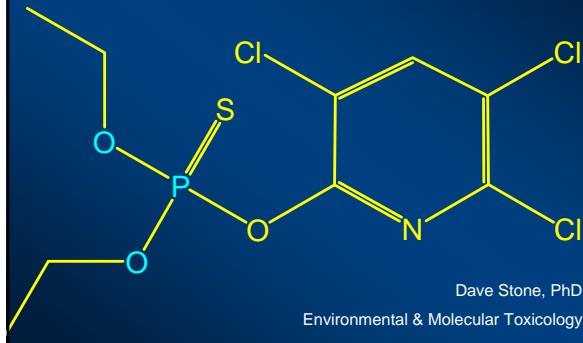
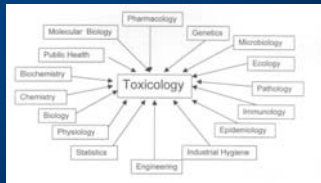


Fundamentals of Toxicology



Outline

- I. A Very Brief History of Toxicology
- II. Exposure & Dose-Response
- III. Risk
- IV. Toxicology in the 21st Century
- V. Case study: Pesticides & Endocrine Disruption



A Very Brief History of Toxicology:

"What is there that is not a poison? All things are a poison and nothing is without poison. Solely the dose determines that a thing is not a poison"Paracelsus, 16th Century



First Occupational Links to Disease:
 -scrotal cancer & chimney sweeps
 -breast cancer and nuns
 -Madam Curie & radiation



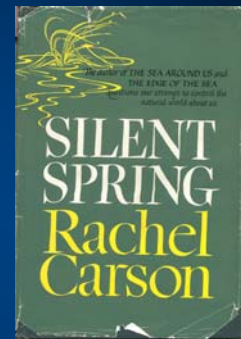
Major incidents:
 -Ginger Jake Syndrome
 -Thalidomide
 -Bhopal & Union Carbide

Examples: Metals



Environmental & Public Awareness:

"For the first time in the history of the world, every human being is now subjected to contact with dangerous chemicals, from the moment of conception until death"
 Rachel Carson, 1962.



Exposure:

The potential for toxicity is dependent upon exposure. The mere presence of a toxic agent is not enough.

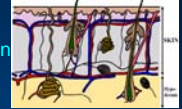


Exposure Questions: Amount - Frequency - Duration

Complete Exposure Pathways:

- 1) A source of contamination
- 2) Transportation through a medium
- 3) A point of exposure
- 4) A route of human exposure
- 5) An exposed population

Skin absorption



Inhalation

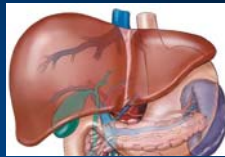


Ingestion



What happens after exposure?

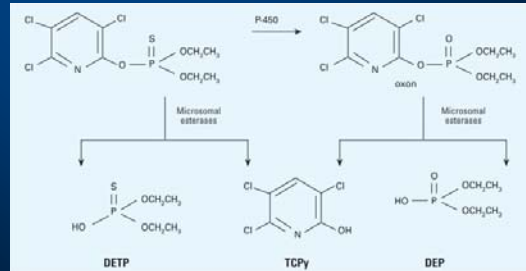
-first major organ to be exposed to chemicals via the portal blood supply
-toxins may be changed by this "first pass" effect prior to entering the bloodstream



Phase I: reactions consist of oxidation/reduction reactions which usually results in more polar (water soluble) metabolites

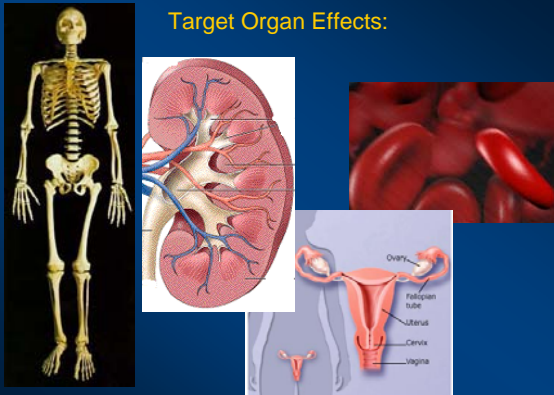
Phase II: consists of various conjugations to enhance elimination.

Metabolism:

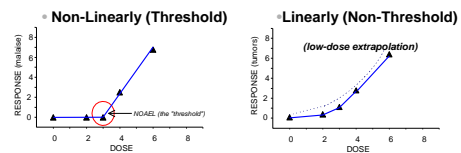


Needham, L. (2005). Assessing Exposure to Organophosphorus Pesticides by Biomonitoring in Epidemiologic Studies of Birth Outcomes. Environ Health Perspect 113, 494-498

Target Organ Effects:

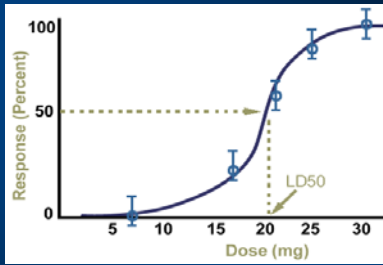


Dose-Response:

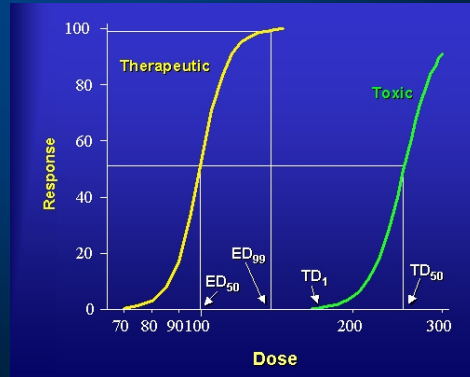


Dose-response testing is often used to determine a reference dose (RfD) for humans. RfD is defined as an estimate of daily oral exposure that is likely to be without an appreciative risk of deleterious effects over a lifetime.

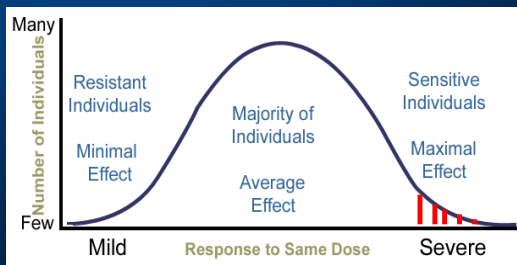
LD₅₀



- How many dose groups were tested? Sample size? Species? Gender?
- How was the agent delivered?
- How steep is the curve? At what dose are effects seen (LOAEL)? At what dose are effects not seen (NOAEL)? What is the maximum tolerated dose?
- What are appropriate uncertainty factors?



Population Susceptibility:



Sensitive populations

- Pregnant and nursing mothers & *in utero* exposures
- Infants, young children & the elderly
- People with pre-existing conditions, especially respiratory & CV disease
- Emerging role of genetics
- Subsistence or unusual exposure scenarios



Toxicology in the 21st Century



- Genomics
- Epigenomics
- Transcriptomics
- Proteomics
- Metabolomics
- Metabonomics
- Pharmacogenomics
- Toxicogenomics
- Bioinformatics

Assay testing; not animals

Risk Context Needed

High Throughput Screening

Biomonitoring

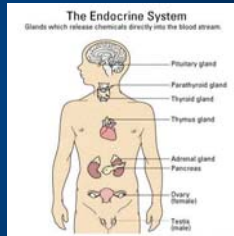
Bioinformatics

QuickTime™ and a decompressor are needed to see this picture.

QuickTime™ and a decompressor are needed to see this picture.

National Academy of Science 2007

Case Study: Pesticides & Endocrine Disruption



Pituitary Gland: the "master gland" secretes a battery of hormones that directs other endocrine glands to produce hormones, influencing virtually all cells & all physiologic processes.

Hypothalamus: "the power behind the throne;" found above the pituitary gland, produces "releasing factors" that direct the pituitary to release its hormones.



Hermaphroditic fish near sewage outfalls



Declining populations and deformed frogs



Declining reproductive success in a variety of marine species and birds



Natural causes - parasites



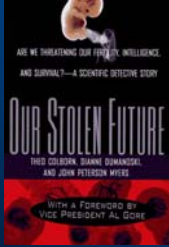
Trematode cysts (seen as little dark spots) completely inhibited limb development in this frog (photograph by S.K. Sessions).



Example of a tadpole with extra, deformed limbs induced by exposure at an early limb bud stage (photograph by S.K. Sessions).

S-methoprene: IGR was originally suspected

What about human health?



- Decreased sperm counts?
- Increased breast cancer?
- Increased testicular cancer?
- Increased incidence of hypospadias?
- Increased behavioral problems (ADD/ADHD)?
- Other effects?

Are sperm counts declining?

- British Medical Journal 1992
- Based on a review of all publications between 1938 and 1991 that reported sperm counts in normal men (61 papers, data on 15,000 men)

A 42% drop in average sperm counts
A significant decrease in semen volume

Other Studies

- Semen analysis in 1,283 men from the United States over a 25- year period: no decline in quality.
- Geographic variations in sperm counts: a potential cause of bias in studies of semen quality.
- Data from men in greater Seattle area reveals no downward trend in semen quality: further evidence that deterioration of semen quality is not geographically uniform.

Again, consider sensitive populations:

Estrogenic effects of soy protein on:

- a developing male fetus (feminize?)
- a newborn girl (early puberty?)
- an adult female (altered breast cancer risk)
- an adult male (lower prostate cancer risk?)

If natural estrogen =	1
DES =	10 (need 0.1x)
Fungal toxins =	0.01 (need 100x)
Soy proteins =	0.0001 (need 1000x)
DDT =	0.000001 (need 100,000x)
Nonylphenols =	0.000003 (need 300,000x)

Focus Questions

How much should we know about chemicals before production and use?

Do we regulate natural and synthetic chemicals differently? And if so, why?

What are some of the factors that influence how you are exposed and respond to chemicals?