Toxicology 102: Toxics and Health

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What is Toxicology?

- The study of poisons, with special attention to the adverse effects on biological systems
  - Changes that result in impaired ability to compensate for additional stress or an increase in susceptibility to other environmental influences
- "The dose makes the poison." – Paracelcus

Toxicology Lingo

- **LC_{50}** and **LD_{50}** – "Lethal Concentration 50" and "Lethal Dose 50" – the concentration or dose that will result in mortality to one-half of the population exposed
  - Used to describe general level of acute toxicity (e.g., non-toxic, slightly toxic)

Toxicology Lingo (cont'd)

- **NO(A)EL** – "No Observed (Adverse) Effect Level" – the highest experimental dose or concentration at which no statistically significant difference between controls and treated animals can be detected

- **Threshold** – the dose or concentration below which no adverse effect is detected

Toxicology Lingo (cont'd)

- **LO(A)EL** – "Lowest Observed (Adverse) Effect Level" – the lowest experimental dose or concentration at which a statistically significant difference between controls and treated animals is detected

Measures of “Time”

- **Acute** – usually up to 14 days
- **Subacute** – approximately 21 days; not long enough to be called "chronic"
- **Subchronic** – up to 10% of an animal’s lifespan; between 5 – 90 days
- **Chronic** – more than 10% of an animal’s lifespan; more than one year

The Risk Assessment Process

- **Hazard identification**
  - What could be the adverse outcome(s)?
- **Dose-response analysis**
  - What quantity causes which effect(s)?
- **Exposure assessment**
  - Who will be exposed? How? How often?
- **Risk characterization**
  - How likely is the effect to occur?

Hazard Identification

- Mortality
- Tumors (benign or malignant)
- Reproductive/developmental outcome
- Behavioral effects
- Changes in body weight or ratio of organ weight to body weight
- Organ failure
- Tissue morphology changes
- Enzyme activity (urinalysis or blood test)

Some Known and Potential Health Effects of Dioxins and Furans

- Chloracne and other skin effects
- Changes in ability of liver to process fats, sugar, and protein
- Endocrine changes
- Reproductive and developmental problems
- Weakened immune system
- Cancer

Some Known and Potential Health Effects of Polychlorinated Biphenyls

- Acne and rashes
- Nose and lung irritation
- Gastrointestinal discomfort
- Depression and behavioral changes
- Liver and kidney damage
- Endocrine changes
- Impaired reproduction
- Cancer

Some Known and Potential Health Effects of Chlorinated Pesticides

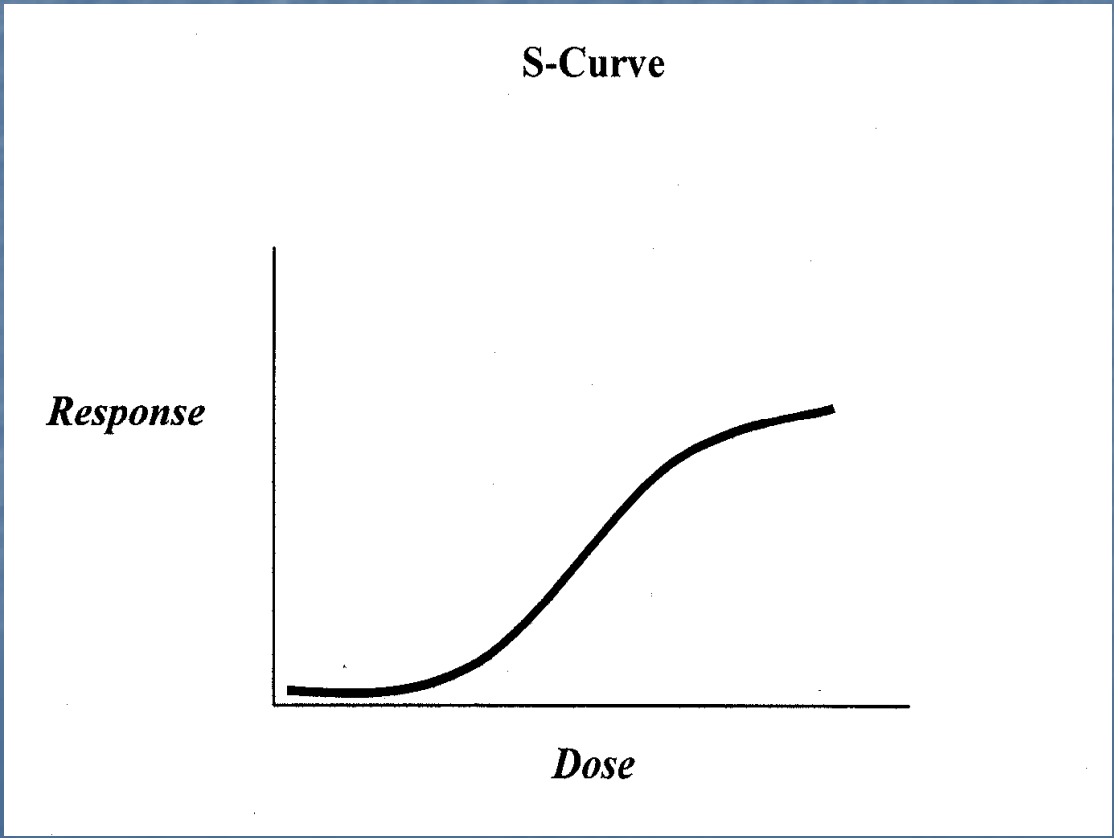
- Nervous system effects including tremors, seizures headache, dizziness, and excitability
- Nausea and vomiting
- Pre-term births and reproductive problems
- Damage to the liver and the adrenal gland
- Cancer

Some Known and Potential Effects of Mercury

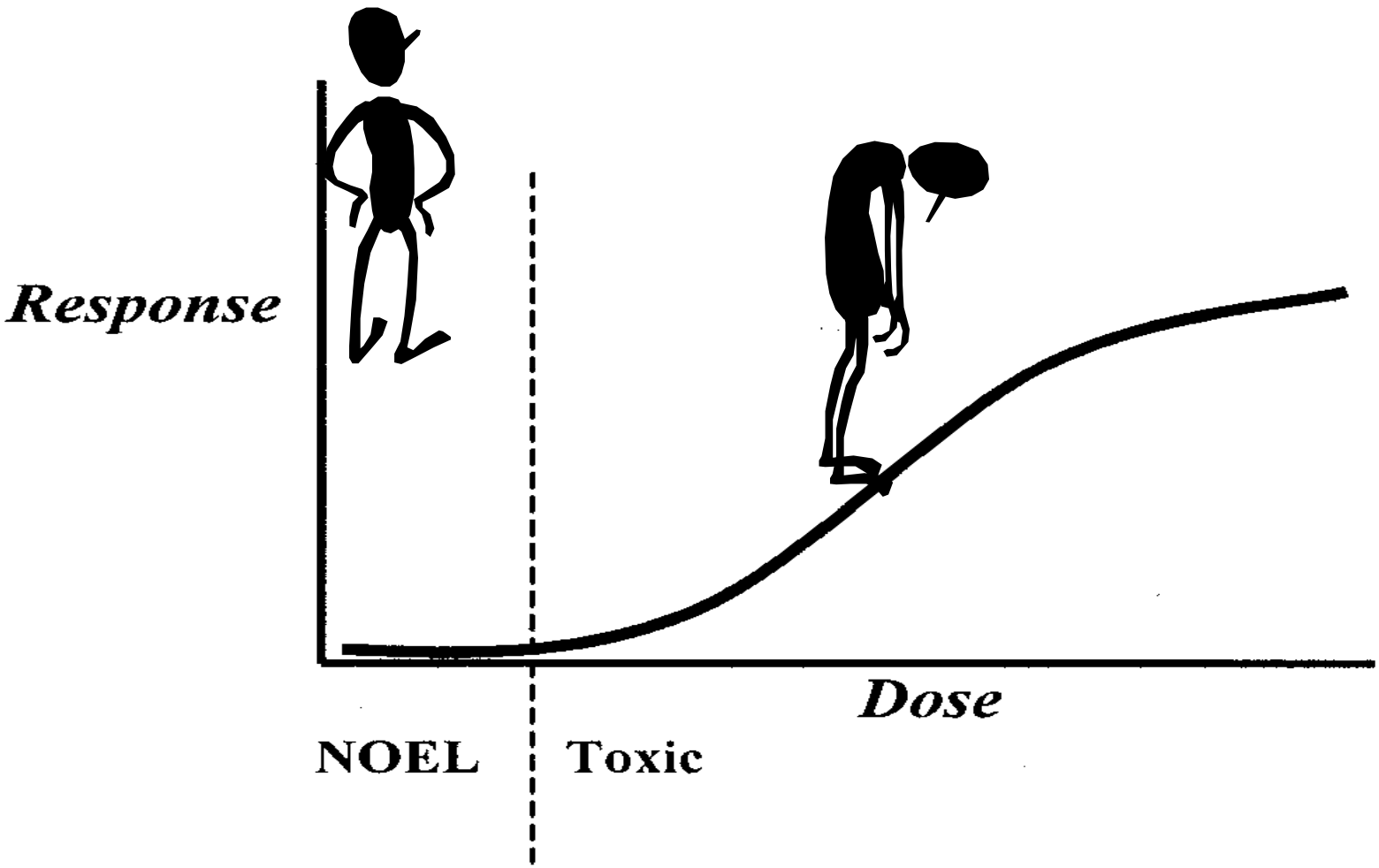
- Nervous system damage including personality changes, tremors, vision change, loss of muscle coordination, memory difficulties
- Kidney damage
- Lung irritation/coughing
- Nausea, vomiting, diarrhea
- Increased heart rate and blood pressure

Dose-Response Assessment

- How does the response (effect) change with increasing dose?



Toxicology



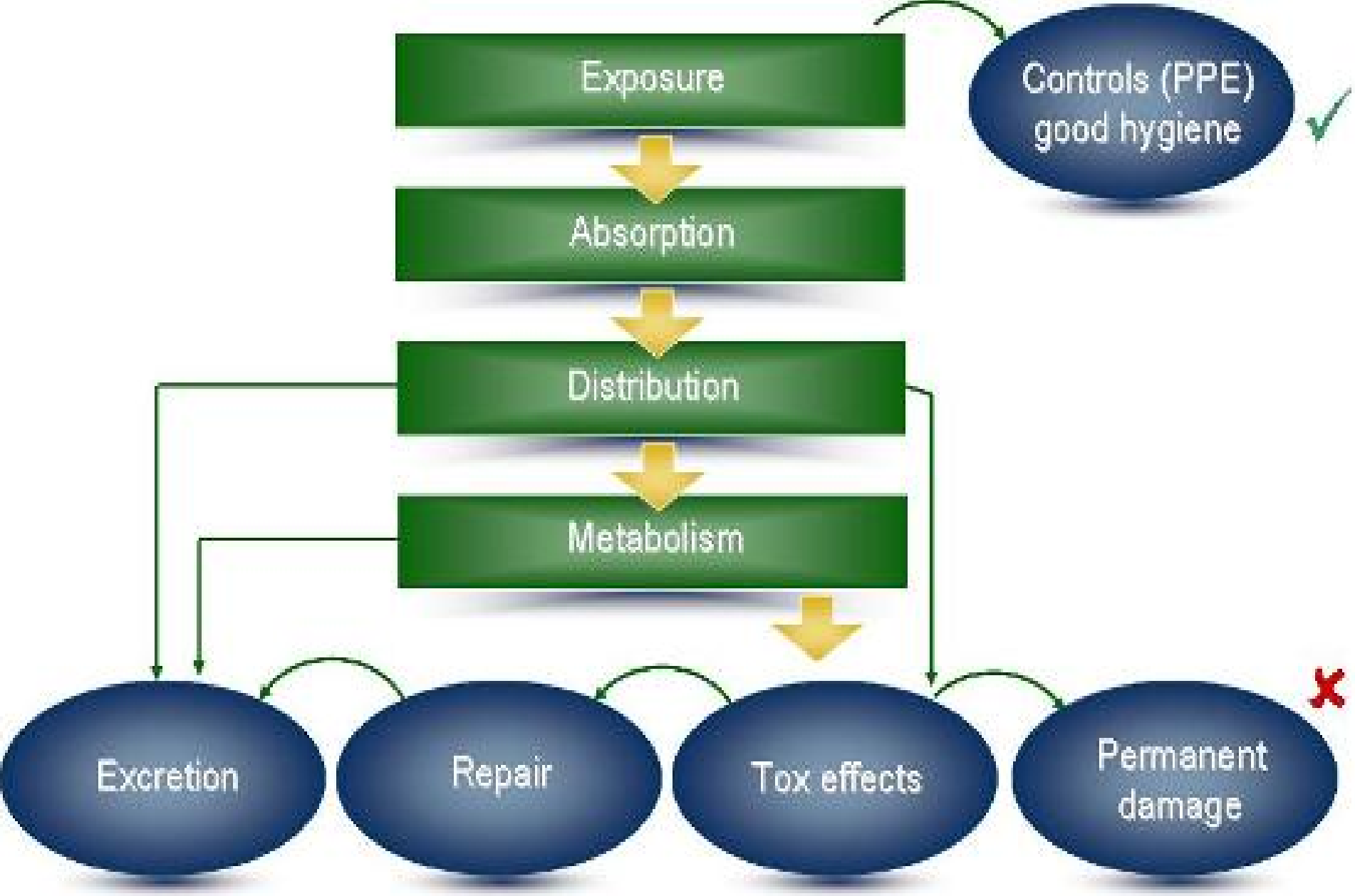
Dose-Response Assessment (cont'd)

- It is helpful to understand "ADME":
  - **Absorption** – how does (and how much of) the substance enter the body?
    - Lungs, small intestine, directly to bloodstream?
  - **Distribution** – where does the substance go?
    - Pb goes to bone; Cd to kidneys; DDT to adipose
    - BUT…the toxic effect may be seen elsewhere

Dose-Response Assessment (cont'd)

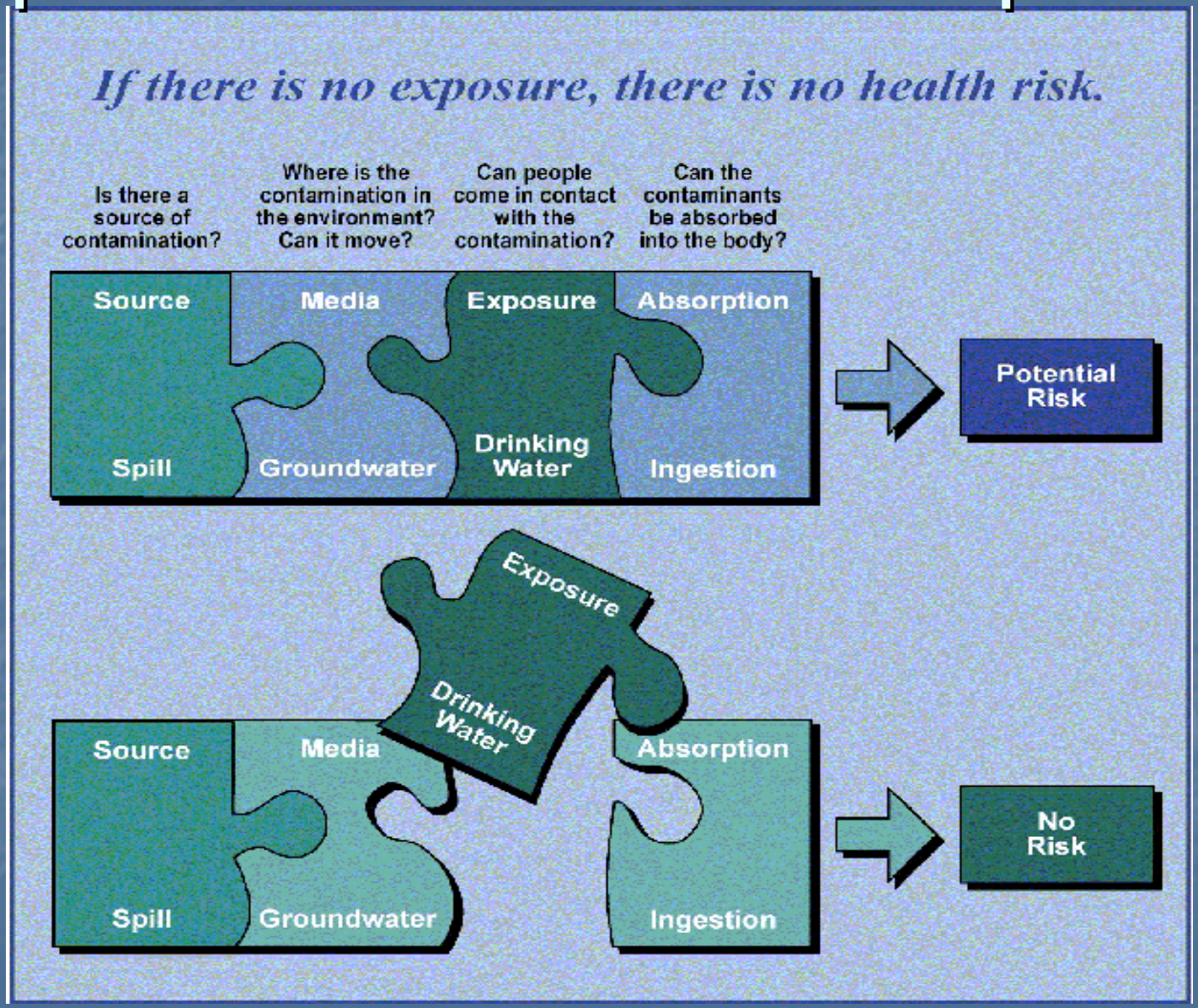
- **Metabolism** – What happens to the substance when it interacts with a cell/tissue/organ system?
  - CYP450, COX-2, GSH, ROS can make a substance MORE or LESS toxic

- **Excretion** – How long does the substance persist in the body? How is it removed?
  - Longer excretion time leads to higher body burden
  - Urine, feces, sweat, breast milk, weight loss?



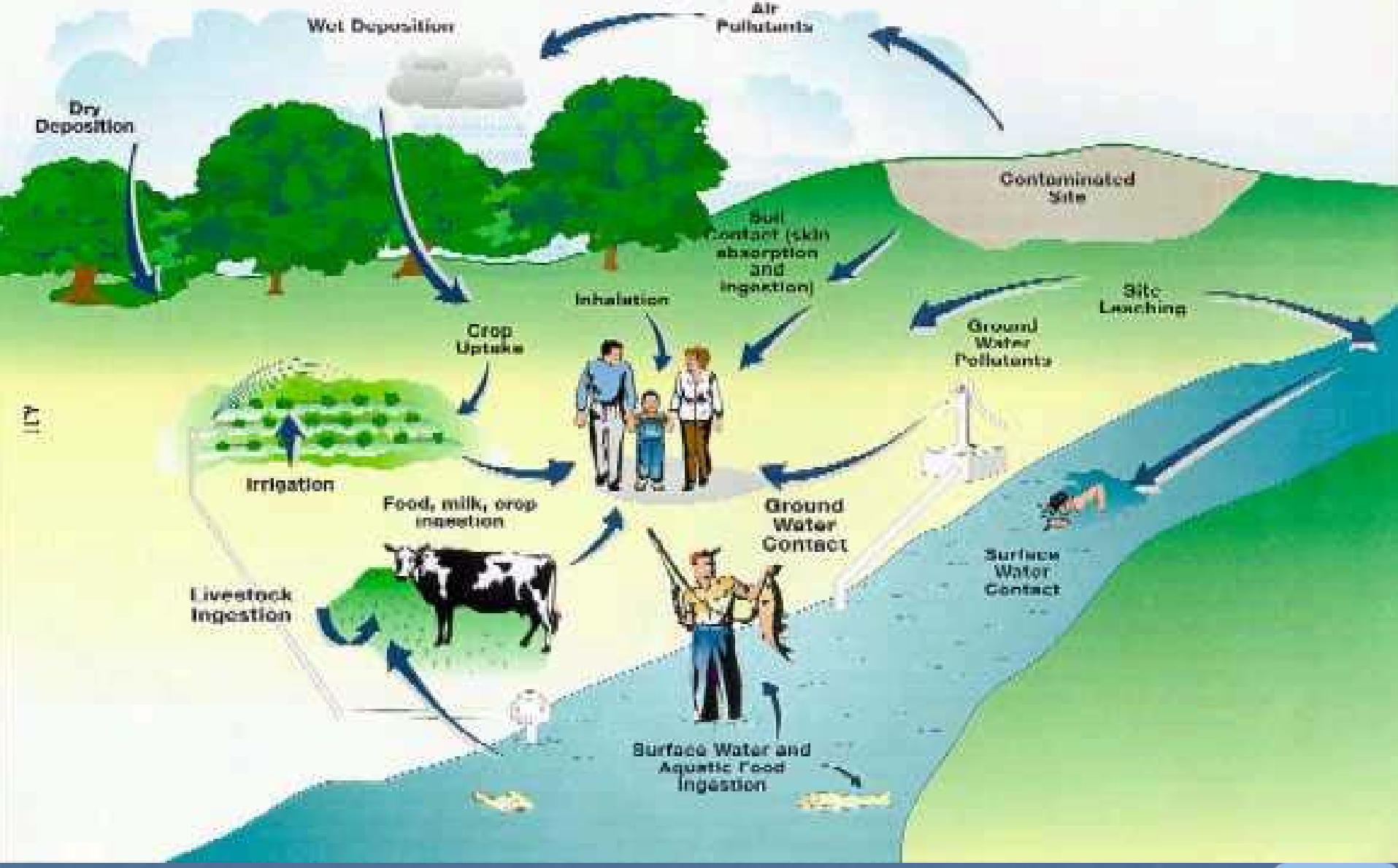
http://www.cee.vt.edu/ewr/environmental/teach/gwprimer/btex/intake.gif

Exposure Assessment is Important



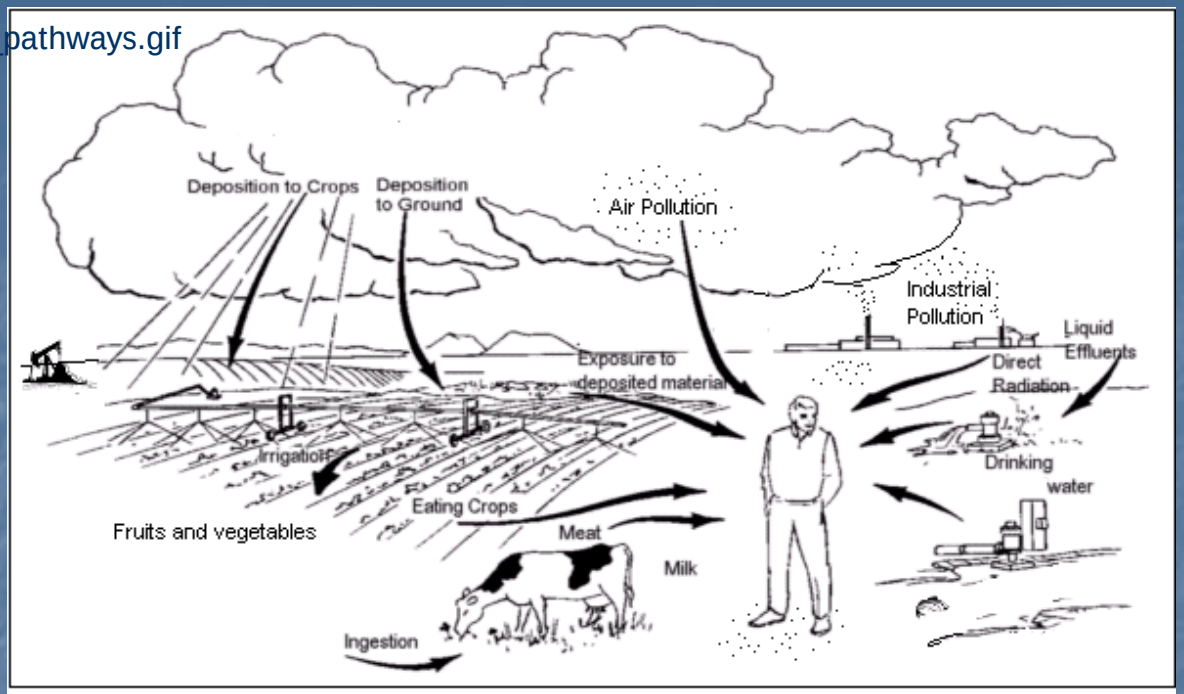
http://www.mmr.org/irp/genprog/riskinfo/risk.htm

Health Risk Exposure Pathways

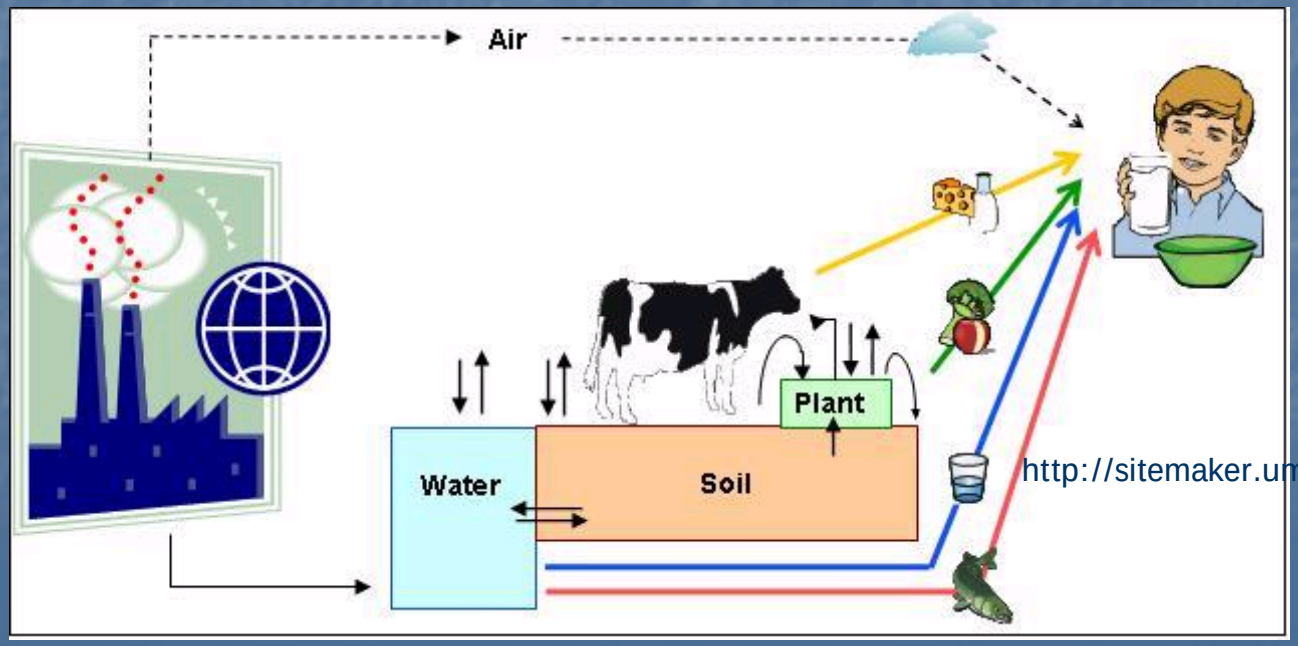


http://www.mvs.usace.army.mil/eng-con/expertise/fusrap/Pathways.jpg

http://www.ehib.org/faqs/images/exposure_pathways.gif



Pathways to exposure from contamination

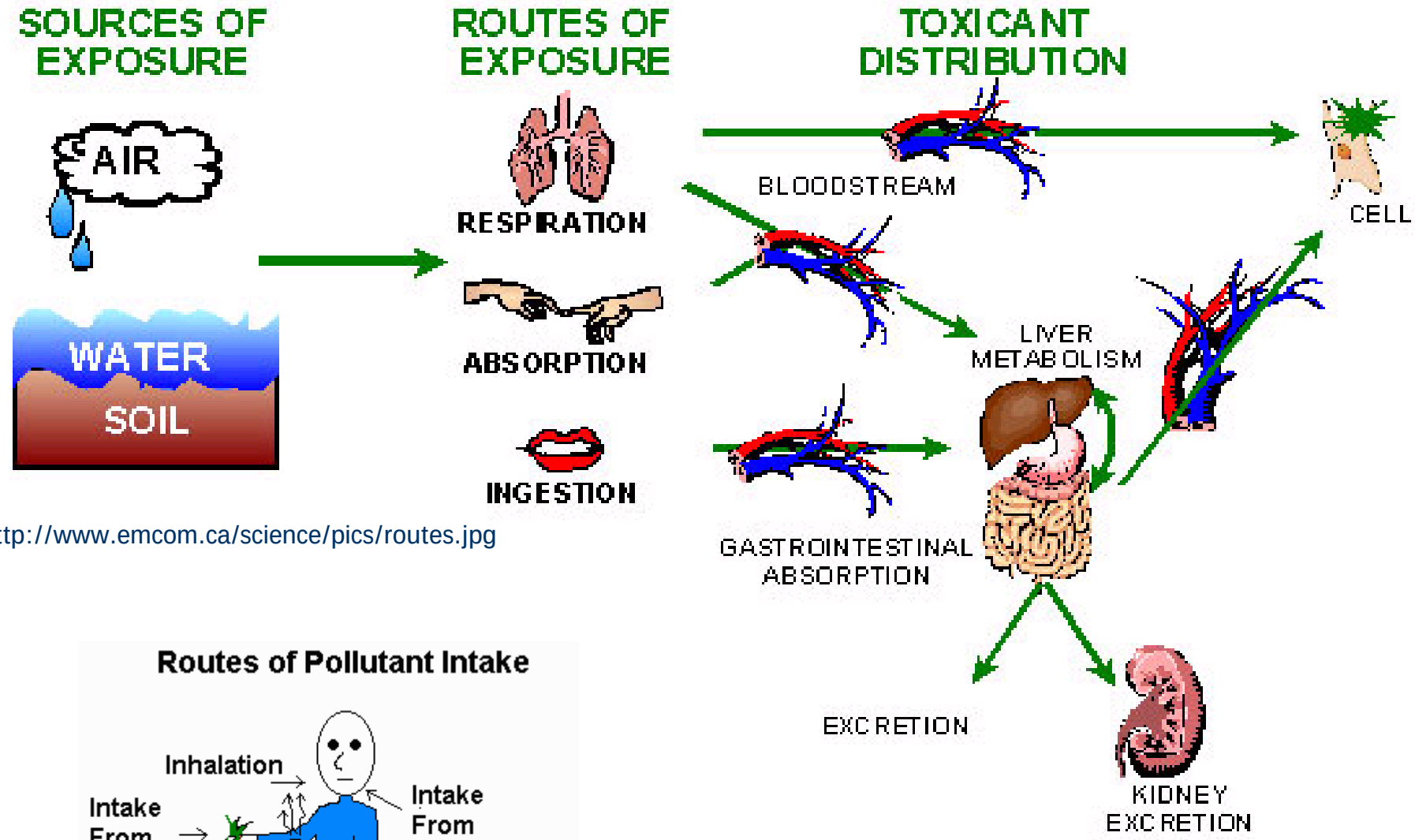


http://sitemaker.umich.edu/shaked/files/factorytoperson.jpg

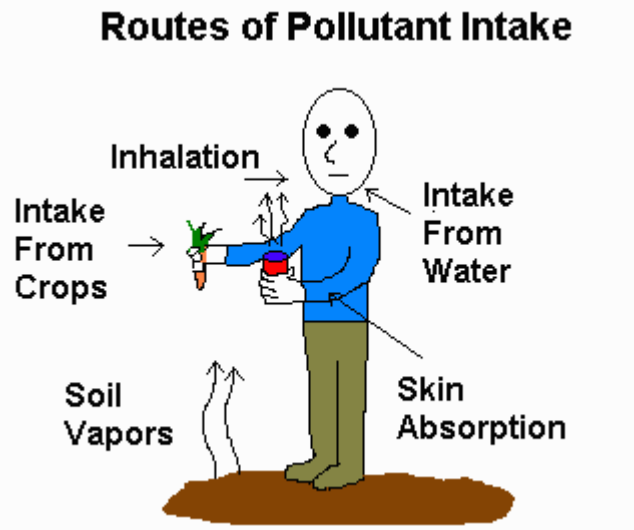
Exposure Assessment

- Who? – Children? Workers? Smokers?
- What (else)? – Other medications, alcohol?
- Where? – Skin? Stomach? Lungs? Eyes?
- When? – Every day? Only *in utero*?
- How? – A little all the time or a lot at once?

- Ultimately concerned with the duration, frequency, and intensity of the exposure



http://www.emcom.ca/science/pics/routes.jpg



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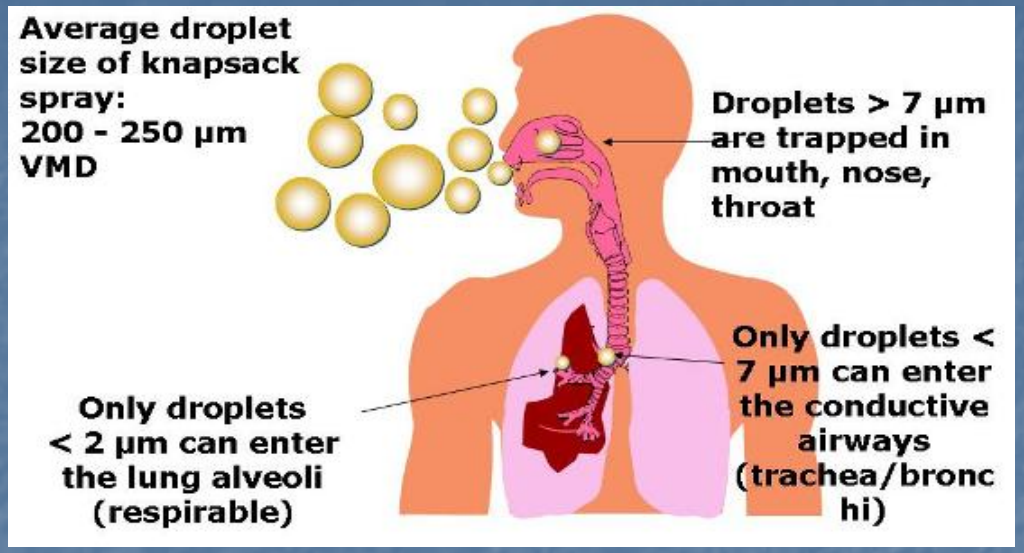
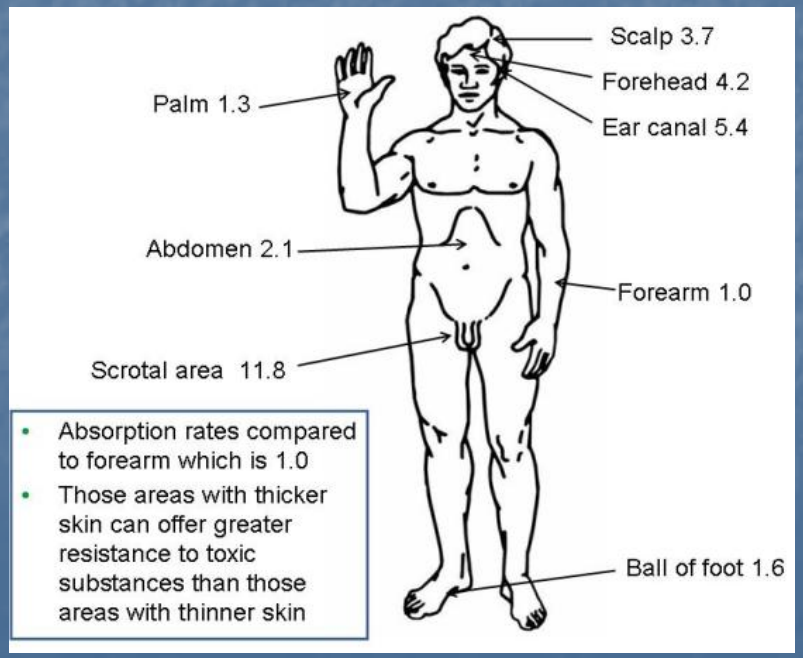
Considerations for Inhalation & Dermal Exposure

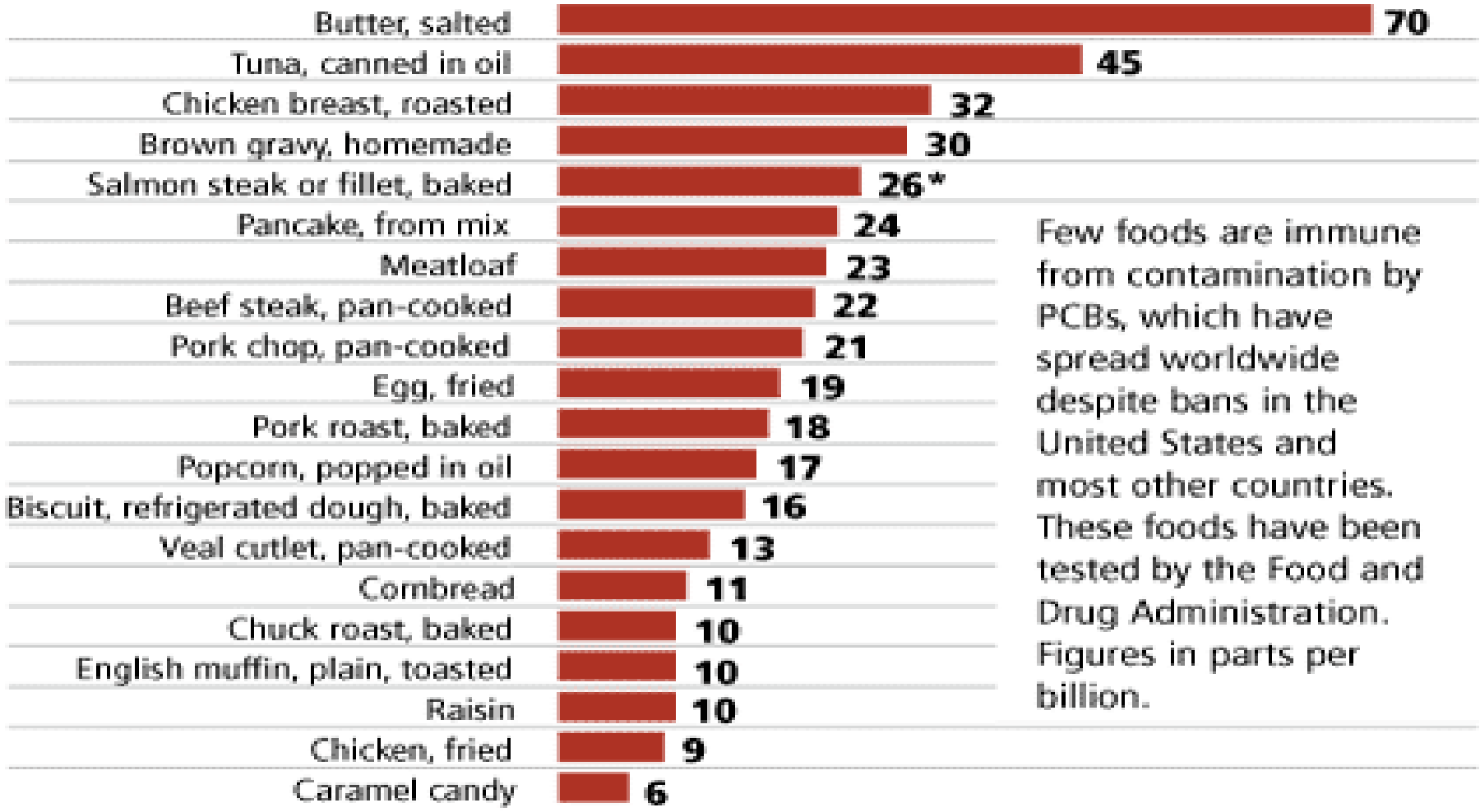




http://www.stewardshipcommunity.com

Michigan DNRE

PCB LEVELS IN OTHER FOODS



Few foods are immune from contamination by PCBs, which have spread worldwide despite bans in the United States and most other countries. These foods have been tested by the Food and Drug Administration. Figures in parts per billion.

All amounts in parts per billion (ppb). *Puget Sound salmon tested higher.
Source: FDA

SEATTLE POST-INTELLIGENCER

Michigan DNRE

PCBs, Furans, and Dioxins in Food

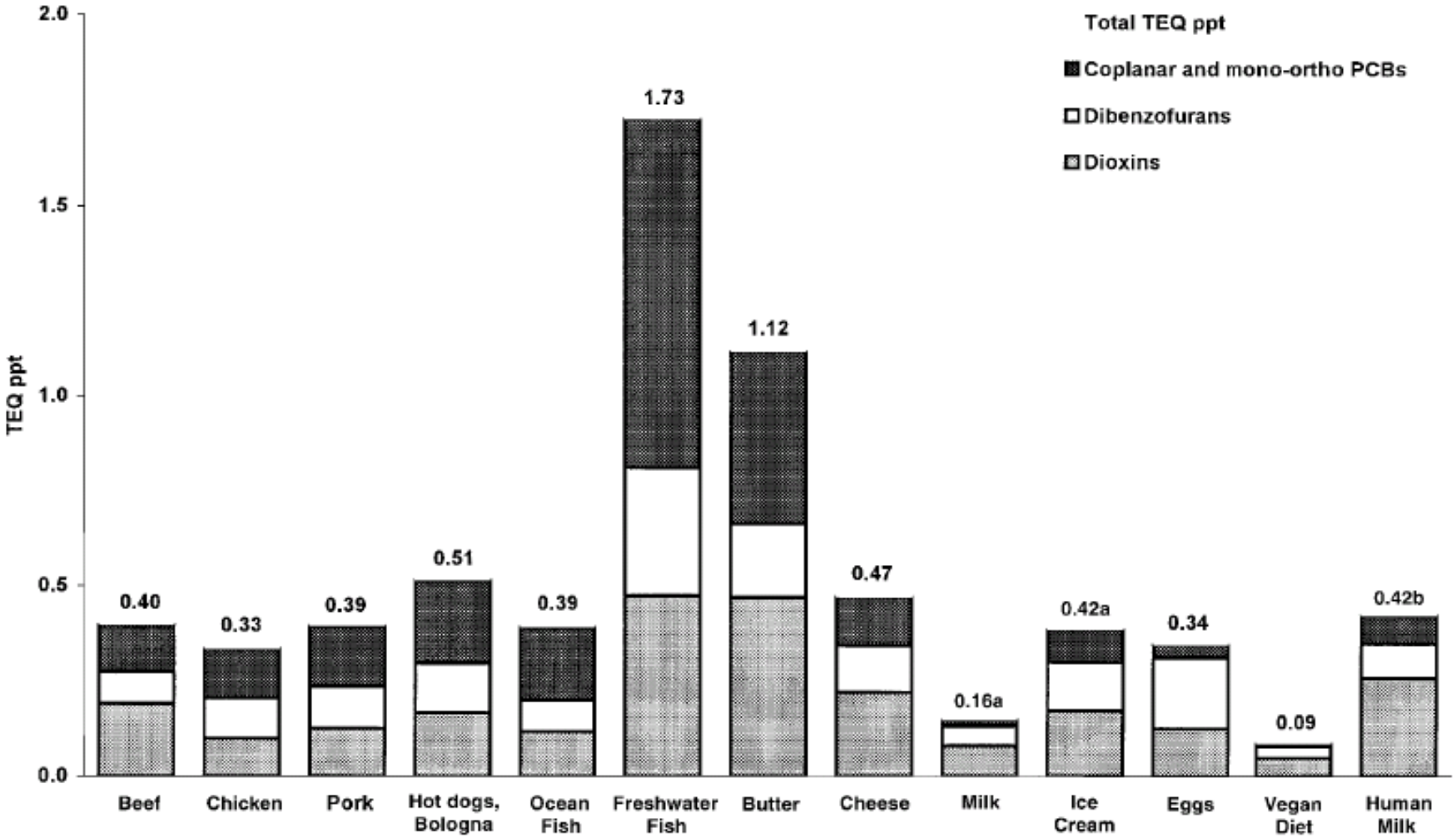
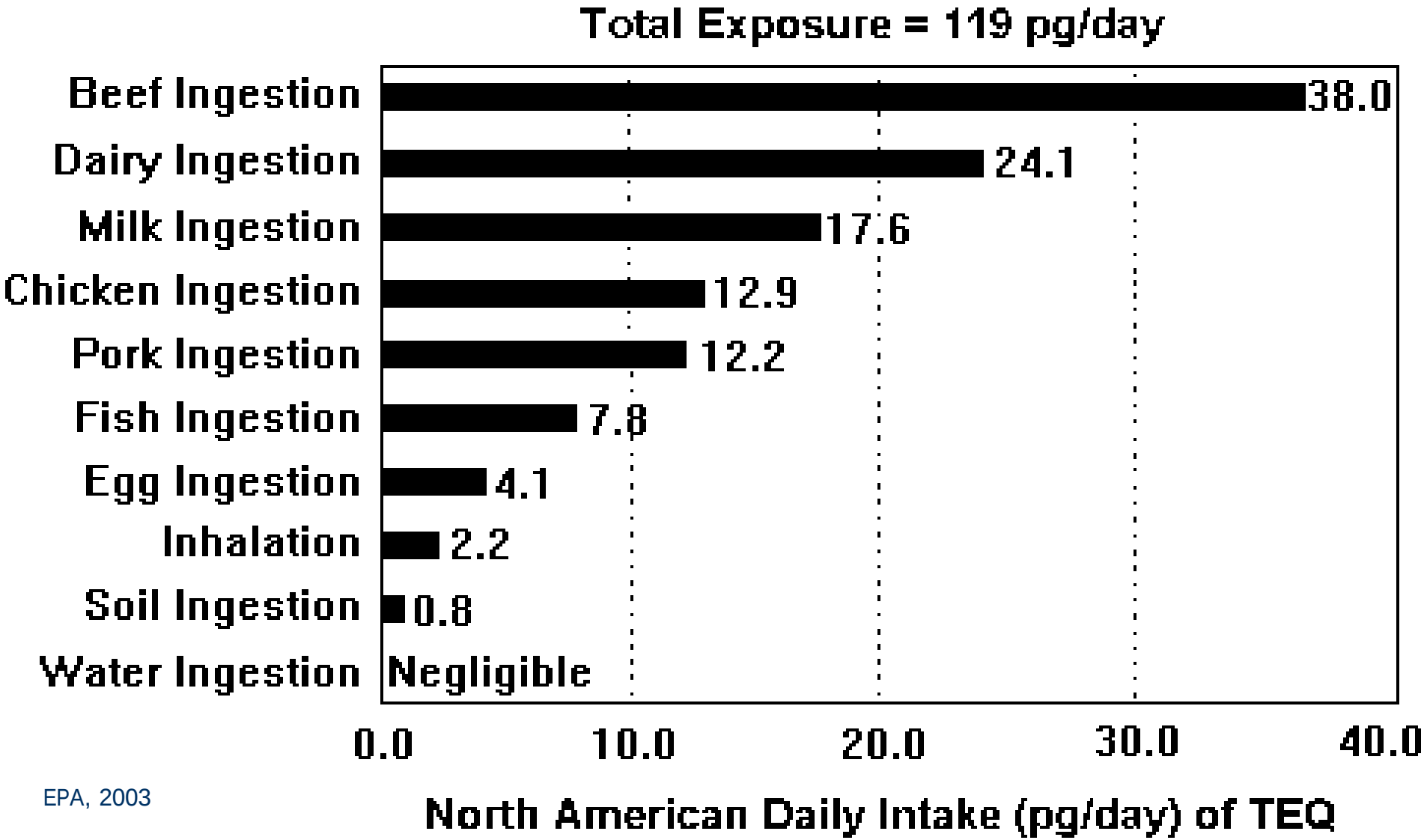


FIGURE 1. Dioxin, dibenzofuran, and PCB TEQs in collected foods and in human milk, pg/g (ppt) wet weight. (A) Nondetects = ½ limit of detection. a, Corrected by factor of 1.08 to compensate for missing PCB data. b, Actual value may be higher. Not corrected to compensate for missing PCB data.

Schecter et al., 2001

Divvying Up Dioxin



EPA, 2003

Risk Characterization

- Probability of an adverse effect occurring
- Requires statistical models (some relatively complicated) and mathematical calculations (some require computers)
- Explain the uncertainty in the assessment

- The State of Michigan regulates to zero increased effects from noncarcinogens
- Acceptable carcinogen risk is 1 in 100,000

Key Assumptions

- Adult body weight = 70 kg
- Water intake = 2 liters/day
- Inhalation rate = 20 m^3/day
- Lifetime exposure = 70 years
- Linear extrapolation for cancer risk (i.e., no threshold)

Uncertainty Factors

- Animal to human extrapolation
- Human variability/sensitivity
- Subchronic study duration to chronic
- LOAEL to NOAEL
- Database gaps
- Typically choose 1, 3, or 10 as the factor

Unresolved Issues

- Toxicity of mixtures
- Lack of data on children and women of childbearing age
- Effects of long-term, low-level exposure