Incorporation of Toxicology Through Student Led Chemistry Seminars

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St. Catherine University Demographics

- St. Paul MN
- Founded by the Sisters of St. Joseph in 1905
- ~ 5000 students
- ~2500 students in the undergraduate day program
- Largest women’s college in the United States
- Apart of the Associated Colleges of the Twin Cities
- ~10 chemistry majors a year
- Original signer of the Beyond Benign Green Chemistry Commitment
Green Chemistry Student Learning Objectives

**Theory**: Have a working knowledge of the Twelve Principles of Green Chemistry

**Laboratory Skills**: Possess the ability to assess chemical products and processes and design greener alternatives when appropriate

**Toxicology**: Have an understanding of the principles of toxicology, the molecular mechanisms of how chemicals affect human health and the environment, and the resources to identify and assess molecular hazards

**Application**: Be prepared to serve society in their professional capacity as scientists and professionals through the articulation, evaluation, and employment of methods and chemicals that are benign for human health and the environment
Chemistry Seminar: Toxicology

- Junior and Senior chemistry majors are required to take four semesters of chemistry seminar
- Meets Every Friday for 65 minutes
- Topic rotates between Green Chemistry, Toxicology, Polymers, and Nanomaterials
- Journal Club: Juniors give one 15 min seminar on a research article, seniors give two 15 min seminars on a research article.
- Several outside speakers related to the topic of career development visit the class each term.
Chemical Research in Toxicology: Day 1

- Explain GCC
- Recap basic toxicology principals learned in previous coursework
- Recap how they have assessed hazards in the past
- Explain seminar format – with examples
  - Background on toxin, where it is found/used, level of toxicity
  - Why is your compound toxic
    - Present possible mechanisms
  - Methods of detoxification – alternatives
  - Present article from the journal *Chemical Research in Toxicology*
- Review how to access journal and find background
- Draw for topics
- Draw for presentation date
Risk = f (Hazard x Exposure x vulnerability)

- Acute chemical hazard – Exposed once and it has an effect. Ex: HCN (used in gas chambers)

- Chronic chemical hazard – Multiple exposures or constant low exposure over time. Ex: (Pb/Hg poisoning)
Accessing hazard: NFPA

**Chemical**: organic compounds, proteins, enzymes

**Biological**: bacteria, virus, fungi

**Physical**: Corrosive compounds, irritants, asphyxiants
Review: Vocabulary, EPA hazard classification

Carcinogen: Causes cancer
Tumor Promoter: Can’t cause tumors but promotes once formed
Mutagen: Mutates DNA – leads to cancer
Teratogen: Causes birth defects or kill fetus

Class I: most toxic – Danger
Class II: toxic - Warning
Class III: Slightly toxic – Caution
Class IV practically not toxic

Class I or II
# Globally Harmonized System (GHS) Pictograms

<table>
<thead>
<tr>
<th>Flame Over Circle</th>
<th>Environment (Non-Mandatory)</th>
<th>Skull and Crossbones</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxidizers</td>
<td>Aquatic Toxicity</td>
<td>Acute Toxicity (Fatal or Toxic)</td>
</tr>
</tbody>
</table>
Overview of Chemical Mechanism in Toxicology

- Corrosive
- Asphyxiation
- Mutates DNA → Causes protein misfolding, altered function
- Mutates DNA repair enzymes → DNA mutations not fixed
- Body converts substance to a more toxic substance
- Body converts substance to a less toxic substance
- Reacts with proteins or enzymes and causes them to lose reactivity. This in turn causes a cascade of ill effects by affecting protein-protein interactions. Ex: loss of ATP production or heart contractions.

- Common organic mechanisms leading to toxicity
  - Protein crosslinking, generation of reactive oxygen species, Schiff base formation, Michael addition
Case studies in Chemical Research in Toxicology:

- Hydrazine
- Hg or Pb poisoning
- Silver nanoparticles
- Polyaromatic hydrocarbons (PAH’s)
- Dichlorodiphenyltrichloroethane
- Asbestos
- Trichloroethylene
- Sulfer mustard gas
- Aflatoxin
- Thalidomide
- Trichloroethylene
- Fromaldehyde
- Thalidomide
- Ti oxide or Zn oxide nanoparticles
- Sarin gas
- Nitriles – cyanide production
- Chromium oxidation Cr$^{6+}$ toxicity
- MDMA
- Nicotine-derived nitrosamine ketone (NNK)
- Organophosphates (sarin gas)
- Arsenic
- Cocaine
- Thimerosal
Goal one:

- Background info on your toxin.
- Where is it found or how is it synthesized
- How toxic is it?
The Toxicology of Arsenic

- 55\textsuperscript{th} most abundant element in the Earth’s Crust
- Toxic forms that are most commonly found in nature are arsenite and arsenate.

- Methylated forms of As exist in biological systems and have various toxicity levels.
Goal two:

- Why is your element or compound toxic?
- Give mechanism if known.
Arsenite toxicity

- Inhibits citric acid cycle by reacting with lipoic acid (a cofactor for pyruvate dehydrogenase)
- This diminishes ATP production and in turn cell function
Arsenate toxicity

- Inhibits glycolysis by replacing phosphate
- This reduces ATP production and in turn cell function

Phosphate

\[
\begin{align*}
\text{HO} & \quad \text{O} \\
\quad & \quad \text{P} \\
\text{HO} & \quad \text{OH} \\
\quad & \quad \text{OH}
\end{align*}
\]

Arsenate (As\(^{+5}\))

\[
\begin{align*}
\text{HO} & \quad \text{As} \\
\quad & \quad \text{O} \\
\text{HO} & \quad \text{OH} \\
\quad & \quad \text{OH}
\end{align*}
\]

- 1,3-arseno-3-phosphoglycerate is created instead of 1,3 bisphosphate glycerate in step 5 of glycolysis
Glycogenesis → Glycogen → Glycogenolysis

Glucose

Glycolysis:
1. ATP → ADP
2. ATP → ADP
3. ATP → ADP
4. NAD⁺ → NADH
5. NADH → NAD⁺
6. ATP → ADP
7. ATP → ADP
8. ATP → ADP
9. ATP → ADP

*Do steps 5-9 twice

1,3-diphosphoglycerate

3-phosphoglyceric acid

2-phosphoglyceric acid

Phosphoenol pyruvic acid

Pyruvic Acid

Galactose → ATP → ADP

Fructose

Fructose-6-phosphate

Fructose-1,6-diphosphate

Glycolysis:

C. Ophardt, c. 2003

Lactic Acid

Citric Acid Cycle
Goal three:

• Give a method of detoxification or how the mechanism can be stopped
Detoxification using BAL

Reduced lipoic acid attached to pyruvate dehydrogenase

Catalytic activity of PDH diminished

Treat with 2,3-dimercaptopropanol

Catalytic activity of PDH restored
Other mechanism examples

- Protein Modification / DNA Adduction
- Imine formation
- Michael addition
- Generation of ROS
Toxicity of Lipid Peroxidation Byproducts: Malondialdehyde (MDA)

- Proceeds by imine formation
- Modified protein function
- Hindered interaction with microphages
- Inflammatory responses
- Immune response
Toxicity of lipid peroxidation byproducts: DNA Adduction of Malondialdehyde (MDA)

- MDA has shown to form adducts with dG, dA, and dC bases.
- This results in A → G, G → T, and C → T mutations.
- If unrepaired, this could potentially lead to protein malfunction or cancer.
- Above is a proposed mechanism of adduction with Cytosine.
Toxicity of lipid peroxidation byproducts: Michael Addition to Acrolein

- Michael addition
- Keto Enolization
- H+ transfer
- Immune formation
- Tautomeration
- -H2O
Toxicity of lipid peroxidation byproducts: DNA Adduction of Acrolein

Deoxyguanosine

Michael addition

\[ \text{DNA Adduction of Acrolein} \]

\[ \text{N}^2\text{-propano-2'}\text{-deoxyguanosine} \]

Normal G:C pairing

Vs.

G:A mispairing

Adduction Reduces Capacity to H-bond with Carbonyl on Cytosine
Journal Club Presentation 10-15 minutes

- Using Chemical Research in Toxicology journal is important. Reports on chemistry and mechanisms not clinical studies.
- Previewed topics to make sure there is pertinent articles on the toxin.
- Warn students that there may be ambiguity regarding the toxicity of their compound. Ex: BPA
- Warn students that the mechanism may be unkown or not agreed upon.
- Format forces students to look up multiple articles cited in their selected journal article to obtain needed background.
- Gives students ownership over their chemical.
- Opens up conversation due to interest. Ex: Sarin gas
- Reinforces Organic Chemistry and Biochemistry.

\[ \text{Green chemists make better Chemists} \]
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