



## Toxicity

The degree to which a substance (a toxin or poison) can harm humans or animals

Acute toxicity involves harmful effects in an organism through a single or short-term exposure

Subchronic toxicity is the ability of a toxic substance to cause effects for more than one year but less than the lifetime of the exposed organism.

Chronic toxicity is the ability of a substance or mixture of substances to cause harmful effects over an extended period, usually upon repeated or continuous exposure, sometimes lasting for the entire life of the exposed organism.

## Toxicology vs. Toxicity

#### Toxicology

 the study of chemical or physical agents that interact with biological systems to produce a response in the organism

#### Toxicity

The relative *ability* of a substance to cause injury to biological tissue

### **Dose Units**

expressed in terms of quantity administered

- Per unit of weight
  - mg/kg
  - ug/kg
  - ppm
  - ppb
- Skin Surface
  - mg/cm<sup>2</sup>

- . In the air/Inhaled
  - ppmv (parts of vapor/gas PER million parts of air BY volume)
  - mg/m<sup>3</sup>

## Toxicity vs. Hazard

- Toxicity
  - CAPACITY of a material to produce an injury or do harm...like RISK
- Hazard
  - POSSIBILITY or potential
     of exposure to a material that
     will cause injury when a
     specific amount is used
     under specified conditions

## Effects of exposure are dependent on:

- Dose
- Rate of exposure
- Physical state of material
  - Temperature
- Site of absorption/exposure
  - Diet
  - General state of health

## Dose/Response relationship

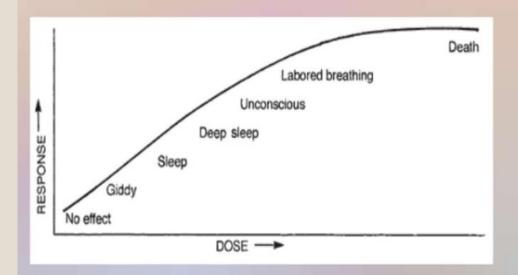
### • The dose makes the poison...

...the characteristics of exposure to a chemical and the type of effect caused by the chemical

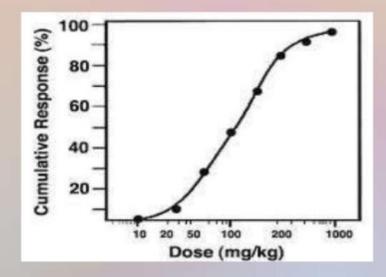
...in other words HOW exposed and HOW MUCH exposed to that causes the effect being studied.

### Types of Dose Response Curves

 Individual – describes a graded response to varying doses of a chemical  Population – distribution of responses to different doses in a population of individuals



Ethanol Dose Response on single human



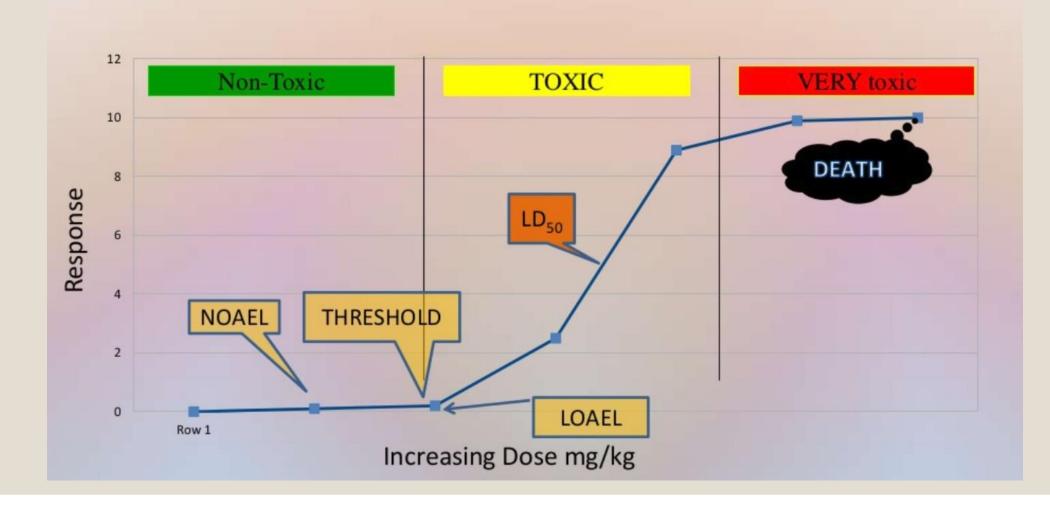
Simple example of mouse population – carcinogenic effect

#### What is....

- NOAEL No Observable Adverse Effect Level
- Threshold the DOSE at which there are no ill effects from exposure
- LOAEL Lowest Observable Adverse Effect Level

The body is able to eliminate toxins fast and efficiently enough not to see adverse effects...**NOAEL**. Eventually the body reaches a point where toxins IN = toxins OUT...**THRESHOLD**. Finally beyond this point the body can't metabolize & eliminate toxins fast enough and we start to see adverse effects...**LOAEL**.

## Dose Response Curve



## Dose Response Acronyms

- TD<sub>LO</sub> Toxic Dose Low lowest dose by any route EXCEPT inhalation.
  - mg/kg; mg/cm<sup>2</sup>; ppm
    - Over ANY given period of time
    - Reported to produce ANY toxic effect in humans OR to produce any tumors or reproductive effects in animals
- TC<sub>LO</sub> Toxic Concentration Low lowest concentration in air.
  - ppmv; mg/m<sup>3</sup>
    - Over ANY period of time that produces any toxic effect in humans
    - Reported to produce ANY toxic effect in humans OR to produce any tumors or reproductive effects in animals

- LD<sub>LO</sub> Lethal Dose Low lowest dose of a substance (other than the LD50)
   by ANY route EXCEPT inhalation that has caused death in a humans or
   animals
- LD<sub>50</sub> Lethal Dose Fifty calculated dose expected to kill 50% of a test population by ANY route EXCEPT inhalation.
- LC<sub>LO</sub> Lethal Concentration Low lowest concentration (other than LC50)
   IN AIR reported to have caused death in animal or human.
- LC<sub>50</sub> Lethal Concentration Fifty calculated concentration IN AIR over a specified period of time that kills 50% of a test population

## Factors that influence toxicity

#### **Chemical Factors**

- Composition
- Physical characteristics
- Physical properties
- Presence of impurities
- Breakdown products
- Carrier

#### **Exposure Factors**

- Dose, concentration
- Route of exposure
- Duration of exposure

### Factors continued...

#### Person exposed

- Heredity
- Immune system
- Nutrition
- Hormones
- Age
- Gender
- Health status
- Pre-existing conditions

#### **Environmental**

- Carrier
- Additional chemicals
- Temperature
- Air pressure

## ROUTES OF EXPOSURE!

- Ingestion
- Injection
- Inhalation
- Absorption

## Types of Toxicity

- Acute effects usually within 24 to 72 hours after exposure, however should occur within 14 days of exposure
  - May be as serious as death or temporary as drunkenness
- Chronic effects manifest several weeks, months or years after exposure
  - May have been an isolated exposure or repeated over many years
- Local action of toxic substance on specific area of contact
  - Such as skin, mucous membranes, eyes, throat
- Systemic effect or action is distributed through the body
  - Inhalation of chloroform effects the brain

### Few more definitions

- Carcinogen substance that will induce a malignant tumor in a person following reasonable exposure
- Mutagen affects the genetic system of exposed people or animals and may cause cancer or undesirable mutations in future generations
- Teratogen compound that affects the fetus through the mother causing death or significant deformities
  - (may have no effect on mother!)

# Signs & Symptoms Chemical Exposure & Heat Stress

#### Chemical Exposure

- Behavior changes
- Breathing difficulties
- Complexion/skin color change
- Coordination difficulties
- Coughing
- Dizzyness
- Drooling
- Diarrhea
- Fatigue/Weakness

- Irritability
- Irritation of eyes, nose, respiratory tract, skin or throat
- Headache
- Light-headed
- Nausea
- Sneezing
- Sweating
- Tearing
- Tightness in chest

# Signs & Symptoms Chemical Exposure & Heat Stress

Heat Exhaustion & Heat Stroke

- Heat Exhaustion
  - Clammy skin
  - Confusion
  - Dizziness
  - Fainting
  - Heat rash
  - Light-headedness
  - Nausea
  - Profuse sweating
  - Slurred Speech
  - Weak Pulse

- Heat Stroke (may be fatal)
  - Confusion
  - Convulsions
  - Hot skin, high temperature
  - Incoherent speech
  - Convulsions
  - Sweating stops (residual sweat may still be present)
  - Unconsciousness



#### Definitions

- Toxin: a substance with harmful effects on living systems.
   Includes heavy metals, biotoxins, and many industrial chemicals.
- Detoxification: to remove or neutralize the toxic quality of toxins.
- Xenobiotic: a chemical substance present within, but not made within a living thing - a substance that is "a stranger to life."
- Persistent Organic Pollutants (POPs): hazardous xenobiotics that resist degradation within living systems.
- Toxic load: the sum total of toxins within a given living system.

#### **DETOXIFICATION**

#### **\*DEFINATION OF DETOXIFICATION:**

Reactions which convert certain substances into compounds which are more water soluble &thus readily excreted from the body. (Toxic to less toxic)

Toxicity may not be eliminated but reduced.

Detoxification is also called drug metabolism or biotransformation.

#### DETOXIFICATION

- ■<u>Definition</u> –series of biochemical reactions occurring in body to convert foreign (often toxic) compounds to nontoxic or less toxic more easily excretable forms.
- Word DETOXIFICATION IS MISLEADING
- Detoxified products may be more toxic than original form but more water soluble (polar) and easily excretable compounds.
- Methanol 

   Formaldehyde

#### **DETOXIFICATION OF XENOBIOTICS** DETUXIFICATION OF AENOBIOTICS

Xenobiotic or waste metabolite in the diet or peripheral circulation

Phase I reactions

Reduction Oxidation Hydroxylation Hydrolysis

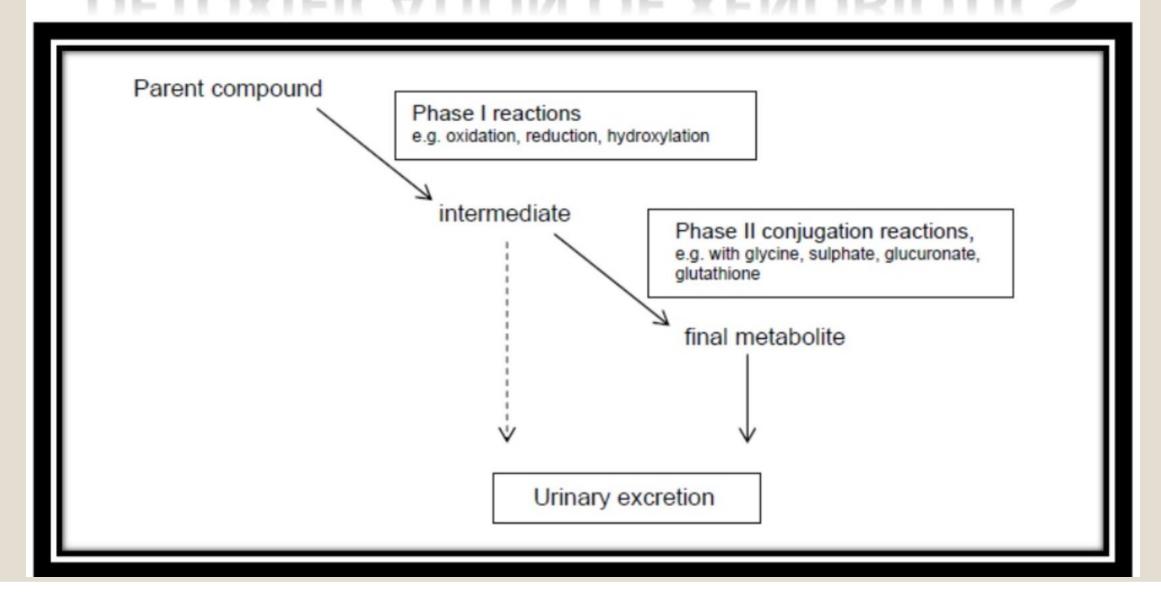
Phase II reactions Primary

metabolite

Conjugation Sulfation Methylation Glucuronidation

Secondary metabolite, suitable for

excretion



Oxidation

Ethanol → Acetic acid

Methanol → Formic acid

Benzaldehyde → Benzoic acid

Alcohol

Aldehydes

**Amines** 

Aromatic hydrocarbons

Sulfur compounds

Aliphatic amine → Aliphatic acid + Urea

Drugs

#### Oxidation

Most of the oxidation reactions are catalysed by monooxygenase or cytochrom  $P_{450}$ 

Many reactions of cytochrome P<sub>450</sub> involve the addition of a hydroxyl group to xenobiotics



Hydroxylation

### **DETOXIFICATION OF XENOBIOTICS** DETUALFUM OF AERODIUMS

### **Hydroxylation**

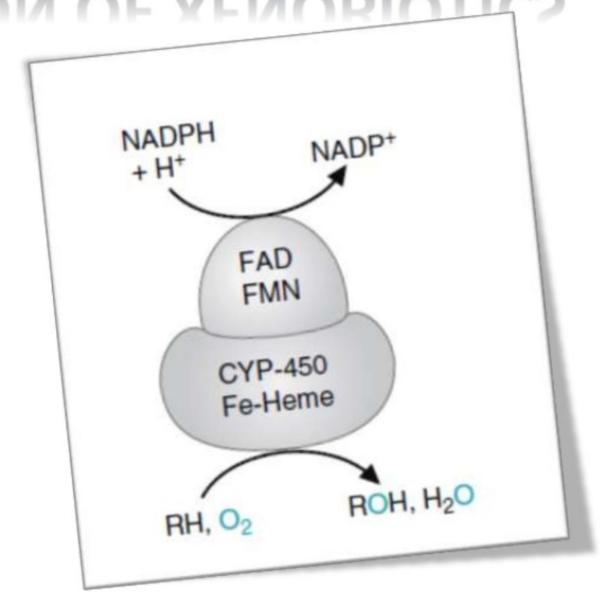
$$RH + O_2 + NADPH + H^+ \rightarrow R - OH + H_2O + NADP$$

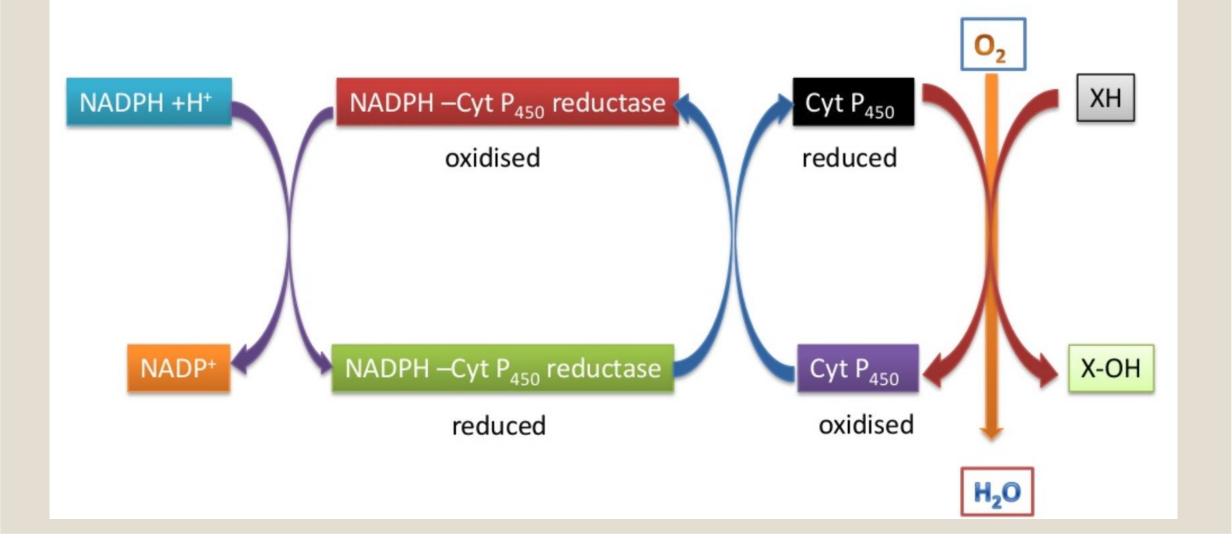
Reduced cytochrome P450 Oxidized cytochrome P450

$$RH + O_2 \rightarrow R - OH + H_2O$$

The responsible enzymes are called monooxygen ases or cytochrome  $P_{450}$ 







Reduction

It is less common and less important than oxidation.

 $\begin{array}{c} \text{Picric acid} & \xrightarrow{\text{Reduction}} & \text{Picramic acid} \\ \text{Chloral hydrate (Sedative)} & \xrightarrow{\text{Reduction}} & \text{Trichloro ethyl alcohol} \end{array}$ 

Hydrolysis

Many drugs are detoxified by hydrolysis.

Atropine (Psychoactive) Tropic acid + Tropine

Conjugation

Conjugation
means the chemical
combination of one
compound with another
compound.

Glucuronic acid

Glutathione

Sulfate

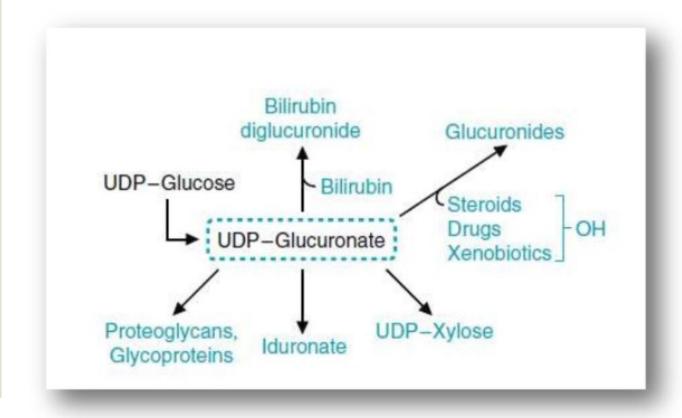
Glycine

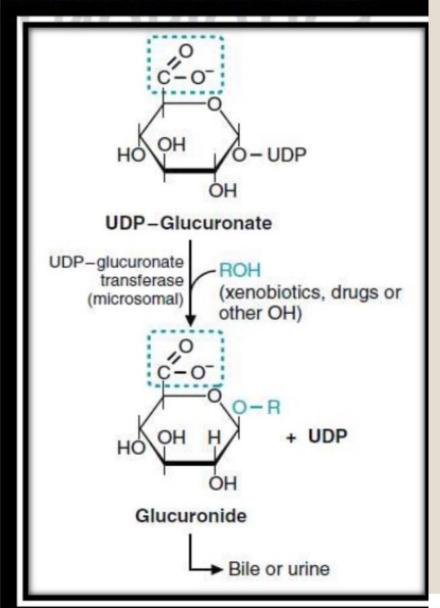
Cysteine

Acetate

Glutamine

Conjugation with Glucuronic acid





Conjugation with Glucuronic acid

Benzoic acid + UDP-Glucuronic acid → Benzoyl glucuronide + UDP

Paracetamol + UDP-Glucuronic acid → Conjugated product + UDP

Diclofenac sodium + UDP-Glucuronic acid → Conjugated product + UDP

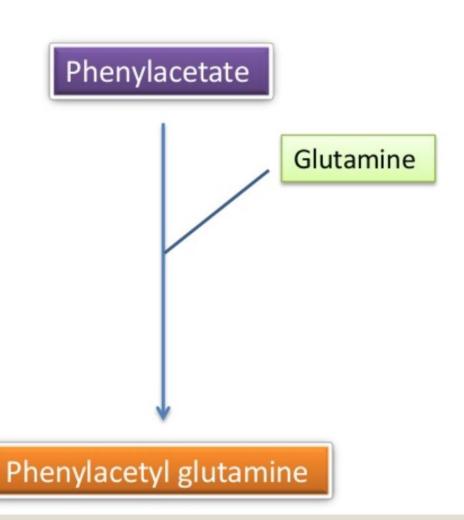
#### Conjugation with Glycine

# Conjugation with Glutathione

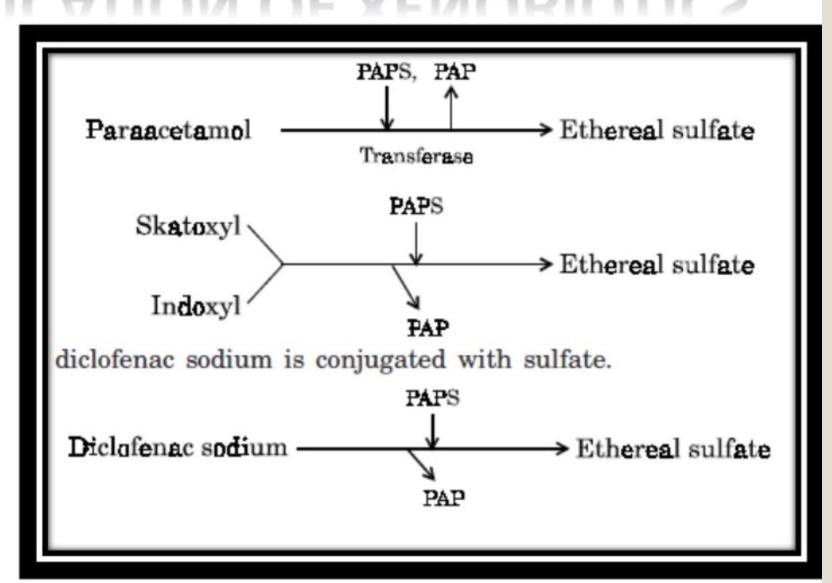
Glutathione (GSH;  $\gamma$ -glutamylcysteinylglycine),  $H_{3}N-C-CH_{2}-CH_{2}-C-N-C-C-NH-CH_{2}-COO^{-}$  HGlutathione
(GSH;  $\gamma$ -glutamylcysteinylglycine)

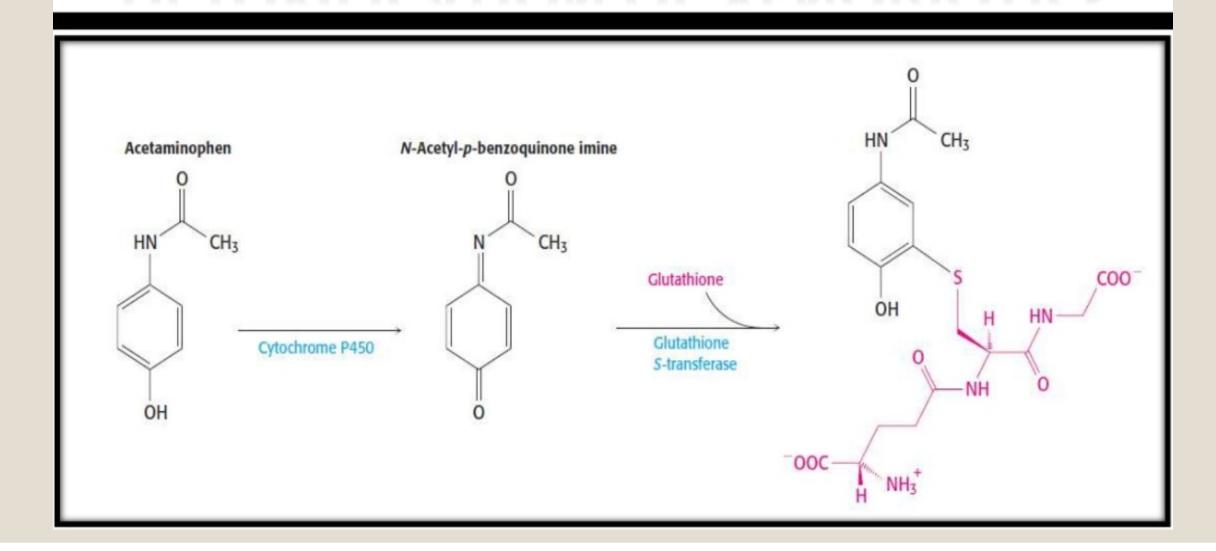
 $\begin{array}{c} \textbf{Dichloronitrobenzene} & \xrightarrow{\text{Glutathione}} & \textbf{Conjugated product} \\ \textbf{(A carcinogen)} & \xrightarrow{\text{Glutathione-S-Transferase}} & \textbf{Mercapturic acid} \rightarrow \textbf{Urine} \end{array}$ 

Conjugation with Glutatmine

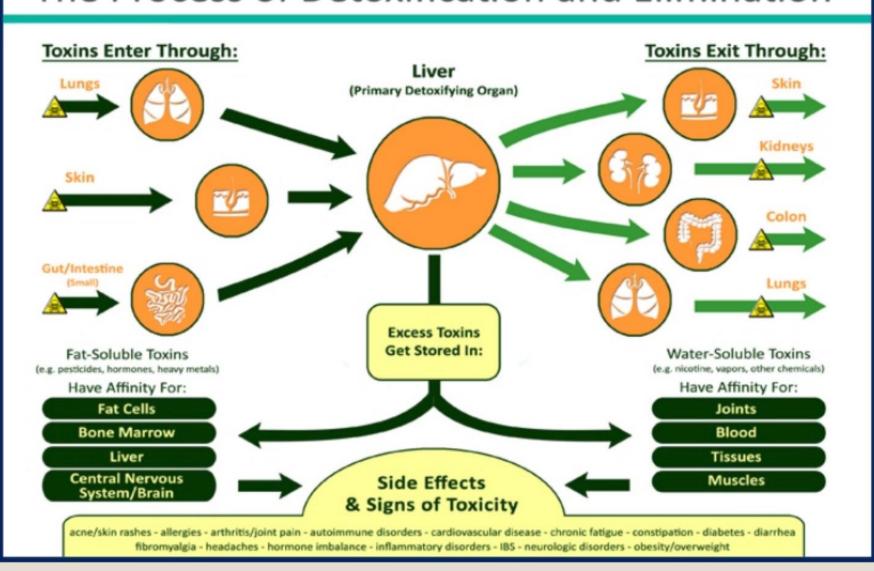


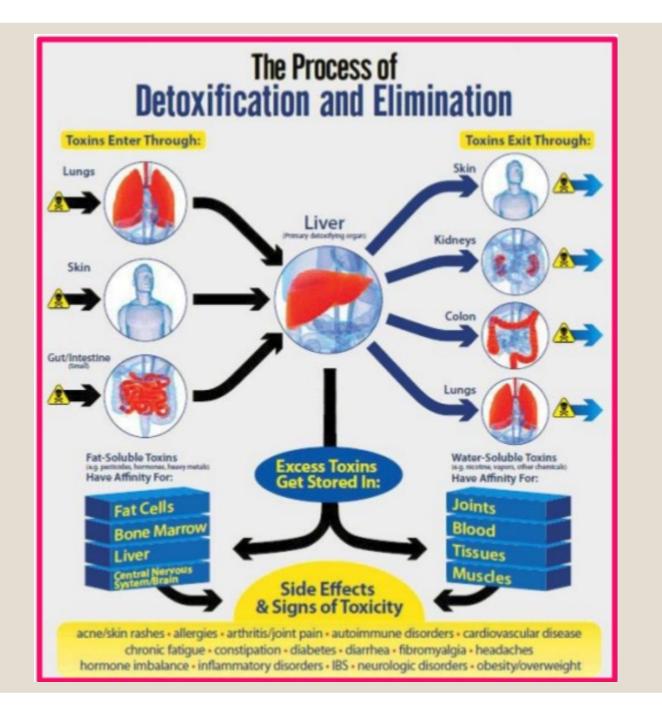
Conjugation with sulfate





#### The Process of Detoxification and Elimination





#### How Toxicity Challenges Our Natural Detoxification Systems

#### Truth

Ubiquitous Too many to count Complex interactions

#### Consequences

Altered brain function
Gut disturbances
Reproductive effects
Hormone disruption
Nutrient depletion
Inflammation
Cancer
Diabetes
Autoimmune disease
Degenerative disease
Cardiovascular disease
and more...

#### **Our Exposure to Damaging Toxins**

Flame retardants
PBDEs

Heat- and stainresistant chemicals PFOAs

> Bisphenols From plastics

Mercury From fish

Combustion chemicals
MTBE

Acrylamides
From fried foods

The CDC's Fourth National Report on Human Exposure to Environmental Chemicals

Tested 212 chemicals and found *ALL* to be in the blood and urine of most Americans!

Six chemicals in particular, found in virtually every person, were identified by the CDC as important health hazards!

#### Lipophilic Toxins

Low molecular weight, non-polar, fat-soluble toxins easily move into or through phospholipid membranes and into cells. They distribute widely and can accumulate to hazardous levels. High molecular weight lipophilic toxins are especially difficult to eliminate.

#### Common, Hazardous Lipophilic Toxins

volatile organics	polyaromatic hydrocarbons	mold toxins
polyvinyl chlorides	industrial solvents	ciguatera toxin
pesticides	combustion products	microcystin
phlalates	perfluoro-octanoic acid	dioxins
bisphenols	tetrachloroethylene	PCBs
flame retardants	dinoflagellate toxins	organohalides

#### **Attention Please!**

#### Doctors Needed to Engage this Problem

Growing awareness of the connection between toxicity and chronic disease.

J Environ Public Health, 2012;2012:356798. doi: 10.1155/2012/356798. Epub 2012 Jan 19.

Environmental determinants of chronic disease and medical approaches: recognition, avoidance, supportive therapy, and detoxification.

Sears ME, Genuis SJ.

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#### Abstract

The World Health Organization warns that chronic, noncommunicable diseases are rapidly becoming epidemic worldwide. Escalating rates of neurocognitive, metabolic, autoimmune and cardiovascular diseases cannot be ascribed only to genetics, lifestyle, and nutrition; early life and ongoing exposures, and bioaccumulated toxicants may also cause chronic disease. Contributors to ill health are summarized from multiple perspectives--biological effects of classes of toxicants, mechanisms of toxicity, and a synthesis of toxic contributors to major diseases. Healthcare practitioners have wide-ranging roles in addressing environmental factors in policy and public health and clinical practice. Public health initiatives include risk recognition and chemical assessment then exposure reduction, remediation, monitoring, and avoidance. The complex web of disease and environmental contributors is amenable to some straightforward clinical approaches addressing multiple toxicants. Widely applicable strategies include nutrition and supplements to counter toxic effects and to support metabolism; as well as exercise and sweating, and possibly medication to enhance excretion. Addressing environmental health and contributors to chronic disease has broad implications for society, with large potential benefits from improved health and productivity.

#### Glutathione (GSH)

A molecule of primordial importance

Free radical and anion binding sites: COOH = carboxyl NH = amino SH = sulfhydryl

Phase 1 anions are stabilized and polarized, made ready for active membrane transport

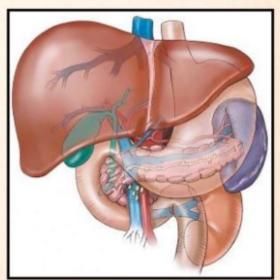
- 1. GSH maintains intracellular redox balance by mopping up oxidative stress.
- 2. Glutathione-S-transferases conjugate GSH to phase 1 drugs, toxins, and xenobiotics, preparing them for transport out.
- 3. GSH-dependent membrane transporters and efflux pumps play key roles in toxin elimination.

#### The Biotransformation of Lipophilic Toxins

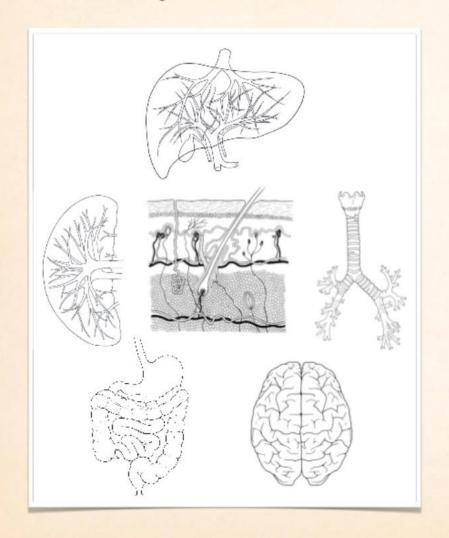
Phase 1 reactions add a functional group to a fat soluble toxin so the new structure can be conjugated (joined to) a phase 2 substrate.

Phase 2 reactions continue the biotransformation process to create a water soluble compound suitable for elimination into bile or blood for transport and elimination by the bowel or kidneys.

Phase 1	Phase 1 Phase 2	
Fat soluble	Water soluble	
Oxidation -	→ Sulfate conjugation	
Reduction =	→Glucuronide conjugation	
Hydrolysis -	→ Glutathione conjugation	
Acetylation -	→ Amino acid conjugation	



#### Key Phase 1 and 2 Pathway Sites

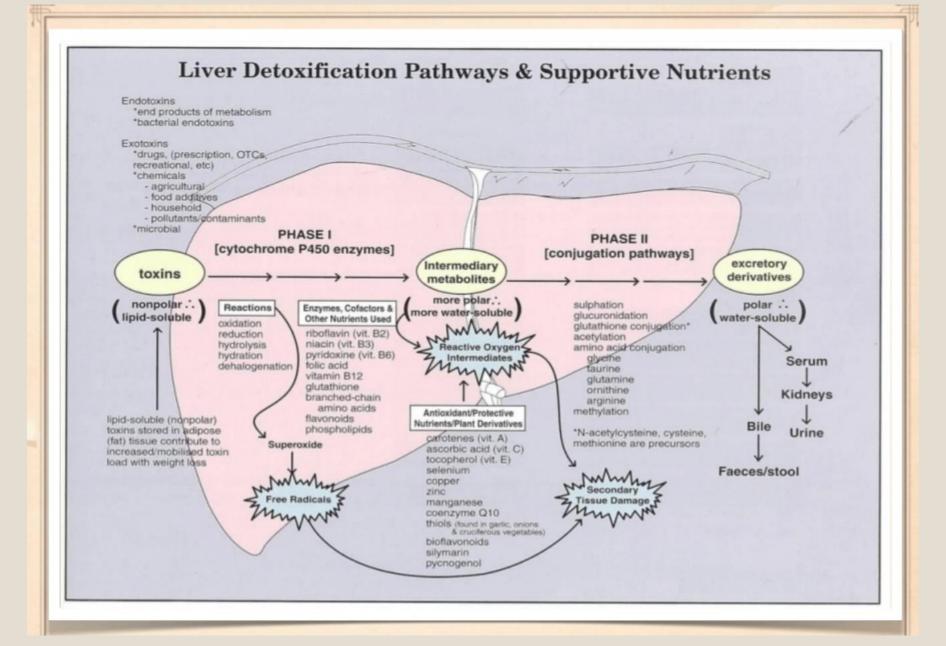


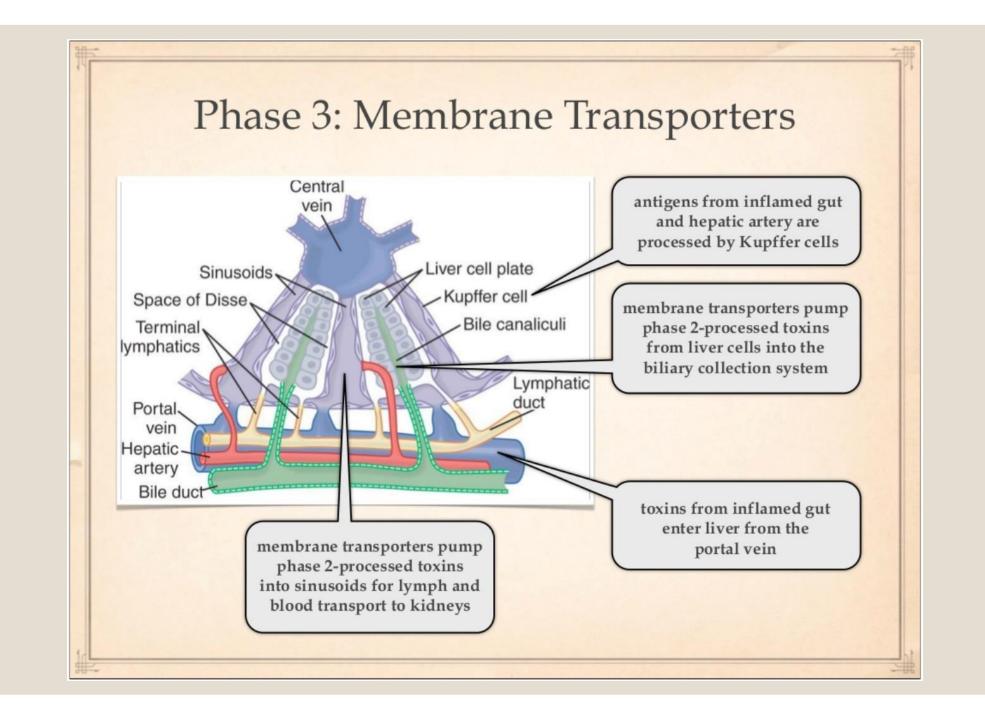
The liver handles 70% of the biotransformation work in the body. Other active sites for these pathways include:

- 1. kidneys
- 2. lungs
- 3. skin
- 4. intestinal cells
- 5. endothelial cells of the bloodbrain barrier

#### What these locations have in common:

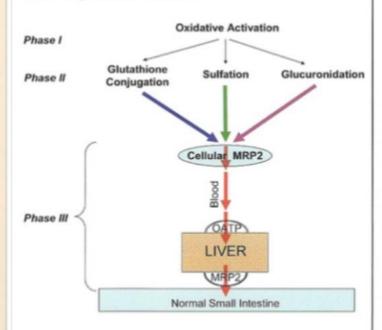
- 1. organs of detoxification
- 2. key tissue barriers





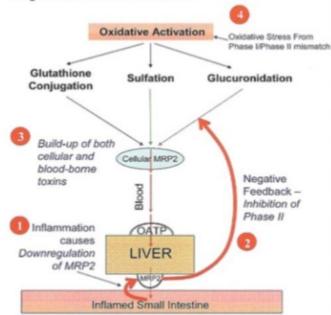
#### Natural Detoxification Pathways

#### **Healthy Detoxification**



Transporters between liver and intestines function well. This permits conjugates to enter the intestines for excretion. Also the transporters bring chemicals, such as glutathione, into the intestines, allowing for detoxification of the intestines as well.

#### Impaired Detoxification



Intestinal inflammation down regulates transporters. This leads to accumulation of toxins in the intestines and throughout the body. Oxidative damage caused by toxic buildup in the intestines causes further intestinal inflammation inhibition of transporters.

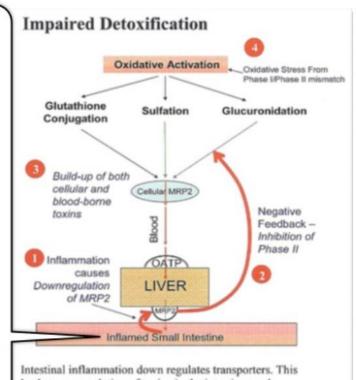
Slide courtesy of Chris Shade, PhD, of Quicksilver Scientific

#### Disrupting the Detoxification Chain

With compromise of small intestinal barrier integrity...

- 1. Small intestinal inflammation overworks phase 3 transporters.
- 2. **Phase 3 slowing** down-regulates phase 2 conjugation.
- 3. **Phase 2 slowing** results in a backlog of un-conjugated toxins.
- 4. Free radical damage rises due to the phase 1/phase 2 mismatch.

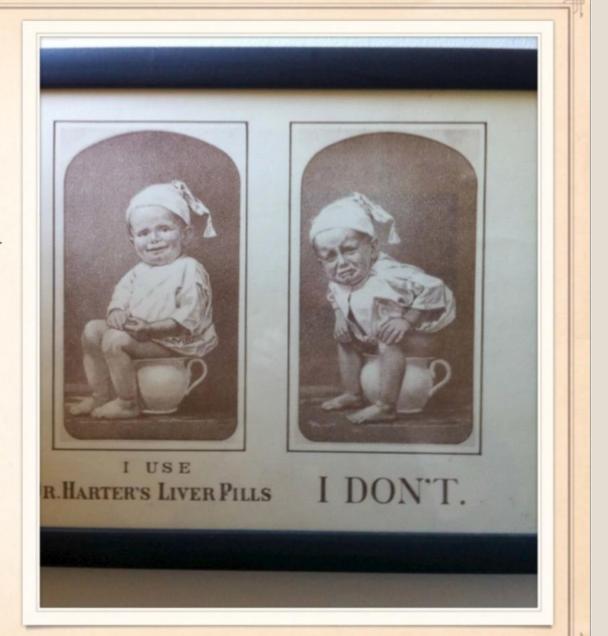
...comes systemic damage caused by chronic toxicity.



Intestinal inflammation down regulates transporters. This leads to accumulation of toxins in the intestines and throughout the body. Oxidative damage caused by toxic buildup in the intestines causes further intestinal inflammation inhibition of transporters.

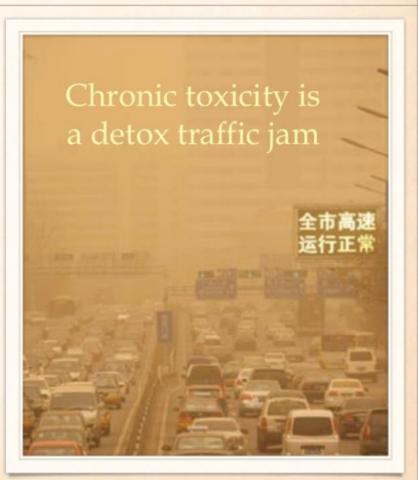
#### The Sluggish Bowel

Traffic jams in the gut space invite trouble.



# The main problem is not exposure level, but *toxicity retention* caused by slowed detoxification pathways.

- Sluggish and/or leaky bowel = slowed elimination, overworked transporters.
- Slowed phase 3 activity = retained toxicity as elimination doors close.
- Slowed phase 2 activity = phase 1/2 mismatch, more oxidative stress.
- Poor nutrition = added systemic pathway malfunctions.
- Weak genes = susceptibilities to slowed detox function at various systemic pathway points.
- Higher environmental exposure = greater risk of detox traffic jams.



#### How to Repair and Amplify Your Body's Detoxification Systems

- Get professional help. Find a good source of detoxification expertise.
- Repair the gut. Restrict reactive foods and restore a healthy gut microbiome.
- Mercury speciation testing. Assess the need for mercury detox support.
- Test for biotoxin susceptibility. As warranted based on history.
- Test for stealth infection. As warranted based on history.
- Get nutrition counseling. For help with dietary changes, detox support.
- Try acupuncture. And other methods for balancing energy flow.
- Healthy lifestyle change. Find the structure and support you need.

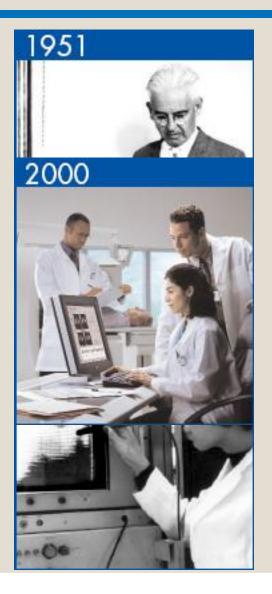


Warrior One Pose



#### History

□1946 → first uses of nuclear medicine
 □1950s → Widespread clinical use of nuclear medicine began
 □1960s → measuring blood flow to the lungs and identifying cancer
 □1970s → most organs of the body could be visualized with nuclear medicine procedures
 □1980s → Radiopharmaceuticals, monoclonal antibodies, FDG
 □1990s → PET



## What is Nuclear Medicine?

- Nuclear medicine is very unique, because it helps doctors view <u>how</u> your body is functioning.
- This type of imaging takes very small amounts of radioactive pharmaceuticals and follows their path and progress through your body.
- X-rays or CAT scans can show how something in your body looks, but Nuclear Medicine can show how your body actually works.

# What is Nuclear Medicine? (continued...)

- Nuclear medicine is a type of molecular imaging where radioactive pharmaceuticals (often called "radiopharmaceuticals") are used to evaluate the body's functions and processes
- This type of imaging can be used on all types of living things, but NMTCB is concerned with using this technology to help diagnose and treat human beings.

# What is Nuclear Medicine? (continued...)

- NUCLEAR MEDICINE <u>IMAGING</u> procedures look at the bodily functions to help make your diagnosis.
- NUCLEAR MEDICINE <u>THERAPY</u> can actually be used to treat the body. If you are undergoing a therapy process, then larger amounts of radiation will be used to treat cancer or thyroid disease.

## What are radioisotopes?

- The isotopes of an element have the same number of protons in their atoms (atomic number) but different masses due to different numbers of neutrons.
- □ In an atom in the neutral state, the number of external electrons also equals the atomic number.
- These electrons determine the chemistry of the atom.
- The atomic mass is the sum of the protons and neutrons.
- □There are 82 stable elements and about 275 stable isotopes of these elements.
- □When a combination of neutrons and protons, which does not already exist in nature, is produced artificially, the atom will be unstable and is called a radioactive isotope or radioisotope.
- There are also a number of unstable natural isotopes arising from the decay of primordial uranium and thorium.
- Overall there are some 1800 radioisotopes.

#### What are radioisotopes?

- At present there are up to 200 radioisotopes used on a regular basis, and most must be produced artificially.
- Radioisotopes can be manufactured in several ways.
  - 1. The most common is by neutron activation in a nuclear reactor. This involves the capture of a neutron by the nucleus of an atom resulting in an excess of neutrons (neutron rich).
  - 2. Some radioisotopes are manufactured in a cyclotron in which protons are introduced to the nucleus resulting in a deficiency of neutrons (proton rich).
- The nucleus of a radioisotope usually becomes stable by emitting an alpha and/or beta particle (or positron). These particles may be accompanied by the emission of energy in the form of electromagnetic radiation known as gamma rays. This process is known as radioactive decay.
- Radioactive products which are used in medicine are referred to as radiopharmaceuticals.

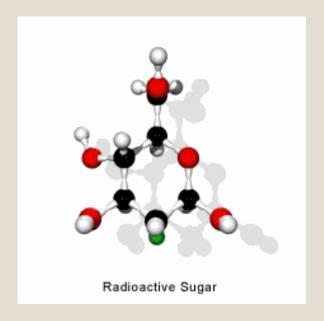
## Radioisotopes

PET

- Radionuclides used in PET scanning are typically isotopes with short half lives
  - Oxygen-15 (~2 min)
  - Nitrogen-13 (~10 min)
  - Carbon-11 (~20 min)
  - Fluorine-18 (~110 min)
- These radionuclides are incorporated either into compounds normally used by the body such as glucose (or glucose analogues), water or ammonia, or into molecules that bind to receptors or other sites of drug action (radiotracers).

#### FDG

- Most clinical PET studies in oncology utilize [18F] 2-Fluoro-2-Deoxy-D-Glucose more commonly known as "FDG".
- □FDG, an analog of glucose, becomes trapped in the cells that try to metabolize it. Its concentration is tissue builds up in proportion to the rate of glucose metabolism. Because tumors have a high rate of glucose metabolism, they concentrate FDG, and appear as "hot spots" in PET images.



# What will they do to me during a nuclear medicine procedure?

- You will be given an "imaging agent." This could be given to you in a variety of ways: possibly by swallowing a pill, through an injection, an inhaler, or even a special meal you will need to eat.
- 2. The imaging agent will travel to the specific organ or tissue that needs to be studied.
- 3. You will have pictures of your body taken with a specialized camera from inside a scanner.
- 4. Your medical team will receive the images of your body to review and evaluate.

## Radiotherapy

- Rapidly dividing cells are particularly sensitive to damage by radiation.
- For this reason, some cancerous growths can be controlled or eliminated by irradiating the area containing the growth.
- Many therapeutic procedures are palliative, usually to relieve pain. For instance, strontium-89 and (increasingly) samarium 153 are used for the relief of cancer-induced bone pain. Rhenium-186 is a newer product for this.
- Treating leukemia may involve a bone marrow transplant, in which case the defective bone marrow will first be killed off with a massive (and otherwise lethal) dose of radiation before being replaced with healthy bone marrow from a donor.

#### TAT

- A new field is Targeted Alpha Therapy (TAT), especially for the control of dispersed cancers. The short range of very energetic alpha emissions in tissue means that a large fraction of that irradiative energy goes into the targeted cancer cells, once a carrier has taken the alpha-emitting radionuclide to exactly the right place.
- Therapy using boron-10 which concentrates in malignant brain tumors. The patient is then irradiated with thermal neutrons which are strongly absorbed by the boron, producing high-energy alpha particles which kill the cancer.

#### Advantages

- It provides doctors with information about both structure and function.
- It's a way to gather the medical information that would otherwise be unavailable, require surgery, or necessitate more expensive diagnostic tests.
- Often identify abnormalities very early in the progress of a disease, long before many medical problems are apparent with other diagnostic test.
- It determines the presence of a disease based on biological changes rather than changes in anatomy.
- Combination with CT scan can give the image of both bone and soft tissue.
- It's extremely safe because
  - The radioactive tracers, or radiopharmaceuticals, used are quickly eliminated from the body through its natural functions.
  - The tracers used rapidly lose their radioactivity.
  - The dose of radiation necessary for a scan is very small.

## Why is Nuclear Medicine so important?

- Nuclear medicine imaging can help with early detection or discovery of changes in your body's functions.
- Physicians need an accurate diagnosis first, so they can formulate an ideal treatment plan specifically for <u>you</u>r needs!
- This detection could help your care team avoid having to perform invasive procedures and possibly treat the problem without surgery.

## What about the radiation?

- Very small amounts of radiation are given during nuclear medicine imaging scans.
- Larger amounts are used for therapy in order to target very specific areas.
- The scanners (equipment) do <u>not</u> give off radiation.

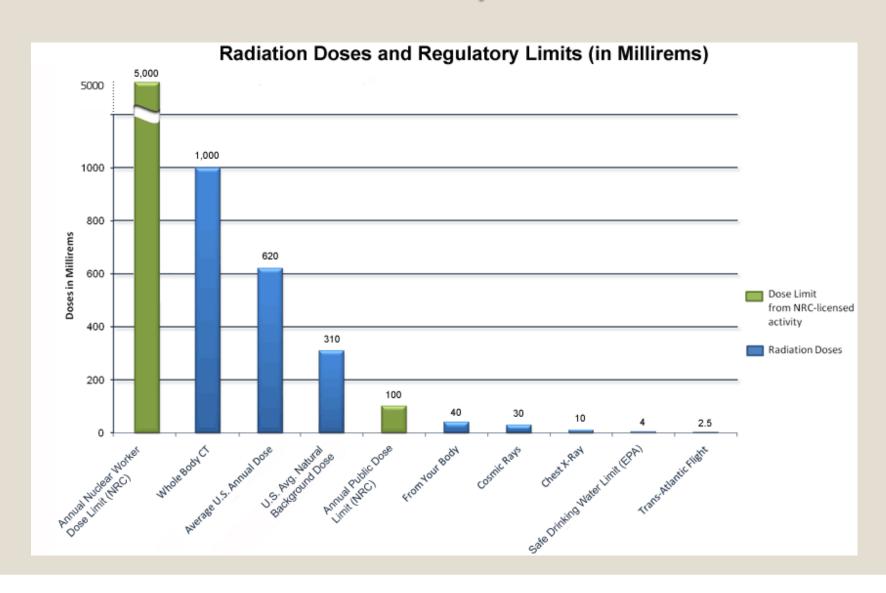
#### But I <u>really</u> don't like the idea of radiation...

- Radiation is actually in small doses all around us!
- On average, Americans receive a radiation dose of about 0.62 rem (620 millirem) each year. Half of this dose comes from natural background radiation.
- Most of this background exposure comes from radon in the air, with smaller amounts from cosmic rays and the Earth itself.
- Radon in homes, Air travel radiation
- Even bananas! (Bananas are radioactive enough to regularly cause false alarms on radiation sensors used to detect nuclear material at US ports!)

## Radiation is really everywhere?

- Yep, it sure is! We live in a radioactive world, and radiation has always been all around us as a part of our natural environment.
- The annual average dose per person from all sources is about 360 mrem, but it is not uncommon for any of us to receive more than that average does in a given year (largely as a result of medical procedures).

## Radiation Comparison



#### Risk or Benefit?

- Each exposure to radiation carries its own very small risk. So, the third or fourth scan you have carries the <u>exact</u> same risk as the very first.
- -The benefit of having a correct diagnosis and discovering what is going on in your body outweighs the risk of the exam itself.

