TOXICOLOGY

Lecture 1 - Tuesday

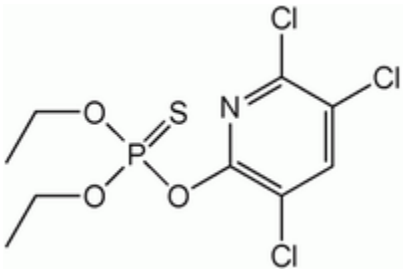
ENVH 111
11/01/11
Megan Cartwright

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



arsenic

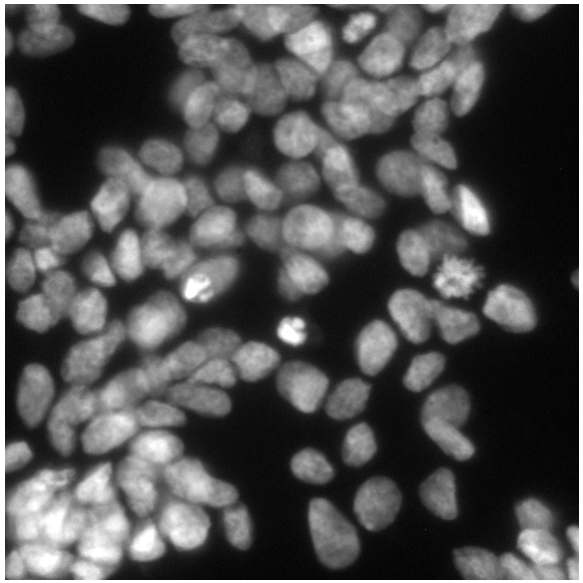
chlorpyrifos

Vitamin A

Gallo, MA. "History and Scope of Toxicology." *Casarett & Doull's Toxicology: The Basic Science of Poisons*. Ed. Klassen, CD. New York: McGraw Hill Medical, 2008. 3-43. Print.
Images (left to right) from <http://en.wikipedia.org/wiki/Arsenic>, <http://en.wikipedia.org/wiki/Chlorpyrifos>, <http://www.vitaminsbyvp.com/files/2545294/uploaded/AV1.jpg>. 30 Oct. 2011.

Toxicology…

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



Gallo, MA. "History and Scope of Toxicology." *Casarett & Doull's Toxicology: The Basic Science of Poisons*. Ed. Klassen, CD. New York: McGraw Hill Medical, 2008. 3-43. Print.

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

Institute of Public Health. “Module 1 – Introduction to Toxicology.” *Toxicology Curriculum for Communities Trainer’s Manual*. Agency for Toxic Substances & Disease Registry, CDC, 2002. Web. 24 Oct. 2011. <http://www.atsdr.cdc.gov/training/toxmanual/>

What determines the extent of damage?

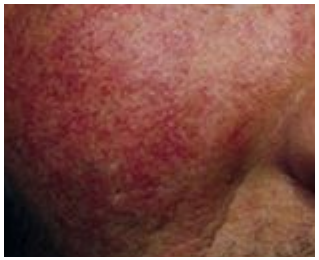
- Dose of toxicant
- Route of exposure
- Duration of exposure to toxicant
- Toxicant's properties
- Individual factors, e.g. genetics, age, overall health, etc.

Institute of Public Health. "Module 1 – Introduction to Toxicology." *Toxicology Curriculum for Communities Trainer's Manual*. Agency for Toxic Substances & Disease Registry, CDC, 2002. Web. 24 Oct. 2011. <http://www.atsdr.cdc.gov/training/toxmanual/>

Dose and exposure

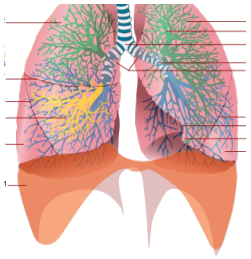
- *Dose* – actual amount of toxicant that enters the body

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

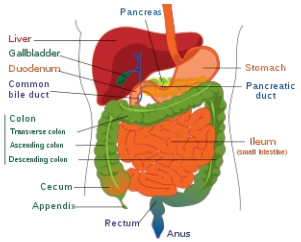


skin

eyes



respiratory tract



GI tract

Images (left to right): 'Skin' and 'eyes' from National Geographic. "Photo of the Day: People & Culture." *National Geographic Magazine.* 2011. Web. 29 Oct. 2011. <http://photography.nationalgeographic.com/photography/photo-of-the-day/people-culture/?page=1>
'Respiratory tract' from Wikipedia. "Respiratory tract." *Wikipedia.* 31 Jan. 2011. Web. 29 Oct. 2011. <http://en.wikipedia.org/wiki/Respiratory_tract>
'GI tract' from Wikipedia. "Human gastrointestinal tract." *Wikipedia.* 25 Oct. 2011. Web. 29 Oct. 2011. <http://en.wikipedia.org/wiki/Gastrointestinal_tract>

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

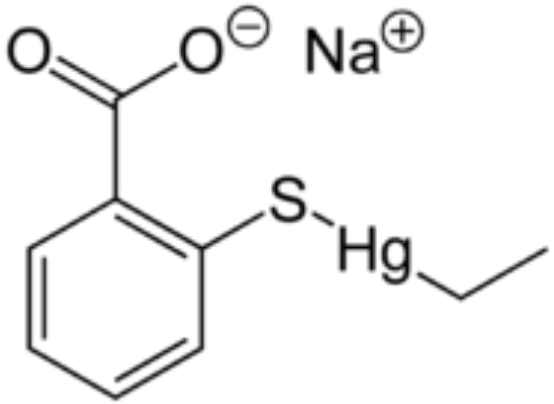
- Chronic exposure – long-term
  - Harmful effects can be recognized with low doses
  - Many different endpoints, e.g. behavioral effects, increased risk of neurodegenerative diseases, cardiovascular diseases

Toxicant's properties

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

inorganic mercury

methyl mercury



Thimerosol

Martin T. "Quantitative Structure Activity Relationship." *U.S. EPA Clean Processes*. 21 Sept. 2011. Web. 29 Oct. 2011. <http://www.epa.gov/nrmrl/std/cppb/qsar/index.html>
Images (middle and right) from: <http://0.tqn.com/d/chemistry/1/0/X/L/1/Methylmercury.jpg>, <http://en.wikipedia.org/wiki/Thimerosol>. 29 Oct. 2011.

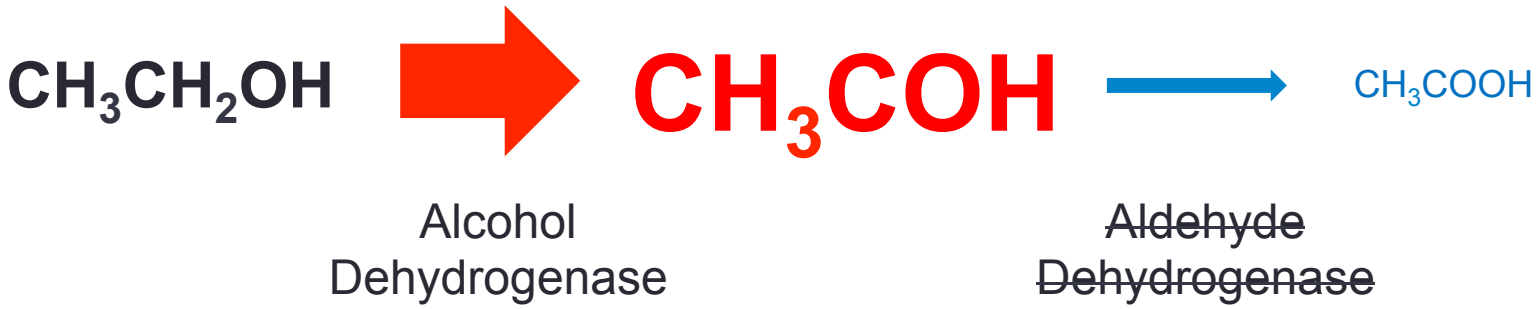
Individual factors affecting intoxication

- *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

Rogers JM and Kavlock RJ. “Developmental Toxicology.” *Casarett & Doull’s Toxicology: The Basic Science of Poisons*. Ed. Klassen, CD. New York: McGraw Hill Medical, 2008. 415-451. Print.
Costa LG. “Toxid Effects of Pesticides.” *Casarett & Doull’s Toxicology: The Basic Science of Poisons*. Ed. Klassen, CD. New York: McGraw Hill Medical, 2008. 883-930. Print.

Individual factors affecting intoxication

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



Parkinson A and Ogilvie BW. "Biotransformation of Xenobiotics." *Casarett & Doull's Toxicology: The Basic Science of Poisons*. Ed. Klassen, CD. New York: McGraw Hill Medical, 2008. 161-304.. Print.
Kaminski NE et al. "Toxic Responses of the Immune System." *Casarett & Doull's Toxicology: The Basic Science of Poisons*. Ed. Klassen, CD. New York: McGraw Hill Medical, 2008. 485-555. Print.

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

Parkinson A and Ogilvie BW. "Biotransformation of Xenobiotics." *Casarett & Doull's Toxicology: The Basic Science of Poisons*. Ed. Klassen, CD. New York: McGraw Hill Medical, 2008. 161-304.. Print.
Kaminski NE et al. "Toxic Responses of the Immune System." *Casarett & Doull's Toxicology: The Basic Science of Poisons*. Ed. Klassen, CD. New York: McGraw Hill Medical, 2008. 485-555. Print.

Example: Acetaminophen overdose

- Acetaminophen (APAP) is an *analgesic* – a pain reliever
- It is the main ingredient in Tylenol and Excedrin

Acetaminophen Hepatotoxicity Working Group. "Acetaminophen Overdose and Liver Injury – Background and Options for Reducing Injury." *CDER, FDA*. 26 Feb. 2008. Web. 29 Oct. 2011. <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM164897.pdf>
Images (left to right) from < http://thekrazycouponlady.com/wp-content/uploads/2010/10/tylenol.jpg > < http://www.southernsavers.com/wp-content/uploads/2010/02/excedrin.jpg>. 29 Oct. 2011.

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 Hepatotoxicity Working Group. "Acetaminophen Overdose and Liver Injury – Background and Options for Reducing Injury." *CDER, FDA*. 26 Feb. 2008. Web. 29 Oct. 2011. <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM164897.pdf>
The Census Bureau. "Population Distribution in 2005." *U.S. Census Bureau, Population Division.* June 2007. Web. 29 Oct. 2011. <http://www.census.gov/population/www/pop-profile/files/dynamic/PopDistribution.pdf>

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

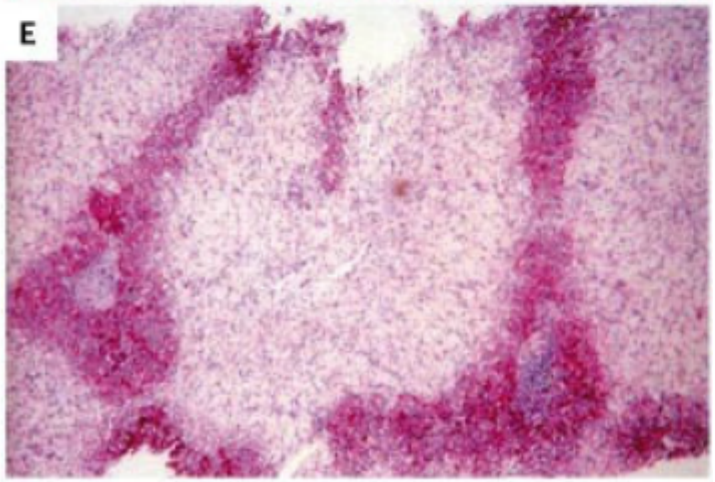
Acetaminophen Hepatotoxicity Working Group. "Acetaminophen Overdose and Liver Injury – Background and Options for Reducing Injury." *CDER, FDA*. 26 Feb. 2008. Web. 29 Oct. 2011. <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM164897.pdf>

The Census Bureau. "Population Distribution in 2005." *U.S. Census Bureau, Population Division.* June 2007. Web. 29 Oct. 2011. <http://www.census.gov/population/www/pop-profile/files/dynamic/PopDistribution.pdf>

Acetaminophen overdose

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

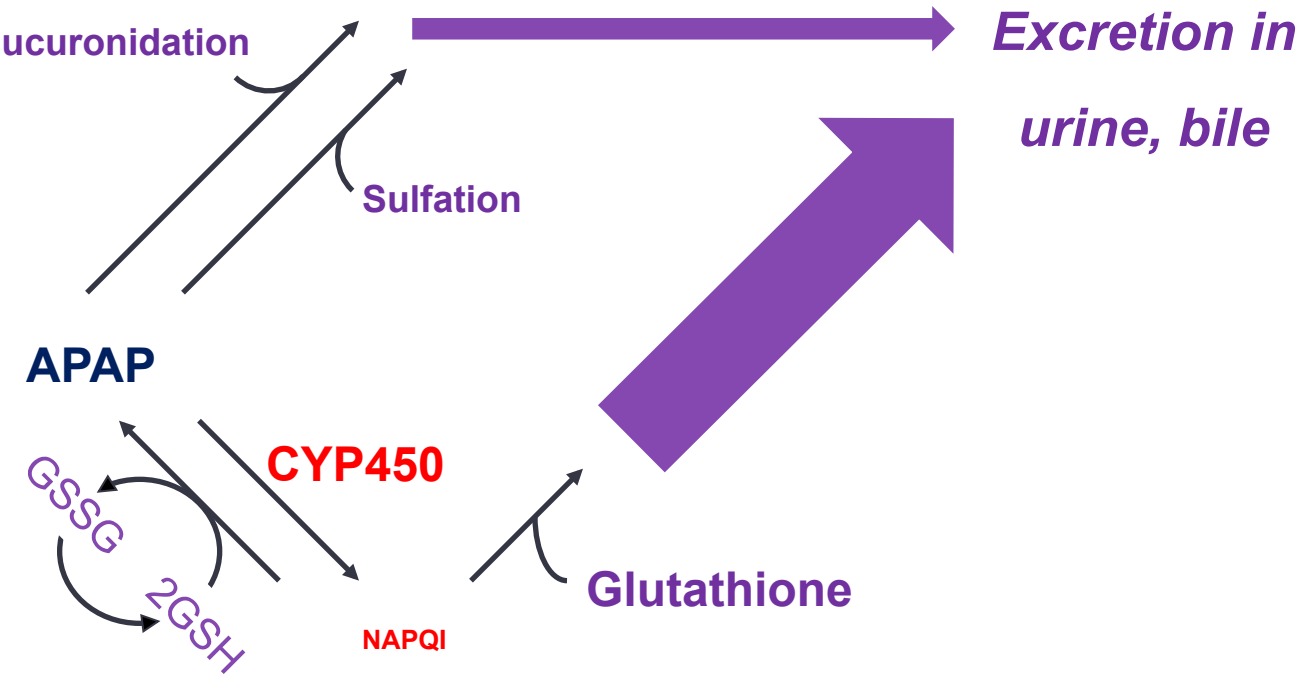
- Widespread liver necrosis leads to acute liver failure, death



Acetaminophen Hepatotoxicity Working Group. "Acetaminophen Overdose and Liver Injury – Background and Options for Reducing Injury." *CDER, FDA*. 26 Feb. 2008. Web. 29 Oct. 2011. <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM164897.pdf>
Image from Lee WM. Drug-induced hepatotoxicity. N Engl J Med 2003; 349:474-485.

Normal acetaminophen dose

- APAP is cleared, minimal toxicity



Adapted from Weldy C. "The Science of Toxicology." Env. Health 111, University of Washington. 28 Oct. 2010.

Acetaminophen overdose

- Too much APAP to be safely cleared; intoxication results

Glucuronidation

Sulfation

Excretion in urine, bile

APAP

CYP450

GSSG

2GSH

Glutathione

NAPQI

APAP-Protein → ***Liver necrosis***

Adapted from Weldy C. "The Science of Toxicology." Env. Health 111, University of Washington. 28 Oct. 2010.

Acetaminophen and alcohol

- Overdose occurs at lower doses, more extreme damage

Glucuronidation

Sulfation

Excretion in urine, bile

APAP

CYP450

GSSG

2GSH

~~Glutathione~~

NAPQI

APAP-Protein

Liver necrosis

Adapted from Weldy C. "The Science of Toxicology." Env. Health 111, University of Washington. 28 Oct. 2010.

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

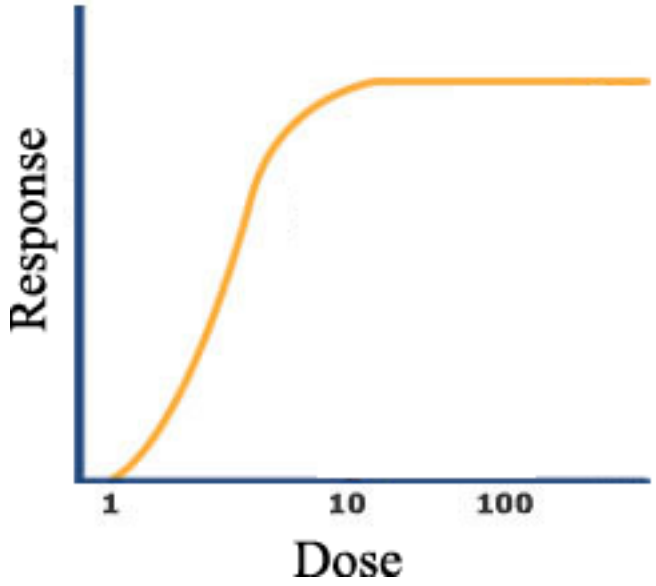
- “All substances are poisons: there is none which is not a poison. The right dose differentiates poison from a remedy.” – Paracelsus (1493 – 1541)

Image from <http://euromin.w3sites.net/Nouveau_site/mineralogiste/biographies/pic/paracelse.htm>. 30 Oct. 2011.

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



Eaton DL and Gilbert SG. "Principles of Toxicology." *Casarett & Doull's Toxicology: The Basic Science of Poisons*. Ed. Klassen, CD. New York: McGraw Hill Medical, 2008. 11-43. Print.
Image adapted from <http://publications.nigms.nih.gov/medbydesign/images/ch1_doseresponse.jpg>. 31 Oct. 2011.

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?

Adapted from Weldy C. "The Science of Toxicology." Env. Health 111, University of Washington. 28 Oct. 2010.

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

Adapted from Weldy C. "The Science of Toxicology." Env. Health 111, University of Washington. 28 Oct. 2010.

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

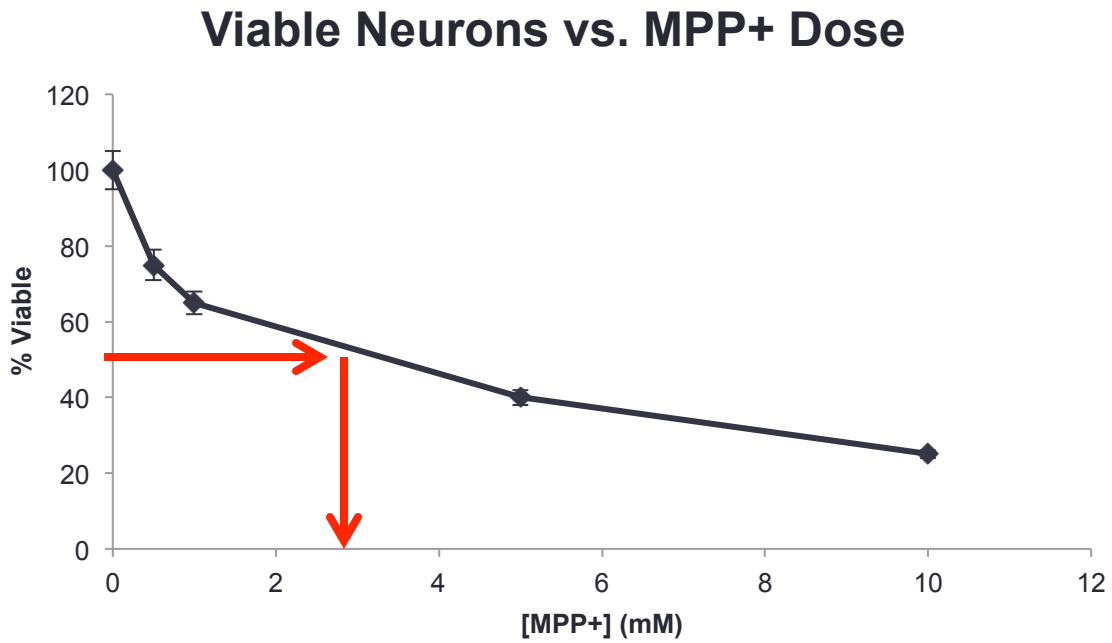
- Disadvantages:
  - Strict regulation, justification, and oversight to prevent unnecessary pain and suffering
  - Much more expensive and time intensive
  - More difficult to link an outcome to a toxicant

Adapted from Weldy C. "The Science of Toxicology." Env. Health 111, University of Washington. 28 Oct. 2010.

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?