Anchoring Concepts: Linking chemistry concepts to toxicology topics within introductory chemistry courses

Amy S. Cannon, Ph.D.
Executive Director
Beyond Benign

2017 Green Chemistry & Engineering Conference
Toxicology for Chemists Symposium
Beyond Benign’s **mission** is to equip educators, scientists, and citizens with the tools to teach and practice green chemistry to achieve a sustainable society.

We **envision** a world where scientists and citizens enter the workforce with the skills to design and choose greener, sustainable technologies that spur the innovation economy.
**Beyond Benign: K–20 Programs**

<table>
<thead>
<tr>
<th>Professional Development</th>
<th>for educators on green chemistry, toxicology and sustainable science</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Green Chemistry Curriculum</strong></td>
<td>that replaces traditional hazardous chemicals in the lab and are based on real-world green technological innovations</td>
</tr>
<tr>
<td><strong>Community Engagement</strong></td>
<td>through green chemistry and sustainable science hands-on activities</td>
</tr>
<tr>
<td><strong>Lead Teacher</strong> Program</td>
<td>that provides K-12 science educators with an opportunity to become green chemistry teacher leaders</td>
</tr>
<tr>
<td><strong>A College Student Fellows</strong> Program</td>
<td>to foster green chemistry and leadership skills for college students</td>
</tr>
<tr>
<td><strong>The Green Chemistry Commitment</strong></td>
<td>for higher education institutions to integrate green chemistry across the sub-disciplines of chemistry</td>
</tr>
<tr>
<td><strong>Toxicology for Chemists Curriculum</strong></td>
<td>that provides the next generation of scientists with the skills to create products that are safe for humans and the environment.</td>
</tr>
</tbody>
</table>
Since 2007

Trained 4,000 K-12 Educators

Developed 180 K-12 Lesson Plans

Inspired and Informed 23,000 Students, Teachers, and Community Members

Created 280 College Fellow Leaders

Guided 40 College and University Green Chemistry Commitment Signers
Green Chemistry Student Learning Objectives

Signing institutions agree that upon graduation, all chemistry majors should have proficiency in the following essential green chemistry competencies:

• **Theory:** Have a working knowledge of the twelve principles of Green Chemistry

• **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

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

• **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

www.greenchemistrycommitment.org
9 PhD granting institutions
- University of California, Berkeley (2014, #1, US News & World Report)
- University of California, Davis (2014, #32, US News & World Report)
- South Dakota State University
- Michigan Tech
- University of Toledo
- University of Toronto (First in Canada!)
- Drexel University

2 MS granting institutions
- Montclair State
- SUNY Fredonia

25 BA or BS granting institutions

4 Community Colleges
4 Methods of Implementing Toxicology

• Independent Course
• Student-Led Course
• Seminar Series
• Integrating into Existing Chemistry Course
Toxicology Working Group

- Addressing the knowledge gap of toxicology and understanding molecular hazards in the chemistry curriculum
- Comprised of Green Chemistry Commitment signers & outside stakeholders
- Collaborate with industry experts
- Organize Symposia and Workshops
  - Society of Toxicology Conference, 2018
  - BCCE, 2018
Toxicology Working Group

Undergraduate
- General Chemistry
- Organic Chemistry
- Biochemistry
- Physical Chemistry
- Inorganic Chemistry
- Analytical Chemistry
- Research

Example Learning Objectives/Questions
- What is hazard? What is toxicology?
- Understanding how structure impacts toxicity
- Toxicokinetics and Toxicodynamics (ADME)
- How does thermodynamics impact toxicity?
- Inorganic chemicals and redox reactions in the body
- Using tools to identify biomarkers for toxicity
- How can I predict the toxicity of my product?
- How can I minimize the toxicity of my chemical process on human health and the environment?

Graduate

Awareness

Predictions
I. Atoms: Matter consists of atoms that have internal structures that dictate their chemical and physical behavior.

A. Atoms have unique chemical identities based on the number of protons in the nucleus

1. The atomic number and mass number are used to determine average atomic weight and identify isotopes, which play a part in understanding techniques such as MS, or NMR, or IR and rates of reactions via kinetic isotope effects.

   a. Stabilization of anions helps to explain pKa values and relative acidities of protons.
Anchoring Toxicology Concepts to Organic Chemistry

Case studies:

- **Relationship Between pKa and Skin Irritation**
- **Design for Biodegradability**
  - Electrophilic Aromatic Substitution
  - Alkanes: nomenclature and isomers
- **Bond strength and persistence**
- **Chirality**
- **Electrophilic-Nucleophilic Reactions**
Relationship Between pKa and Skin Irritation

pKa values can assist in predicting compound toxicokinetic behavior for:

- Skin Irritation
- Gastrointestinal absorption
- Membrane permeability
- Protein binding
- Metabolic transformations

pKa as an indicator of skin irritation:
pKa > 8 and pKa < 4

Case Study:
1. Research structures of chemical structures
2. Research their pKa and predict if they will be skin irritant
3. Identify the most acidic proton
4. Verify prediction based on SDS

Figure 1: Layers of the human skin with Erythema skin irritation location.
### Design for Biodegradability

*Features that increase resistance to aerobic biodegradation:*

<table>
<thead>
<tr>
<th>Feature</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Halogens: Especially chlorine and fluorine and if more than 3 in a molecule</td>
<td><img src="image1" alt="Structure" /></td>
</tr>
<tr>
<td>Chain branching if extensive: Quaternary C’s are problematic</td>
<td><img src="image2" alt="Structure" /></td>
</tr>
<tr>
<td>Tertiary amine, nitro, nitroso, azo, and arylamino groups</td>
<td><img src="image3" alt="Structure" /></td>
</tr>
<tr>
<td>Polycyclic aromatic residues</td>
<td><img src="image4" alt="Structure" /></td>
</tr>
<tr>
<td>Heterocyclic residues</td>
<td><img src="image5" alt="Structure" /></td>
</tr>
<tr>
<td>Aliphatic ether bonds (except in ethoxylates)</td>
<td><img src="image6" alt="Structure" /></td>
</tr>
</tbody>
</table>
**Design for Biodegradability**

Molecular features that generally increase aerobic biodegradability:

<table>
<thead>
<tr>
<th>Feature</th>
<th>Structure</th>
</tr>
</thead>
</table>
| Groups susceptible to enzymatic hydrolysis (esters, including phosphate esters) and amides | ![Structure](https://via.placeholder.com/150) |}
| Oxygen atoms in the form of hydroxyl, aldehyde, or carboxylic acid groups, ketones (not ether, with the exception of ethoxylate groups) | ![Structure](https://via.placeholder.com/150) |
| Unsubstituted linear alkyl chains (especially ≥ 4 carbons) and phenyl rings | ![Structure](https://via.placeholder.com/150) |
Design for Biodegradability

Organic Chemistry Concepts:
- Naming of alkyl chains
- Understanding and identifying isomers
- Condensed and bond-line formula
- Identifying functional groups

Toxicology Concepts:
- Persistence/Biodegradability
- Half-life
Design for Biodegradability

Organic Chemistry Concepts:
- Electrophilic aromatic substitution (electrophilic addition where oxygen is added to a phenyl ring)
- Substituent effects

Toxicology Concepts:
- Persistence/Biodegradability
- Half-life

Dr. Dalila Kovacs, Grand Valley State University
Chirality

Organic Chemistry Concepts:
• Chirality
  • Identify chiral center
  • How many stereoisomers?

Toxicology Concepts:
• Structure and function

Toxicity: a dash or a wedge? Read section 4.2.1.1, page 5851 about the toxicokinetics and toxicodynamics of Thalidomide R and S enantiomers. List the differences between the two enantiomers in their toxicity and efficacy.

Dr. Dalila Kovacs, Grand Valley State University

Electrophilic-Nucleophilic Reactions

Organic Chemistry Concepts:
• Electrophiles and Nucleophiles
• Reactions ($S_N^1$, $S_N^2$, Acylation, Michael Addition, Schiff Base Formation, $S_N^A$)

Toxicology Concepts:
• DNA and protein binding
• Toxicological reaction mechanisms

Electrophilic-Nucleophilic Reactions

Discussion Questions:

• Given the following xenobiotic molecules, propose which of the 6 reaction mechanisms this electrophile will undergo with a biological nucleophile

• Propose a mechanism with a biological nucleophile

![Acrolein](image1.png)  
Acrolein

![Methyl iodide](image2.png)  
Methyl iodide

![Benzoyl chloride](image3.png)  
Benzoyl chloride

![4-nitrochlorobenzene](image4.png)  
4-nitrochlorobenzene
Thank you!

Alicia McCarthy, UML TURI
Dr. Dalila Kovacs, Grand Valley State University
Toxicology Working Group

Amy_Cannon@beyondbenign.org

www.greenchemistrycommitment.org
www.beyondbenign.org
## Electrophilic-Nucleophilic Reactions

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Reaction site</th>
<th>Main reaction mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin sensitization</td>
<td>Chemically modified skin proteins (e.g., Cys, Lys, or Ser residues) leading to T-cell mediated allergic response</td>
<td>Protein haptenation via Sₘ₂, SₘAr, MA, SB, Ac</td>
</tr>
<tr>
<td>Respiratory sensitization</td>
<td>Chemically modified proteins in the lung (e.g., Lys residues)</td>
<td>SB, protein cross-linking, Sₘ₁, Sₘ₂, Ac</td>
</tr>
<tr>
<td>Skin irritation</td>
<td>Skin proteins and lipids in the stratum corneum</td>
<td>SB, Sₘ₂, MA, Ac, Aₜᵣ</td>
</tr>
<tr>
<td>Elevated acute toxicity and cytotoxicity (aquatic or terrestrial)</td>
<td>Cellular GSH; interaction with nucleophiles (-OH, -NH₂, -SH groups) in biological macromolecules (e.g., inhibition of acetylcholine esterase)</td>
<td>Electrophilic reactivity via Sₘ₁, Sₘ₂, acylation, MA, SB (in contrast to polar and unpolar narcosis)</td>
</tr>
<tr>
<td>Mutagenicity and carcinogenicity</td>
<td>DNA or RNA gene mutation via adduct formation, base pair substitutions, and frameshifts; interaction with regulatory molecules</td>
<td>Sₘ₁, Sₘ₂, acylation, MA, SB</td>
</tr>
<tr>
<td>Chromosomal aberration</td>
<td>Alteration of DNA and sequence of genetic material (number of structure of chromosomes), which often alters embryonic development; inhibition of topoisomerases and interaction with nuclear proteins associated with DNA (e.g., histone proteins)</td>
<td>DNA and protein binding mechanisms</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>Attack of hepatocytes, the bile duct, or sinusoidal endothelium, Kupffer, or Ito cells by: 1) direct cell stress, direct mitochondrial impairment, and specific immune reactions; 2) direct and death receptor-mediated pathways leading to mitochondrial permeability transition; 3) apoptosis and necrosis</td>
<td>Protein binding and receptor-mediated mechanisms (e.g., interaction with P-450 enzyme family, leading to damaged mitochondrial functions and possible idiosyncratic effects)</td>
</tr>
</tbody>
</table>