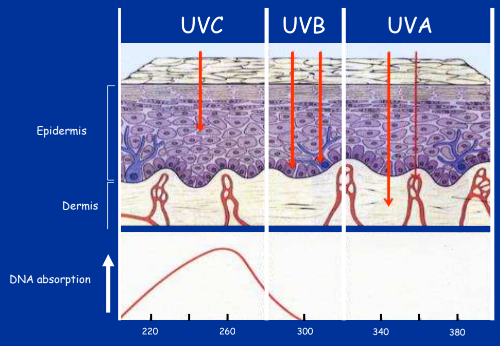






Ultraviolet Light

- Strong epidemiologic relationship to squamous cell ca, basal cell ca , and melanoma-in fair skinned people.
- Causes formation of ***pyrimidine dimers*** in the DNA leading to mutations.
- This type of DNA damage is repaired by the nucleotide excision repair pathway. With extensive exposure to UV light, the repair systems may be overwhelmed, and skin cancer results
- Individuals with defects in the enzymes that mediate DNA excision-repair are especially susceptible.



UV radiation is a low-energy emission and does not penetrate deeply. Hence, the skin absorbs most of the radiation and is the primary carcinogenic

When cells are exposed to UV light in the 240- to 300-nm range, nucleic acid bases acquire excited energy states, producing photochemical reactions between DNA bases. The principal products in DNA at biologically relevant doses of UV light are cyclobutane dimers formed between two adjacent pyrimidine bases in the DNA chain. Both thymine-thymine and thymine-cytosine dimers are formed.