United States Environmental Protection Agency

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....*

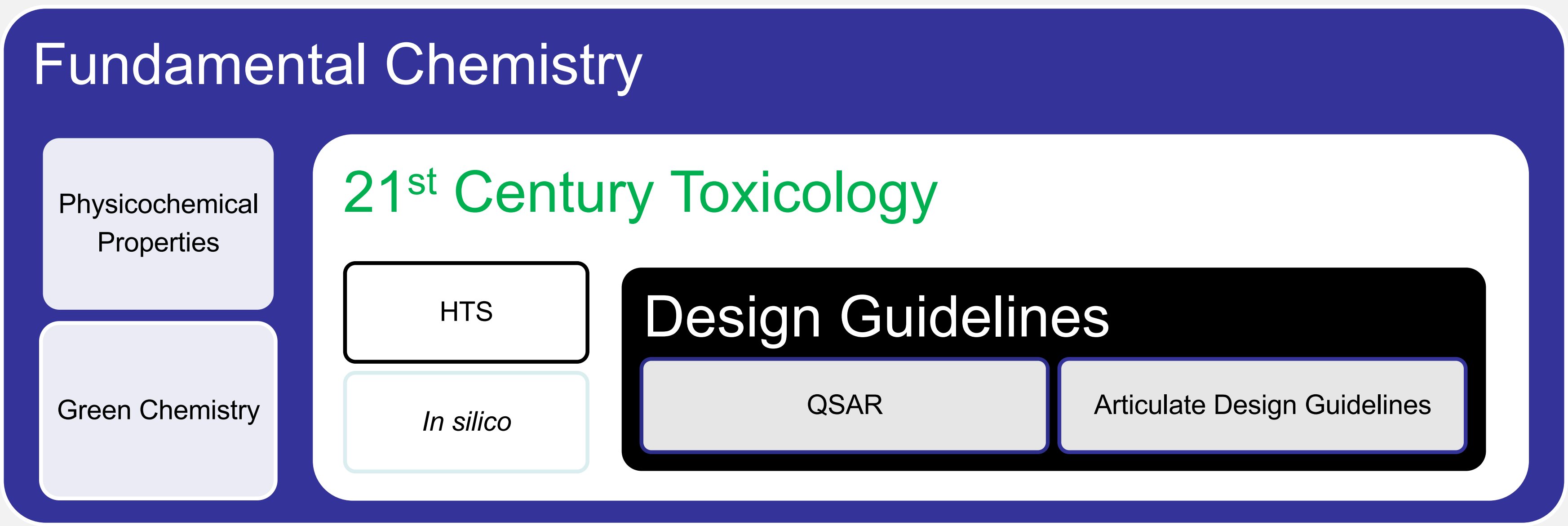
- ***"Synthetic chemistry must have as one of its great objectives the further safeguarding of health and of life in the industries into which chemistry itself has introduced new poisons."***

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

- Hamilton, A. (1928) "Protection against industrial poisoning," in *Chemistry in Medicine*, 1st edn (ed J.S. Stieglitz), The Chemical Foundation, Inc., New York, pp. 374-394.

Courtesy-SC DeVito

Nexus of Chemistry and Safer Chemical Design



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

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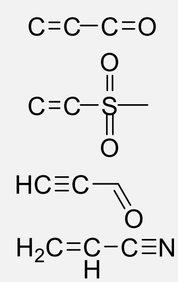
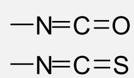
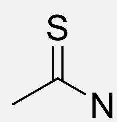
Examples of electrophilic toxicophores

Electrophile	***General Structure***	***Nucleophilic Reaction***	***Toxic Effect***
a,b-unsaturated carbonyl and related groups		**Michael Addition**	**cancer, mutations, toxic to the liver & kidney, neurotoxicity, hemato-toxicity**
isocyanates		**addition**	**cancer, mutagenicity, pulmonary sensitization, asthma.**

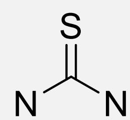
DeVito, S.C.

Functional groups and Toxicophores

thiocarboxamide moiety

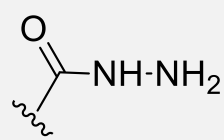


thiourea moiety

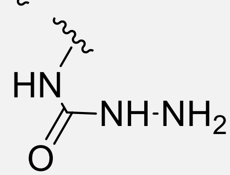


toxicity to the thyroid gland. Can cause hypothyroidism.

hydrazido moiety



semicarbazide moiety



developmental toxicity, osteolathyrism, blood dyscrasias, cancer.

aromatic hydrazino moiety

$Ar-NH-NH_2$

blood dyscrasias, autoimmune disease, cancer.

Computational Chemistry Properties

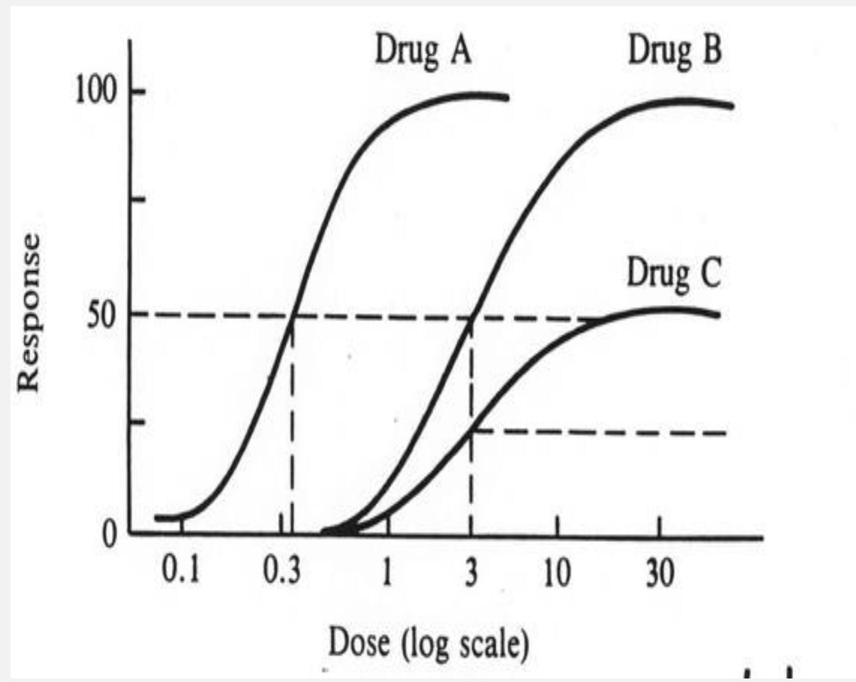
- Molecular
  - Properties that are localized on a single molecule
  - Melting point, log P, molecular weight, molar refractivity, HOMO/LUMO, etc.
- Intermolecular
  - Properties that are derived from the interaction of two molecules
  - Binding constants, free energy of binding, etc.
  - Not likely 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



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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

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Metals toxicity

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

Oxidative stress

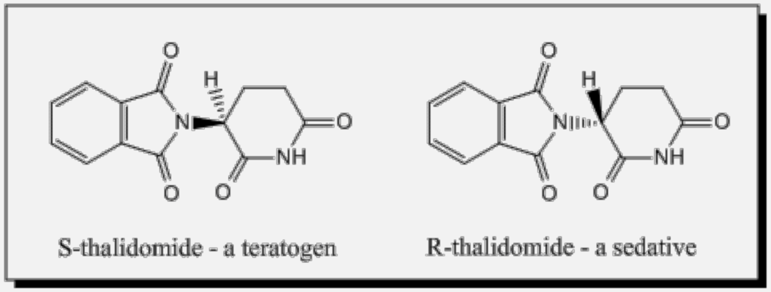
- When discussing oxygen and its radical forms (OH, HOOH, superoxide, etc.) bring in a discussion of its reactivity:
  - –Atmosphere
  - –Biological systems
    - Free radicals and antioxidants
    - Oxidative stress

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



Effect of structure on biodegradation

- Structure affects the rate of biodegradation
- Detergents
  - –Alkyphenol ethoxylates vs. linear alkly ethoxylates
    - Rates of hydrolysis

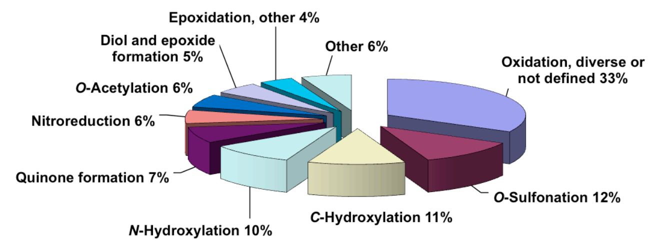
Frontier Molecular Orbitals (FMO)

- HOMO/LUMO gap (ΔE)
- Discuss it 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

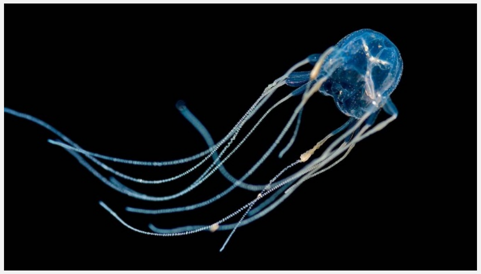
Fig. 6



S. Rendic and F. P. Guengerich (2012) Chem. Res. Toxicol. ***25****, 1316-1383*

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



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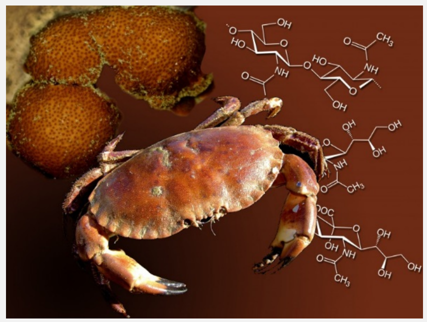
Bio-inspired materials

- Chitin/chitosan



- Mussel byssus

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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