Opportunities to Incorporate Toxicology into the Chemistry Curriculum

Report from the Field

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Science without borders

• The link between chemistry and toxicology is fundamental and the two “fields” are inextricable
• Toxicity obeys the principles of biology and chemistry so why not embrace commonalities?
Safer Chemical Design: Alice Hamilton, MD (1869-1970)

• “Chemistry and medicine have thus made possible real progress in the protection of men and women against industrial poisons. Much remains to be done in this field, even in the light of our present knowledge, and greater progress will be made possible in the future through advances in chemistry. For instance, substitutes which are relatively non-toxic may be found to take the place of toxic compounds now in use."

• Toxicology must join with chemistry in testing the new compounds which chemistry introduces into industry."

• “Synthetic chemistry must have as one of its great objectives the further safeguarding of health and of life in the industries into which chemistry itself has introduced new poisons.”

• “Toxicology must join with chemistry in testing the new compounds which chemistry introduces into industry”."


Courtesy-SC DeVito
Nexus of Chemistry and Safer Chemical Design

Fundamental Chemistry

Physicochemical Properties

Green Chemistry

21st Century Toxicology

HTS

In silico

Design Guidelines

QSAR

Articulate Design Guidelines
Enter the Toxicologist

- Toxicology is the study of adverse effects on living systems
- A working knowledge of the **structure-hazard** (e.g., toxicity) relationship is essential to design safer chemicals
- Chemists are not trained in toxicology
- Toxicologists must engage at the molecular design stage of chemical synthesis
Examples of electrophilic toxicophores

<table>
<thead>
<tr>
<th>Electrophile</th>
<th>General Structure</th>
<th>Nucleophilic Reaction</th>
<th>Toxic Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>a,b-unsaturated carbonyl and related groups</td>
<td>C=C−C=O</td>
<td>Michael Addition</td>
<td>cancer, mutations, toxic to the liver &amp; kidney, neurotoxicity, hemato-toxicity</td>
</tr>
<tr>
<td></td>
<td>C=N−S</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>H=C−C=N</td>
<td>addition</td>
<td>cancer, mutagenicity, pulmonary sensitization, asthma.</td>
</tr>
<tr>
<td></td>
<td>−N=C=O</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>−N=C=S</td>
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</tr>
</tbody>
</table>

DeVito, S.C.
Functional groups and Toxicophores

- Thiocarboxamide moiety
- Thiourea moiety

- Hydrazido moiety

- Semicarbazide moiety

- Aromatic hydrazino moiety

- Toxicity to the thyroid gland. Can cause hypothyroidism.

- Developmental toxicity, osteolathyism, blood dyscrasias, cancer.

- Blood dyscrasias, autoimmune disease, cancer.
Computational Chemistry Properties

• Molecular
  – Properties that are localized on a single molecule
  – Melting point, log P, molecular weight, molar refractivity, HOMO/LUMO, etc.

• Intermolecular
  – Properties that are derived from the interaction of two molecules
  – Binding constants, free energy of binding, etc.
  – Not likely to be ‘atomistic’
Absorption, Distribution, Metabolism, Excretion (ADME)

- Liking with known principles of kinetics
- Absorption
  - Effect of ionization on absorption (Henderson Hasselbalch)
  - Log P
- Distribution
- Metabolism
  - Substitution (e.g.; Sn1/Sn2)
  - Catalysis
- Excretion
  - Water solubility
Toxicodynamics

- Efficacy
  - Binding efficiency and strength (Kd)
- Potency
  - Introduce the concept of dose response
Mechanistic Toxicology

- Introduce the concept of structure-hazard relationship using reactivity
- Michael acceptors and DNA alkylation and reactions with Glutathione (GSH)
  - Aldehydes and ketones
- Shiff’s Base and Toxicity
  - Antifungal
  - Antibiotic
- Reinforce the fact that the reactions, learned in chemistry classes, can be used to describe reactions in biological systems
Metals toxicity

- Metals can act as electrophiles in biological reactions
- Arsenic
- Lead
- Chromium
Oxidative stress

• When discussing oxygen and its radical forms (OH, HOOH, superoxide, etc.) bring in a discussion of its reactivity:
  – Atmosphere
  – Biological systems
    • Free radicals and antioxidants
    • Oxidative stress
Redox Chemistry

- Oxidation reduction plays a major role in the toxicity of many chemicals
  - Nitrate/Nitrite (methemoglobinemia)
  - Chromium 3/Chromium 6 (vast difference in carcinogenicity)
- Also involved in cytochrome P450 activity
  - NADPH; iron
Isomerism

- Provide examples of the effect of isomers on toxicity
- Thalidomide
- Quinine/Quinidine

![Thalidomide molecules: S-thalidomide (a teratogen) and R-thalidomide (a sedative)]
Effect of structure on biodegradation

- Structure affects the rate of biodegradation
- Detergents
  - Alkyphenol ethoxylates vs. linear alkly ethoxylates
    - Rates of hydrolysis
Frontier Molecular Orbitals (FMO)

- HOMO/LUMO gap ($\Delta E$)
- Discuss its potential influence on toxicity with a case study
  - FMO (frontier molecular orbitals) and reduced aquatic toxicity
The Role of Chemistry in Safer Molecular Design

- *Fundamental chemical* reactions are at the core of most adverse reactions
- These reactions are all familiar to chemists

Nature has been, and is, the molecular designer extraordinaire

- Fibers (wood, cotton, silk, wool, etc.)
- Fragrances / Flavors / Dyes / Medicines (flowers, leaves, seeds, bark, insects)
- Biological Toxins (snakes, sea creatures, insects, plants)
- Crude oil / coal / natural gas
- Antibiotics
Bio-inspired materials

- Chitin/chitosan
- Mussel byssus
Summary

- Myriad opportunities to incorporate toxicology into the existing chemistry curriculum.
- Challenge is the availability of “drop-in” resources
- Examples
  - Begin with the familiar (we are all apprentice toxicologists!)
  - Topic matching lecture books