What sorts of questions can toxicology answer?

• How can acetaminophen overdose lead to acute liver failure?

• What occupational exposures are associated with Parkinson’s Disease, and how do we model it in research?

• Why were the claims about vaccines and autism improbable?
Toxicology...

• Is the study of harmful effects of *xenobiotics* – natural or man-made substances foreign to the body
  • *Toxicant* – a xenobiotic that can kill or injure


Toxicology...

- Uses toxicants to study basic biology or model human diseases
  - Pesticides and Parkinson’s Disease
  - Metrazol and epilepsy

What are “harmful effects”?

- Damage to normal function or survival

- Can result in:
  - Death
  - Cancer
  - Impaired organ function, e.g. mental retardation from lead exposure

- Some ways damage or impairment can occur:
  - Premature or accelerated death of cells in tissues
  - Allergic reaction to a chemical
  - Damage to DNA, RNA, proteins
  - Depletion of cellular protective abilities
What determines the extent of damage?

- Dose of toxicant
- Route of exposure
- Duration of exposure to toxicant
- Toxicant’s properties
- Individual factors, e.g. genetics, age, overall health, etc.
Dose and exposure

- **Dose** – actual amount of toxicant that enters the body

- **Route of exposure** – the way the toxicant comes into contact with a body surface


Duration

- *Duration* – length of time of exposure to the toxicant (acute vs. chronic)

  - Acute exposure – short-term (24 h)
    - Usually requires a high dose to have a harmful effect
    - Well researched
    - Major endpoints include death or organ failure

  - Chronic exposure – long-term
    - Harmful effects can be recognized with low doses
    - Many different endpoints, e.g. behavioral effects, increased risk of neurodegenerative diseases, cardiovascular diseases
Toxicant’s properties

- **Chemical properties** – shape, structure, solubility, stability, etc.

![Chemical structures](http://0.tqn.com/d/chemistry/1/0/X/L/1/Methylmercury.jpg) ![Chemical structure](http://en.wikipedia.org/wiki/Thimerosol)

- **Hg**
- **Hg**
- **Hg**
- **Hg**

- inorganic mercury
- methyl mercury
- Thimerosol


Individual factors affecting intoxication

• **Age**

• **Gender**
  - EX: pregnancy alters immune system and liver function; fetus can also act as a toxicant “sink”

• **Weight**
  - EX: individuals with more adipose (fat) tissue can retain more lipophilic (fat-loving) chemicals, e.g. DDT

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Individual factors affecting intoxication

**Genetics**
- EX: 90% of Japanese/Chinese/Korean individuals rapidly metabolize ethanol to acetaldehyde, an irritant, and only slowly clear it.

\[
\text{CH}_3\text{CH}_2\text{OH} \quad \rightarrow \quad \text{CH}_3\text{COH} \quad \rightarrow \quad \text{CH}_3\text{COOH}
\]

- Alcohol Dehydrogenase
- Aldehyde Dehydrogenase

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Individual factors affecting intoxication

• History of exposure to toxicants
  • Prior exposures can alter the body’s protective/detoxification processes
  
• EX: exposure to cadmium, a carcinogen, increases the body’s ability to clear it by stimulating the production of metallothionein
Example: Acetaminophen overdose

• Acetaminophen (APAP) is an analgesic – a pain reliever

• It is the main ingredient in Tylenol and Excedrin
Acetaminophen overdose

- 2005: more than 28 billion doses of APAP purchased in the U.S.
  - 2005 census: 296 million people in the U.S. (95 doses/person/year!)

- 2007: APAP overdose associated with:
  - 56,000 ER visits
  - 26,000 hospitalizations
  - 458 deaths
Acetaminophen overdose

- APAP is not toxic by itself

- APAP metabolized by liver enzymes (Cytochrome P450s) to a toxic metabolite, NAPQI

- NAPQI binds to glutathione (GSH), a protective molecule, and is excreted in the urine
Acetaminophen overdose

- NAPQI reacts with proteins in the liver, causing *necrosis* (rapid, uncontrolled death) of liver cells

- Widespread liver necrosis leads to acute liver failure, death
Normal acetaminophen dose

- APAP is cleared, minimal toxicity

Acetaminophen overdose

- Too much APAP to be safely cleared; intoxication results

Acetaminophen and alcohol

- Overdose occurs at lower doses, more extreme damage

Acetaminophen toxicity

- Damage depends on:
  - Dose of toxicant – 500 mg vs. 5 g vs. 50 g
  - Route of exposure – ingestion
  - Duration of exposure to toxicant – whole bottle in one night vs. over the course of a year
  - Toxicant’s properties – it can be conjugated to glutathione and be activated to NAPQI by the cytochrome P450s
- Individual factors:
  - Ethanol consumption
  - Genetic variation in P450s
  - Nutrition status
Dose makes the poison: the dose-response relationship

“All substances are poisons: there is none which is not a poison. The right dose differentiates poison from a remedy.” – Paracelsus (1493 – 1541)
Dose makes the poison: the dose-response relationship

- Correlation between a toxicant’s dose and an organism’s response

- Typically the greater the dose, the greater the response
Dose-response and toxicological testing

• Based on individual organism’s sensitivity to a toxicant

• Every organism or cell will respond to a toxicant in an individual way

• How does a toxicant have an effect on a population level?

**In vitro toxicological testing**

- *In vitro* – research conducted on tissues, cells, or proteins outside of a whole organism

**Advantages:**
- Can easily expose cells to a toxicant
- Can use *bioassays* to gauge the effect
- More controlled – can more clearly link toxic effects to the toxicant
- Faster and less expensive
- More ethically acceptable

**Disadvantages:**
- Less relevant to what happens in a whole organism

**In vivo toxicological testing**

- *In vivo* – research conducted on whole organisms, e.g. mice, rats, zebra fish, yeast

**Advantages:**
- Can evaluate the progression of toxic effects
- Can more clearly determine the effects of intoxication on a whole organism
- More relevant to modeling or predicting human disease/intoxication

**Disadvantages:**
- Strict regulation, justification, and oversight to prevent unnecessary pain and suffering
- Much more expensive and time intensive
- More difficult to link an outcome to a toxicant

Common testing parameters: LC50, threshold, NOEL, and LOEL

- *LD50* (aka *EC50*) – lethal or effective dose for 50% of the exposed population

- *Threshold* – highest dose where there is no effect

- *NOEL* (No Observed Effect Level) – highest dose at which there is no observed effect

- *LOEL* (Lowest Observed Effect Level) – lowest dose at which there is an observed effect
Dose response *in vitro*: What is the LD50?
Dose response *in vitro*: What are the threshold, NOEL, LOEL?

**Apoptotic Neurons vs. MPP+**

![Graph showing the relationship between % Apoptotic Cells and [MPP+] (mM)](image)