Are You Curious and Ask Questions?  
Do You Want to Help People?  
**Toxicology** might be for you!

2017 SOT Undergraduate Diversity Program

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**What is Toxicology?**

- The traditional definition of toxicology is "the science of poisons."
- A more descriptive definition of toxicology is "the study of the adverse effects of chemicals or physical agents on living organisms."
Hey, We’re Family!

My Education/Career Path to Toxicology

• BS in Biology from Norfolk State University (4 years)
• PhD in Pharmacology and Toxicology from the University of Arizona (5.5 years)
• Postdoctoral fellowship in Pharmacology at UNC-Chapel Hill (5 years)
• College Professor, Cancer Biologist, Toxicologist in Academia at North Carolina Central University (10 years)
Pop Quiz: What is Toxicology?

How is toxicology involved in our everyday lives?

Chemicals are Ubiquitously Present in Our Environment

- Chemicals are natural, biological, or synthetic in origin
  - Natural (food, metals, minerals)
  - Biological (toxins from bacteria)
  - Synthetic (manufactured through chemical processes)
- Approximately 100,000 chemicals are currently in use worldwide.
- About 500 new formulations enter the marketplace annually
Cosmetics and Personal Care Products: Safe or Not?

- Roughly how many chemicals are found in cosmetics?
- How many have been tested by the FDA for safety? Does the FDA require safety tests from companies?
- In Europe, over 1,000 chemicals found in cosmetics have been banned. How many have been banned in the US?
- Some chemicals found include parabens, phthalates, lead, etc.

You want a smoke?

http://guardianlv.com/2013/12/tobacco-ban-solution-rests-on-shoulders-of-e-cig/
Concerns with Electronic Cigarettes

- Studies performed on e-cigarette vapor have detected 31 potentially harmful chemicals (e.g., nicotine, formaldehyde, acrolein, etc.)
- E-cigarettes are linked to acute respiratory diseases, such as asthma and bronchitis
- Up to 40 percent of particles emitted by an e-cigarette can be deposited in the deepest area of a youth’s lungs.


Deepest Area of the Lungs: Alveolar Region
The Key Concept in Toxicology is DOSE

Father of Modern Toxicology
PARACELSUS—1564

“All things are poisonous, only the dose makes it non-poisonous.”

(Dose alone determines toxicity)

Beneficial Versus Toxic Effects: It’s All About Dose!

<table>
<thead>
<tr>
<th>Substance</th>
<th>Non-Toxic or Beneficial Dose</th>
<th>Toxic Dose</th>
<th>Lethal Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol ETHANOL BLOOD LEVELS</td>
<td>0.05 %</td>
<td>0.1 %</td>
<td>0.5 %</td>
</tr>
<tr>
<td>Carbon Monoxide % HEMOGLOBIN BOUND</td>
<td>&lt; 10 %</td>
<td>20 - 30 %</td>
<td>&gt; 60 %</td>
</tr>
<tr>
<td>Secobarital (sleep aid) BLOOD LEVELS</td>
<td>0.1 mg/dL</td>
<td>0.7 mg/dL</td>
<td>&gt; 1 mg/dL</td>
</tr>
<tr>
<td>Aspirin</td>
<td>0.65 gm (2 tablets)</td>
<td>9.75 gm (30 tablets)</td>
<td>34 gm (100 tablets)</td>
</tr>
<tr>
<td>Ibuprofen E.G., ADVIL &amp; MOTRIN</td>
<td>400 mg (2 tablets)</td>
<td>1,400 mg (7 tablets)</td>
<td>12,000 mg (80 tablets)</td>
</tr>
</tbody>
</table>

Principles of Clinical Toxicology (T. Gossel and J. Bricker, eds)
Dose-Response Relationship

“The dose makes the difference between a beneficial and a toxic effect.”

### Effective Dose

- **ED$_{50}$**
- Animals Sleeping (%)
- Phenobarbital (mg/kg) Log Scale

### Lethal Dose

- **LD$_{50}$**
- Animals Killed (%)

**Routes of Exposure**

- **The route (site) of exposure** is an important determinant of the internal dose, magnitude of toxicity, and the organs and tissues affected.
- Different routes may result in different rates of absorption:
  - Dermal (skin)
  - Inhalation (lung)
  - Oral ingestion (gastrointestinal)
  - Injection
- Toxic effects may be local or systemic
An Example of Dose and Exposure

High Levels of Lead in Flint, Michigan Drinking Water

Fall 2015: Lead levels found higher than the acceptable EPA limit of 15 ppb—ranged from 25 ppb and higher, several exceeded 100 ppb

What Led to the High Lead Levels?

GETTING THE LEAD IN
Tests show toxic lead is leaching into Flint’s tap water. Here’s how.

- Lead solder: Copper pipe connections, especially in pre-1986 homes, can contain lead.
- Corrosive water: Researchers have found Flint water to be more corrosive to pipes than water from the Detroit system, Flint’s previous water source.
- Water treatment plant: The city draws and disinfects water from the Flint River.
- Service lines: Pipes connecting water mains and individual homes or businesses can be made of lead. Lead can leach directly from the pipe wall into the water.

Lead into water: Some tap water samples are above the federal threshold for lead.

Biotransformation

- Major mechanism for terminating the biological activity of chemicals
- Occurs in the liver, kidney, lung, and gastrointestinal tract

The LIVER is the primary site of metabolism

Some Chemicals are Transformed (Metabolized) by the Body to Aid Excretion

Liver and Other Organs

Detoxify

Less Toxic Metabolic Product

- Kidney → Urine
- Liver → Feces / Bile
- Lung → Expired Air

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What Does a Toxicologist Do?

- Develop mechanistic understanding of effects of toxicants
- Ensure safer chemical products
- Develop safer drugs and medicines
- Determine risks from chemical exposures
- Develop treatments of chemical exposures
- Ensure a safe food and water supply
- Forensics

Toxicology Employment by Sector

- Industry 46%
- Academic 14%
- Consulting 13%
- Contract Laboratory 11%
- Government 13%
- Other 5%

Industry Breakdown
- Pharmaceutical 66%
- Chemical 10%
- Consumer Product 8%
- Food/Food Ingredients 4%
- Medical Devices 4%
- Petroleum 2%
- Other 6%

2015 Data Ninth Triennial Toxicology Survey
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What Are the Functions of the Pancreas?

http://www.olivelab.org/the-pancreas-overview.html
### Percent of Pancreatic Cancer Deaths in the United States

<table>
<thead>
<tr>
<th>Tissue Type</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung and bronchus</td>
<td>27%</td>
</tr>
<tr>
<td>Prostate</td>
<td>8%</td>
</tr>
<tr>
<td>Colon and rectum</td>
<td>8%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>7%</td>
</tr>
<tr>
<td>Liver and bile duct</td>
<td>6%</td>
</tr>
<tr>
<td>Breast</td>
<td>14%</td>
</tr>
<tr>
<td>Colon and rectum</td>
<td>8%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>7%</td>
</tr>
<tr>
<td>Ovary</td>
<td>5%</td>
</tr>
</tbody>
</table>

- **53,070 new cases in the US in 2016**
- **42,680 deaths in the US in 2016**

(80% mortality rate)

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### Major Concerns of Pancreatic Cancer

- The 5-year survival rate is 9%, the lowest of all major cancers
- Most patients are diagnosed at an advanced stage
- Most pancreatic cancers are resistant to chemotherapy and radiotherapy
- Survival rates have not significantly changed in the past 40 years
Human PIM Kinase Family

Human kinome (518)

Proviral Integration site for the Moloney murine (PIM) leukemia virus

Roles of PIM Kinase Cell Signaling

- Blocks apoptosis
- Pro-survival
- G1/S & G2/M progression
- Cell Proliferation
- Global transcription
- Oncogenic transformation
- Cap-dependent translation
- Stabilization of oncogene products
- Drug resistance

http://www.toleropharma.com/TP-3654.html
The Combination of SGI-1776 (PIM Inhibitor) and Gemcitabine Decreases Cell Viability in PDAC Cells


Do You Like Science?

Do You Want to Help People?

Let's Try Toxicology!