BIO/FOR 430/530:
Biotechnologies: Agriculture, Food & Resources Issues

Spring 2009
Toxicology Basics

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Tons of released drugs taint US water

Associated Press Writers – Sun Apr 19, 5:58 pm ET

U.S. manufacturers, including major drugmakers, have legally released at least 271 million pounds of pharmaceuticals into waterways that often provide drinking water — contamination the federal government has consistently overlooked, according to an Associated Press investigation.

Hundreds of active pharmaceutical ingredients are used in a variety of manufacturing, including drugmaking: For example, lithium is used to make ceramics and treat bipolar disorder; nitroglycerin is a heart drug and also used in explosives; copper shows up in everything from pipes to contraceptives.

FRONTLINE – POISONED WATERS
TONIGHT ON PBS AT 9 PM

Lecture Key Concepts

- Be able to identify the major exposure routes
- Be familiar with methods to assess exposure
- Understand the importance of dose-response in toxicology
- Be able to discuss sources/approaches to obtain dose-response information

What is exposure?

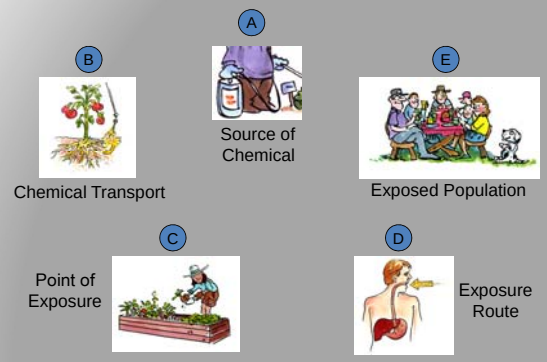
Contact with a substance, typically by swallowing, breathing, or touching the skin or eyes.

Is this exposure?

How about now?

What about this?

Complete Exposure Pathway



Duration of Exposure

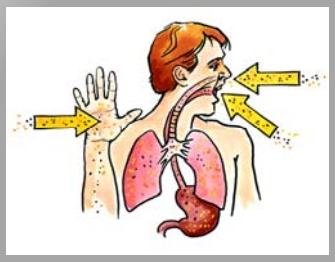
The length of time that an organism is exposed to a chemical is critical to determine toxicity.

Duration and **frequency** contribute to dose. Both may alter toxic effects.

- **Acute** Exposure = typically involves a single or short exposure
- **Chronic** Exposures = multiple exposures over time (frequency)

For cancer, is chronic or acute exposure more relevant? What about paralysis of the nervous system?

What are the 3 common exposure routes?

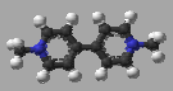


What are other possible exposure routes?

Exposure Route & Toxicity:

Depending on exposure route, some chemicals can have very different toxicities. Why?


Tetrodotoxin


Paraquat


Elemental Mercury

Vulnerable Populations

-Young
-Elderly
-Immunocomprimised
-Organ Transplant
-Pregnant/breast feeding
-Enzymatic deficiency
-Genetic makeup
-Subsistence
-Socio-economic status

Chemical properties & exposure:

Certain chemical-physical properties of compounds affect the potential for exposure. These include:

- -water solubility
- -lipid solubility
- -capacity to bind to soils
- -vapor pressure
- -Henry's constant
- -ability to persist in the environment

What would be the major property of concern for drinking water? Fish tissue?

How do we assess exposure?

-Biomonitoring

-Exposure History

-Epidemiology

-Exposure Modeling

Biomonitoring:

One method for assessing human exposure to chemicals by measuring the chemicals of their metabolites in human specimens, such as blood or urine.

Often, the metabolite (breakdown product) of the chemical is detected in biological samples.

Biomonitoring:

- Urine
- Blood
  - fetal cord
  - whole
  - plasma
- Hair
- Tissue
- Breast milk
- Exhaled air
- Nails
- Saliva
- Biomarkers

Exposure History

Present/Past Occupation

Residence

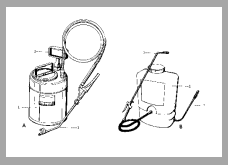
Environmental Concerns

Hobbies

Medical history

Diet/lifestyle

Surveys



Epidemiology

The study of the distribution and factors of disease or health status in a population; the study of the occurrence and causes of health effects in humans.

•Observational epidemiology
- **Prevalence** of disease at a single point in time
- **Incidence**: new cases of a disease (i.e. over 1 year)

•Analytical epidemiology
- Investigating risk factors
  - Relationship between exposure(s) & disease

Epidemiology

"Toxicology is the precise dose on the wrong species. Epidemiology is the imprecise dose on the right species."

Epidemiology is very useful for hazard identification. It can also help determine:

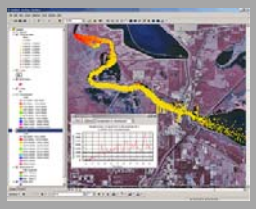
1) **Strength** of association between risk factor & outcome
2) **Consistency** of the association
3) **Specificity** of the association
4) **Temporality** of the association
5) Biological **plausibility**
6) **Dose-response** relationship

Exposure Modeling

Many methods can be expensive. Modeling offers mathematical equations to predict exposure. Models can be flexible and have to be assessed carefully. Typically, information used for modeling exposure focuses on:

- -the chemical agent
- -the physical environment
- -the person of interest
- -the duration of exposure

"All models are wrong. Some models are useful."



Woman Dies after Water-drinking Contest: Water Intoxication eyed in 'Hold Your Wee for a Wii' contest Death

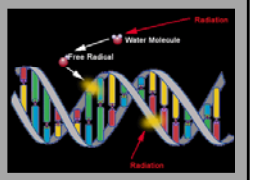
SACRAMENTO, California—A woman who competed in a radio station's contest to see how much water she could drink without going to the bathroom died of water intoxication, the coroner's office said Saturday.

Associated Press
2007

Society of Toxicology 2008

Dose-Response Relationship

- A key concept in Toxicology is the **quantitative relationship** between the **concentration** of a chemical in the body and the **magnitude** of the biological effect it produces.
- The magnitude of the effect of a chemical is usually a function of the amount of chemical to which a person is exposed (i.e., "The Dose Makes the Poison").
- In any given population, there will be a **range of sensitivities**. It is extremely useful to know what is the average sensitivity of a population to a certain dose of a chemical.



Society of Toxicology 2008 (modified)

Toxicity expressed…

- Modify existing body functions
- Change in cellular reactions
- Reversible injury
- Irreversible injury
- Death

What are some examples of toxic effects?







July 3, 2004 © AP Images/Anatoly Medzyk


Nov. 5, 2004 © AP Images/Sergei Supinksy

Effects of Amount on Response

A Small Dose of Toxicology

Effects of Size on Response

A Small Dose of Toxicology

Dose-Response Relationship

- The magnitude of the toxic response is proportional to the concentration (how much) of the chemical at the **target site**.
- The concentration of a chemical at the target site is **proportional to** the dose.
- **Four** important processes control the amount of a chemical that reaches the target site.
  - **Absorption**
  - **Tissue distribution**
  - **Metabolism**
  - **Excretion**

Society of Toxicology 2008 (modified)

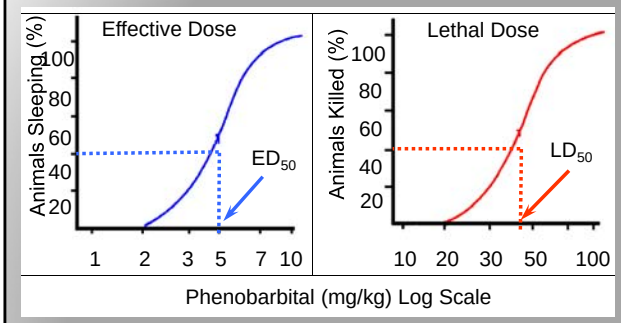
Dose-Response Relationship

The dose determines whether a chemical will be beneficial or poisonous

	Beneficial Dose	Toxic Dose
Aspirin	300 – 1,000 mg	1,000 – 30,000 mg
Vitamin A	5000 units/day	50,000 units/day
Oxygen	20% (Air)	50 – 80% (Air)

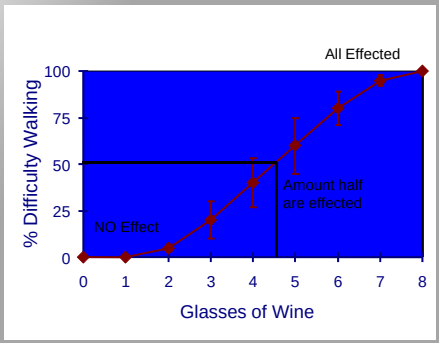
Society of Toxicology 2008 (modified)

Dose-Response Curves



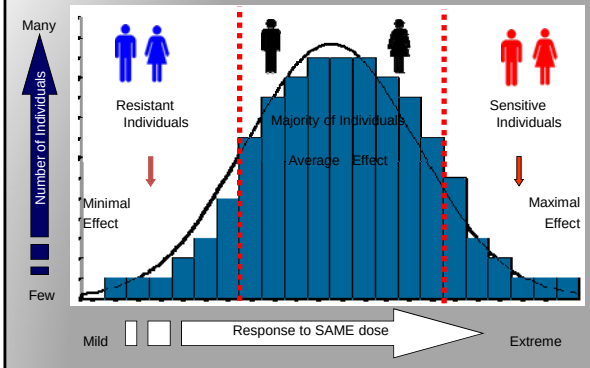
Society of Toxicology 2008 (modified)

Dose-Response



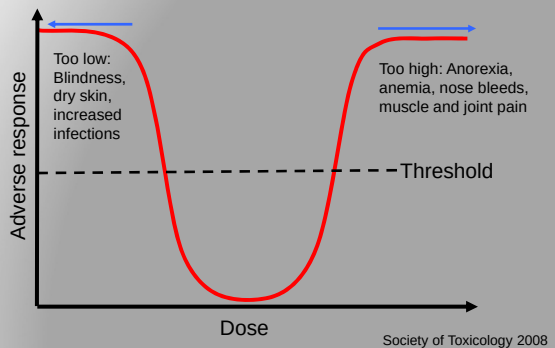
A Small Dose of Toxicology, modified

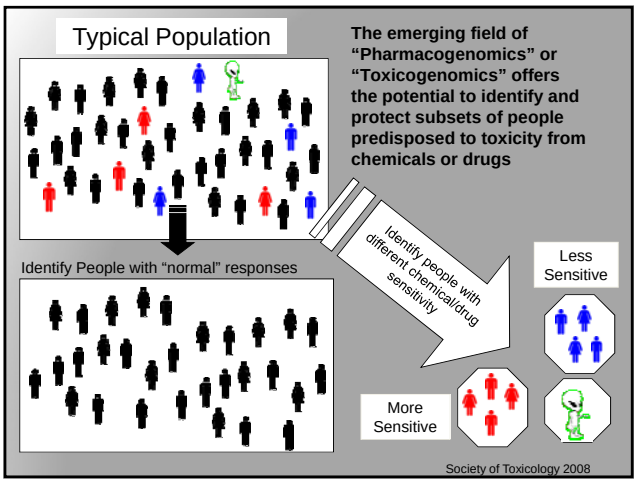
Exposure-Response



Society of Toxicology 2008, modified

Example of Dose-Response for Toxic & Therapeutic Chemicals (Vitamin A)



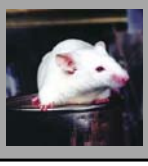


Dose-Response Data

Traditionally, society has used animals to predict toxicity in humans. The primary species are mice and rats. Numerous other animal models exist to characterize toxicity.

Often, animals are exposed to high-doses over short periods of time. How relevant is this to chronic, low-dose exposures that we are more likely to experience?

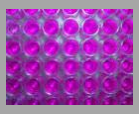
A well-designed dose-response study will include controls and multiple dose groups consisting of several male and female animals. Good animal husbandry practices are critical.



Dose-Response Data: the Future?

Recently, a National Academies Workgroup proposed a road map entitled "Toxicity Testing in the 21st Century." This roadmap highlighted the need to more away from animal testing and into models that are:

- -based on in vitro models to detect changes in biological processes
- -use human cell lines
- -incorporate molecular advances
- -use bioinformatic and computational approaches



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Discussion: Toxicity?

Compound O: LD_{50} (mice) of 5 mg/kg (parts per million)

Compound S: LD_{50} (mice) of 50 mg/kg (parts per million)

Compound U: LD_{50} (mice) of 5 µg/kg (parts per billion)

What if compound U is 10000X less toxic to rats or dogs?

What if O was the only compound that had developmental effects?

What is compound U caused an adverse effect that is species specific (for mice) and not relevant to humans?

How much information do you need on a chemical before allowing it into the marketplace?