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

The Green Chemistry Commitment
TRANSFORMING CHEMISTRY EDUCATION

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

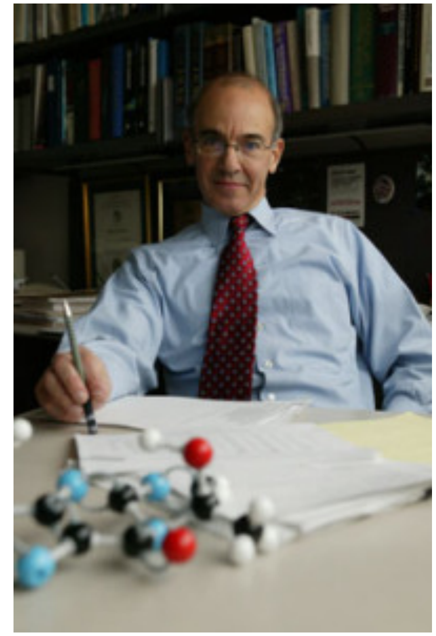
- Topic rotates between Green Chemistry, Toxicology, Polymers, and Nanomaterials

- 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.

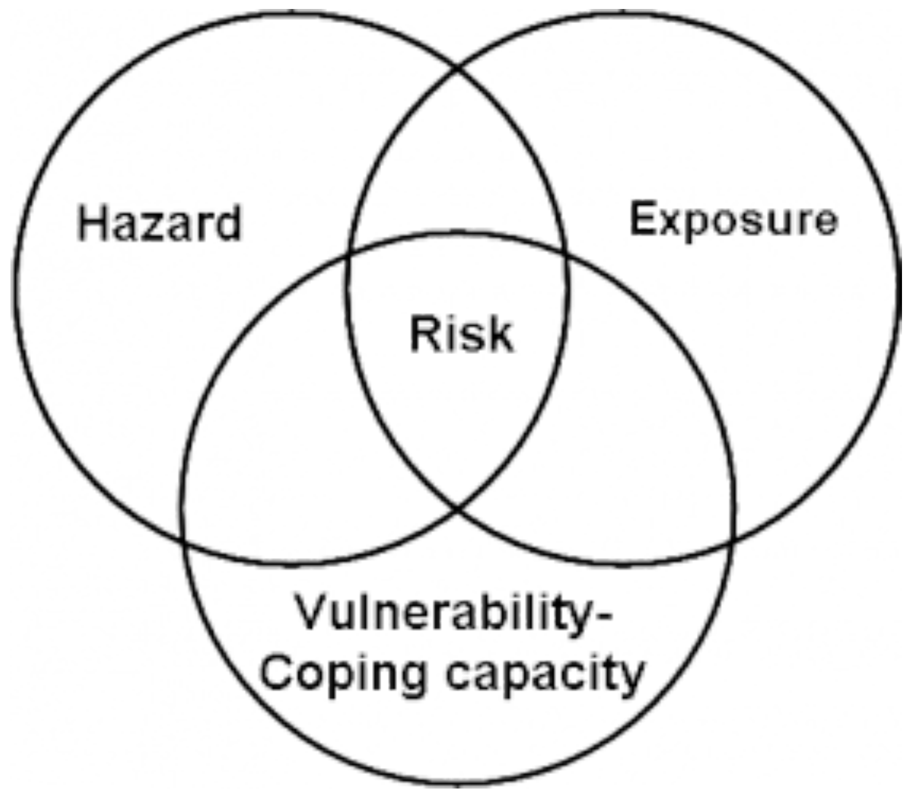
Chemical Research in Toxicology: Day 1

- 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



Stephen Hecht, Editor

Risk = f (Hazard x Exposure x vulnerability)

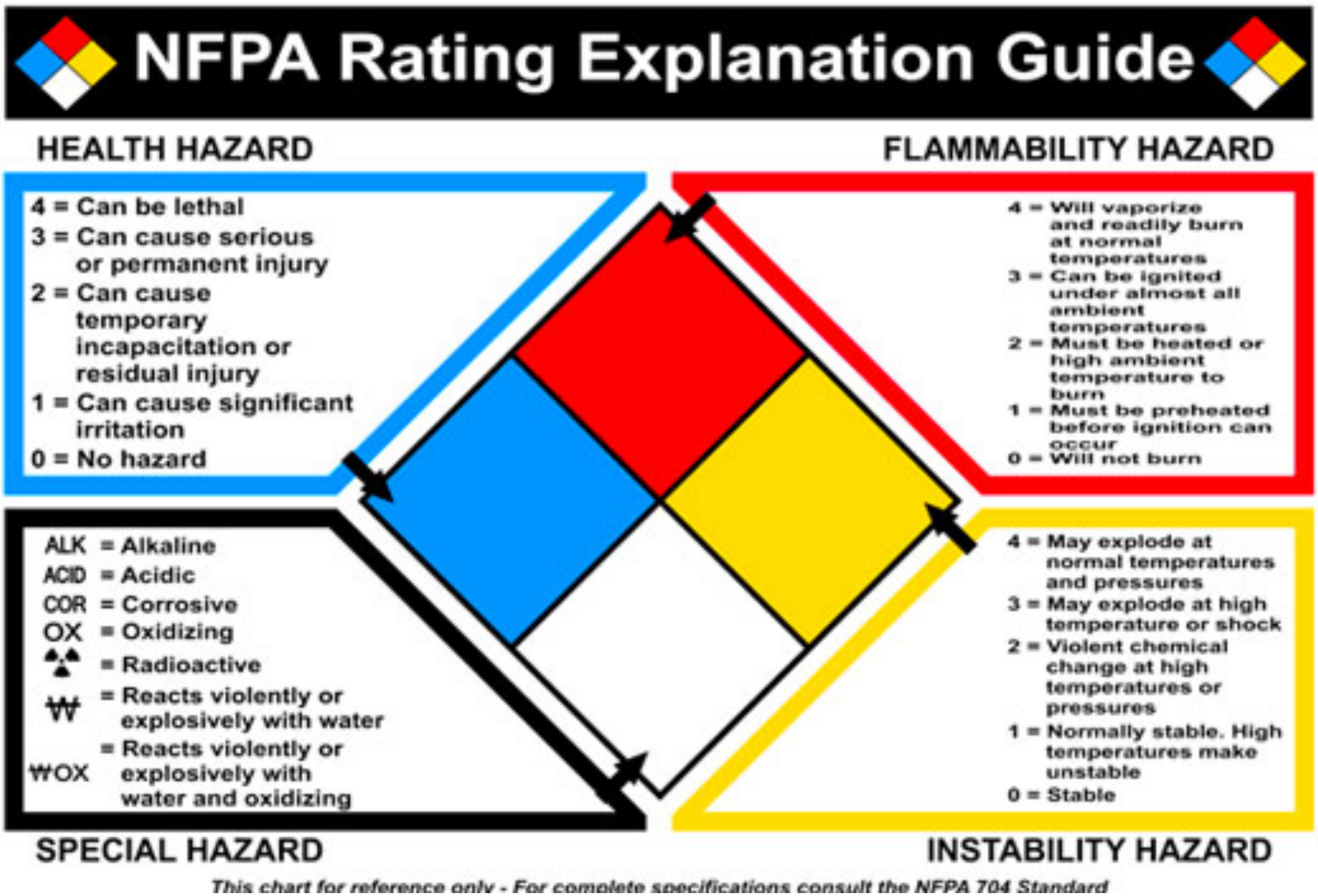


- Acute chemical hazard – Exposed once and it has an effect. Ex: HCN (used in gas chambers)

- 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

Flame Over Circle	**Environment** (Non-Mandatory)	**Skull and Crossbones**
		
• Oxidizers	• Aquatic Toxicity	• Acute Toxicity (Fatal or Toxic)

Overview of Chemical Mechanism in Toxicology

- Corrosive
- Asphyxiation
- Mutates DNA → Causes protein misfolding, altered function
- Mutates DNA repair enzymes → DNA mutations not fixed
- Body coverts 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

Hydrazine

Arsenic

Sulfer mustard gas

Aflatoxin

Bis phenol A

Thimerosal

Cocaine

Trichloroethylene

Fromaldehyde

Thalidomide

Chromium oxidation Cr^{6+} toxicity

Ti oxide or Zn oxide nanoparticles

MDMA

nicotine-derived nitrosamine ketone (NNK)

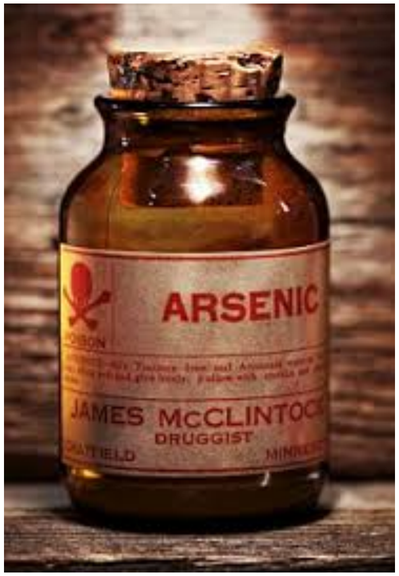
Sarin gas

Nitriles – cyanide production

Organophosphates (sarin gas)

Goal one:

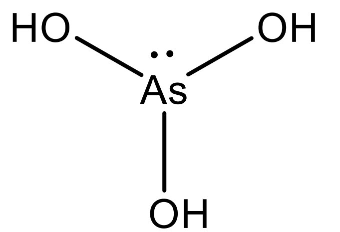
- Background info on your toxin.
- Where is it found or how is it synthesized
- How toxic is it?

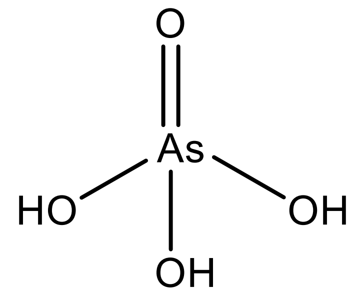


The Toxicology of Arsenic

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

As





Arsenic
LD50 = 763 mg/kg
A1 Carcinogen

Arsenite (As^{+5})
LD50 = 41 mg/kg
A1 Carcinogen
Mutagen

Arsenate (As^{+5})
LD50 = 100 mg/kg
A1 Carcinogen
Teratogen,
Mutagen

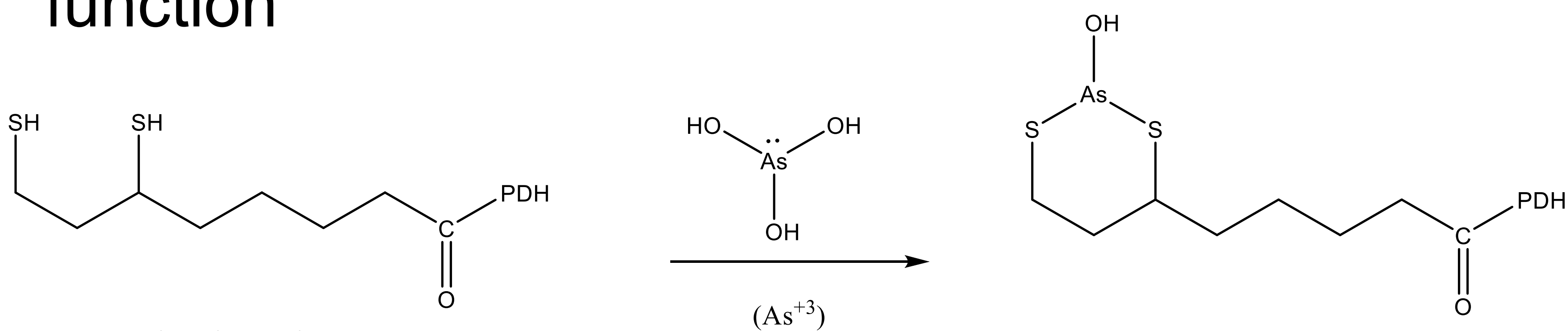
- Methylated forms of As exist in biological systems and have various toxicity levels.

Goal two:

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

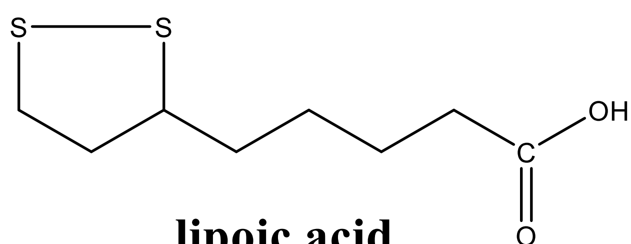
Arsenite toxicity

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

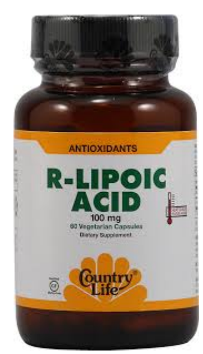


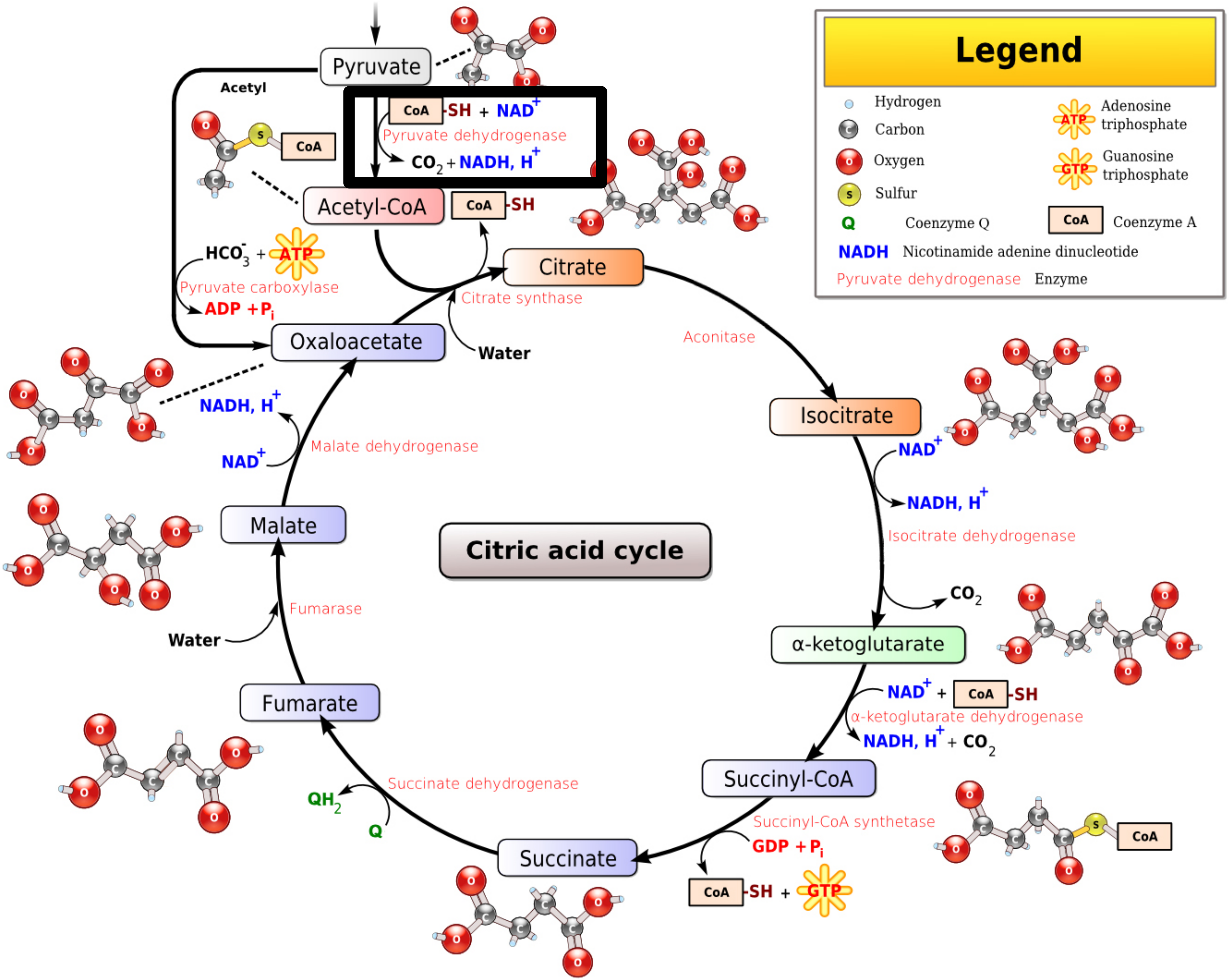
Reduced lipoic acid attached to pyruvate dehydrogenase

Catalytic activity of PDH diminished



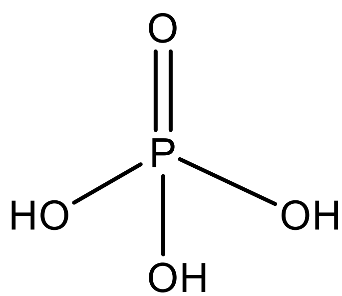
lipoic acid



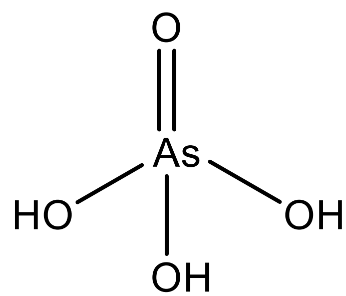

Legend
Hydrogen
Carbon
Oxygen
Sulfur
Q Coenzyme Q
NADH Nicotinamide adenine dinucleotide
Pyruvate dehydrogenase Enzyme
ATP Adenosine triphosphate
GTP Guanosine triphosphate
CoA Coenzyme A
Pyruvate
Acetyl
CoA-SH + NAD+
Pyruvate dehydrogenase
CO2 + NADH, H+
Acetyl-CoA
CoA-SH
HCO3- + ATP
Pyruvate carboxylase
ADP + Pi
Citrate
Citrate synthase
Water
Oxaloacetate
Aconitase
Isocitrate
NAD+
NADH, H+
Isocitrate dehydrogenase
CO2
α-ketoglutarate
NAD+ + CoA-SH
α-ketoglutarate dehydrogenase
NADH, H+ + CO2
Succinyl-CoA
Succinyl-CoA synthetase
GDP + Pi
CoA-SH + GTP
Succinate
Succinate dehydrogenase
QH2
Q
Fumarate
Fumarase
Water
Malate
Malate dehydrogenase
NAD+
NADH, H+
Citric acid cycle

Arsenate toxicity

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

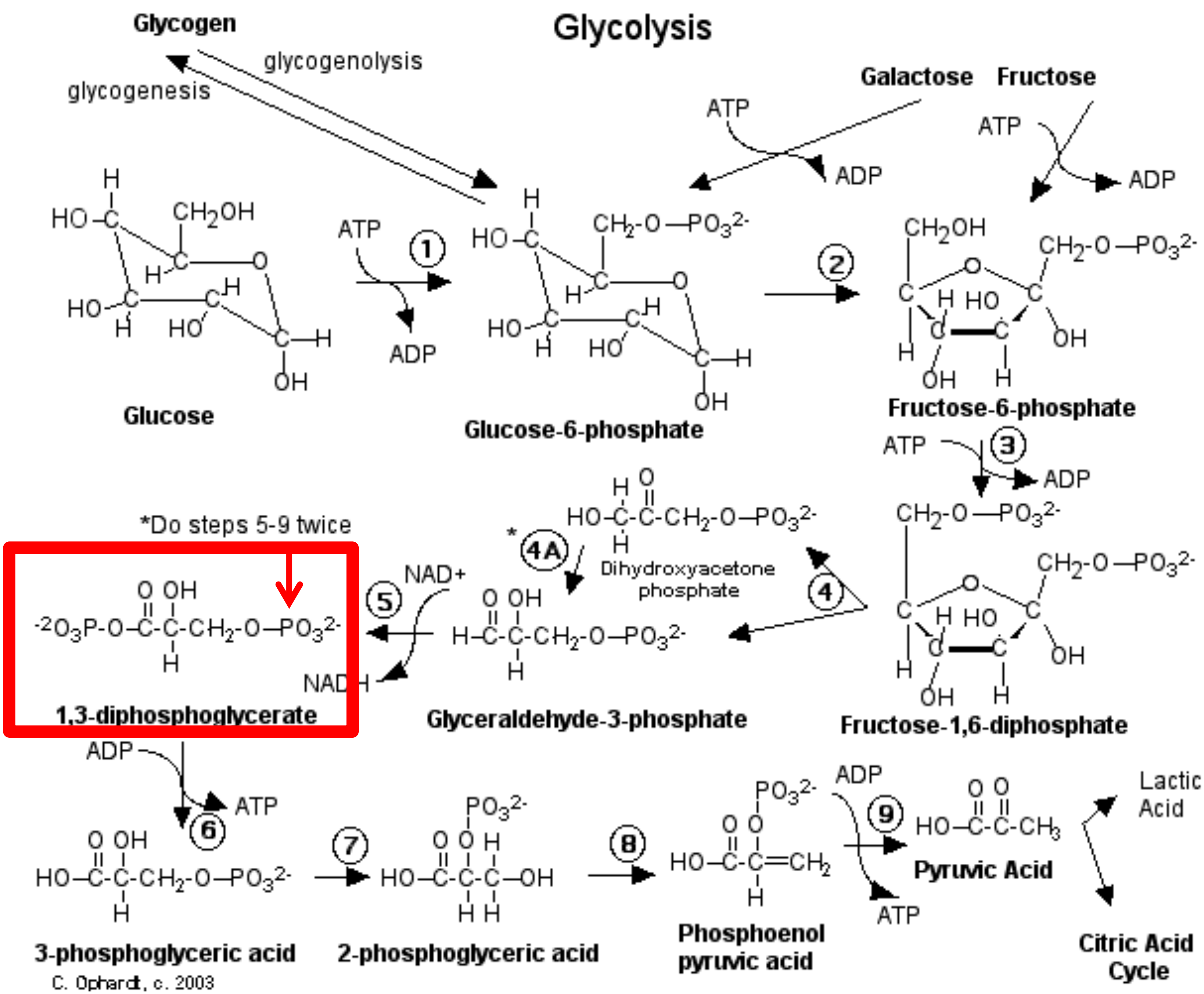


Phosphate



Arsenate (As^{+5})

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

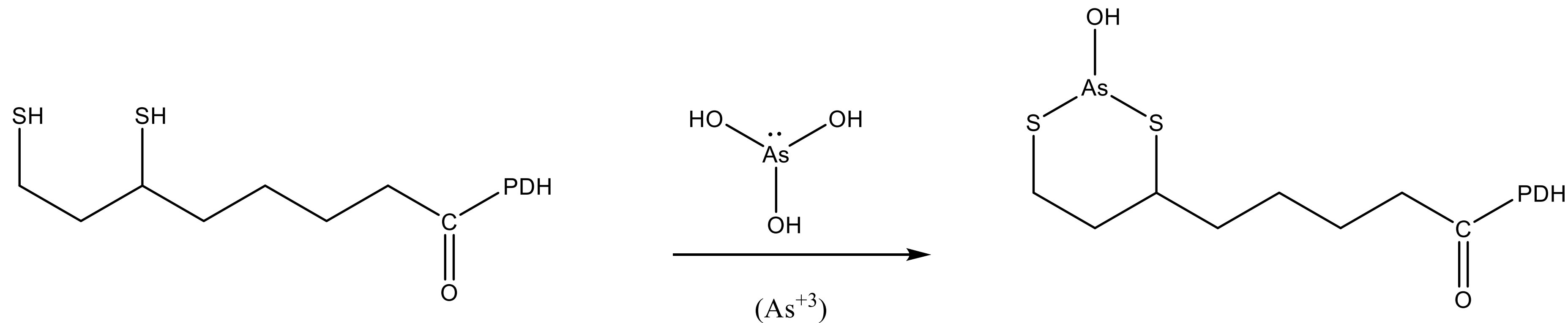


Glycolysis
Glycogen
glycogenolysis
glycogenesis
Galactose
Fructose
ATP
ADP
Glucose
Glucose-6-phosphate
Fructose-6-phosphate
Fructose-1,6-diphosphate
Dihydroxyacetone phosphate
Glyceraldehyde-3-phosphate
*Do steps 5-9 twice
NAD+
NADH
1,3-diphosphoglycerate
3-phosphoglyceric acid
2-phosphoglyceric acid
Phosphoenol pyruvic acid
Pyruvic Acid
Lactic Acid
Citric Acid Cycle
C. Ophardt, c. 2003

Goal three:

- Give a method of detoxification or how the mechanism can be stopped

Detoxification using BAL



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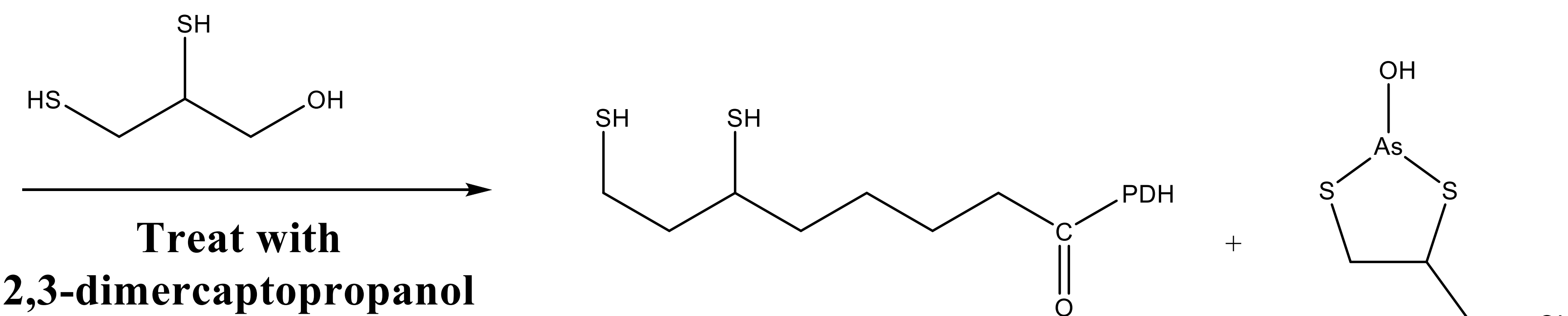


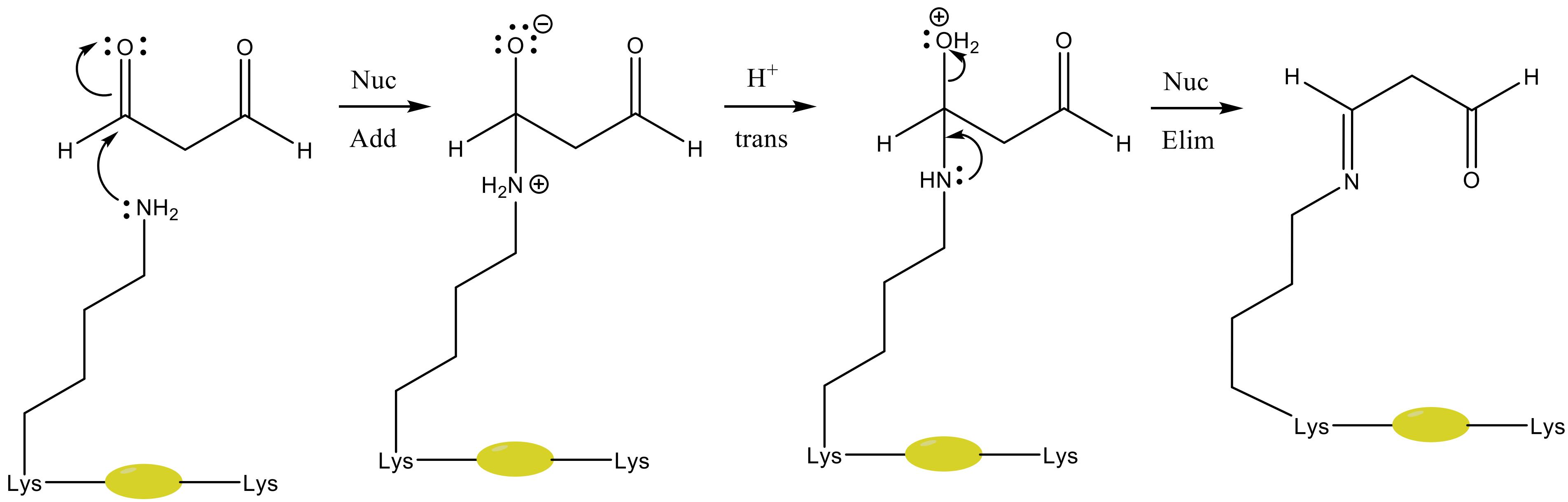
Catalytic activity of PDH restored

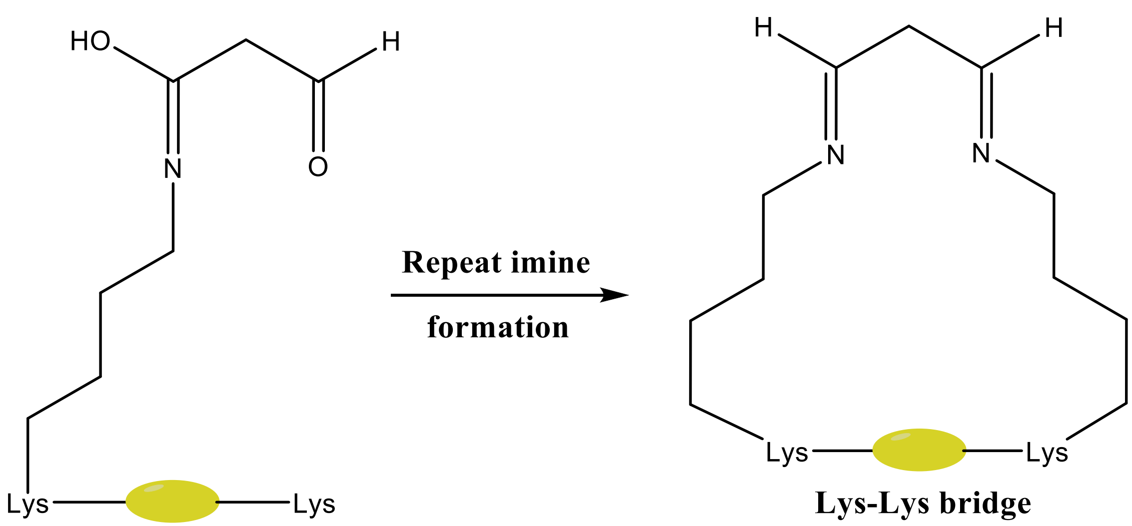
Other mechanism examples

- Protein Modification / DNA Addution

- Imine formation
- Michael addition
- Generation of ROS

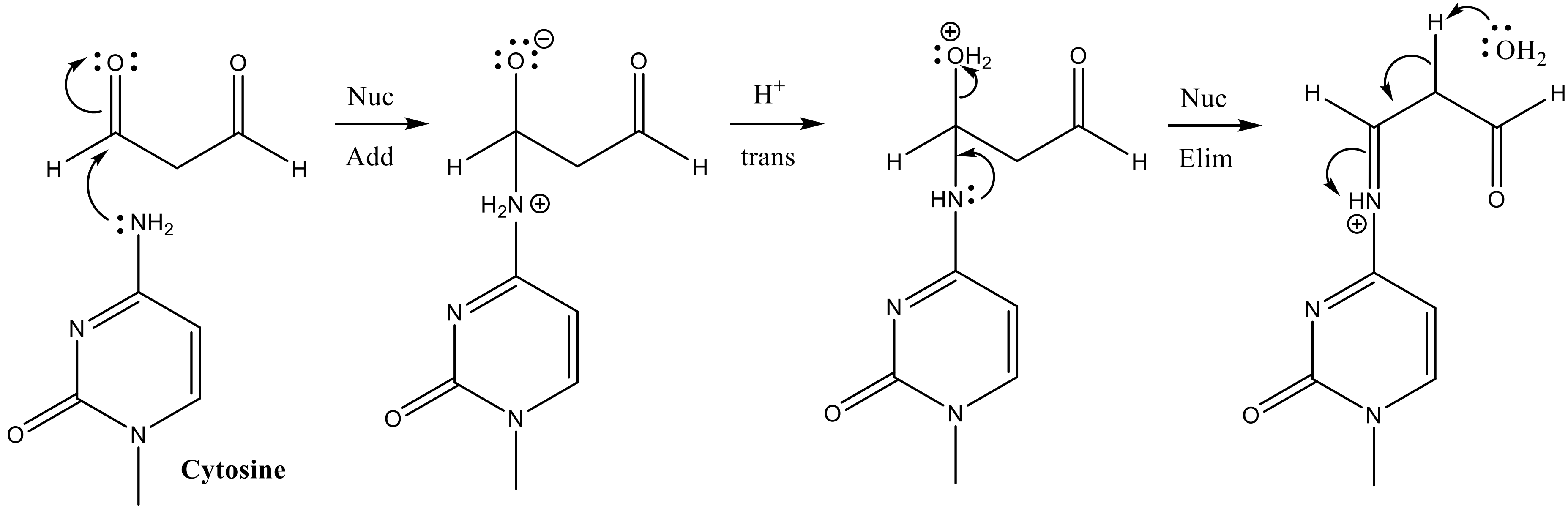
Toxicity of Lipid Peroxidation Byproducts: Malondialdehyde (MDA)

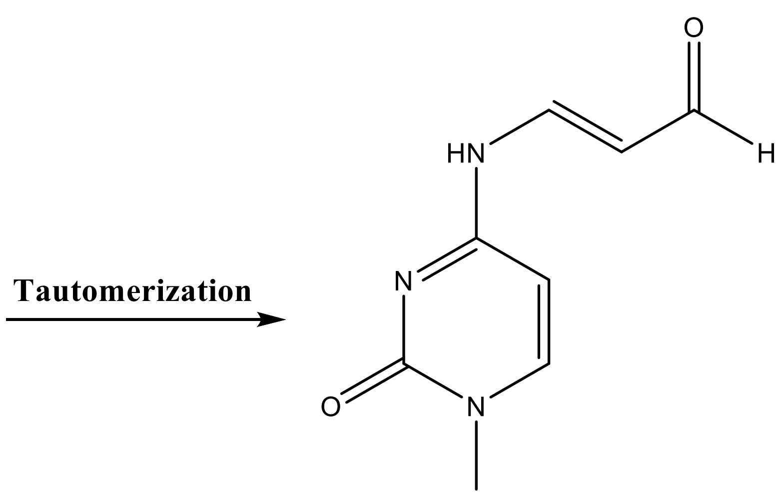




- Proceeds by immine formation
- Modified protein function
- Hindered interaction with microphages
- Inflammatory responses
- Immune response

Toxicity of lipid peroxidation byproducts: DNA Adduction of Malondialdehyde (MDA)

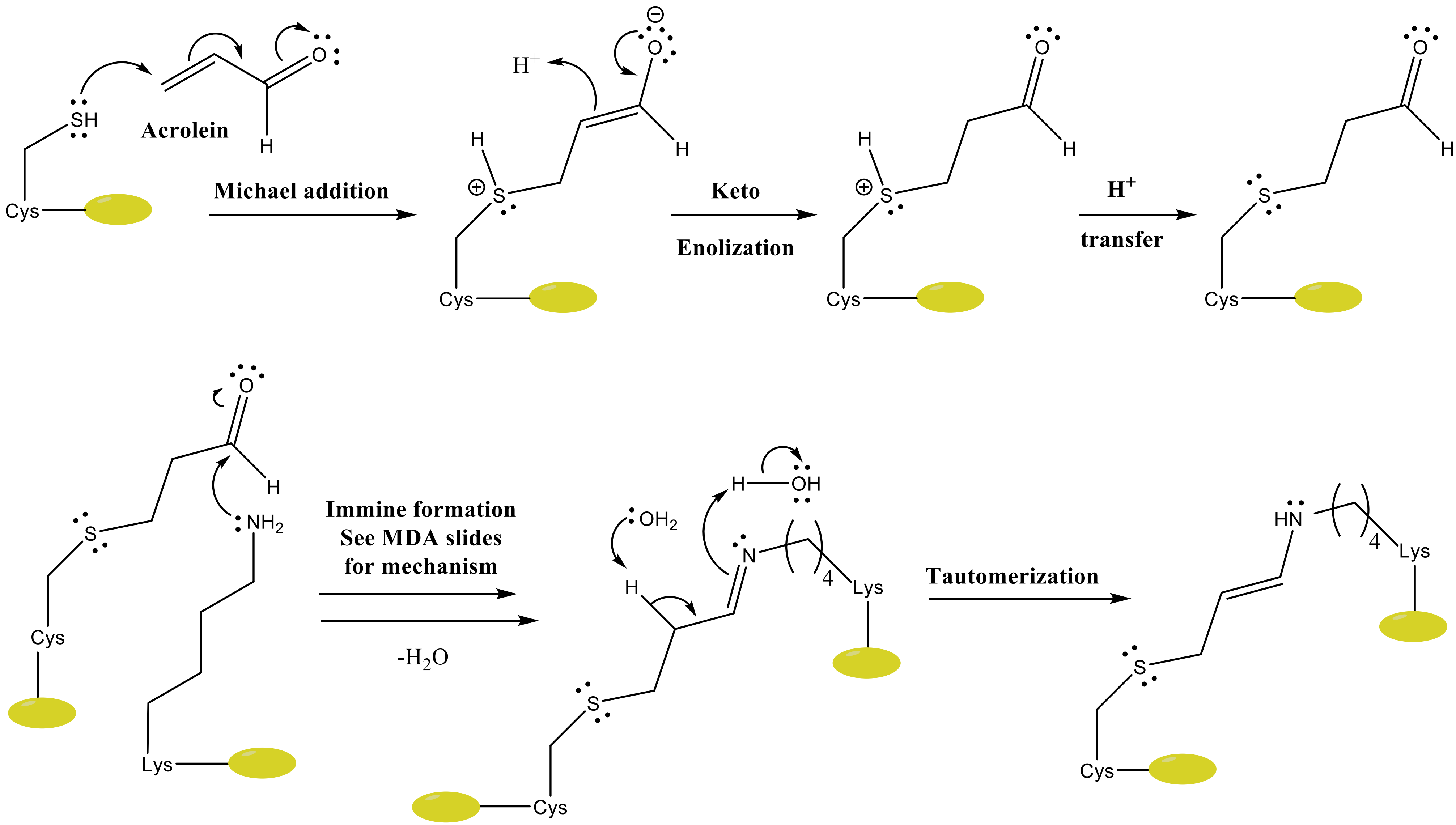




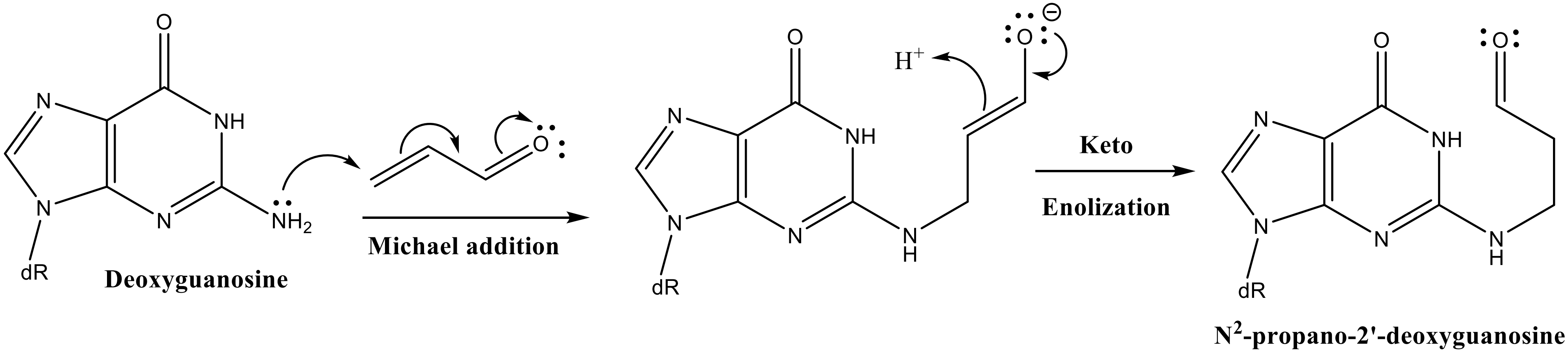
N^4-(3-oxopropenyl)deoxycytidine

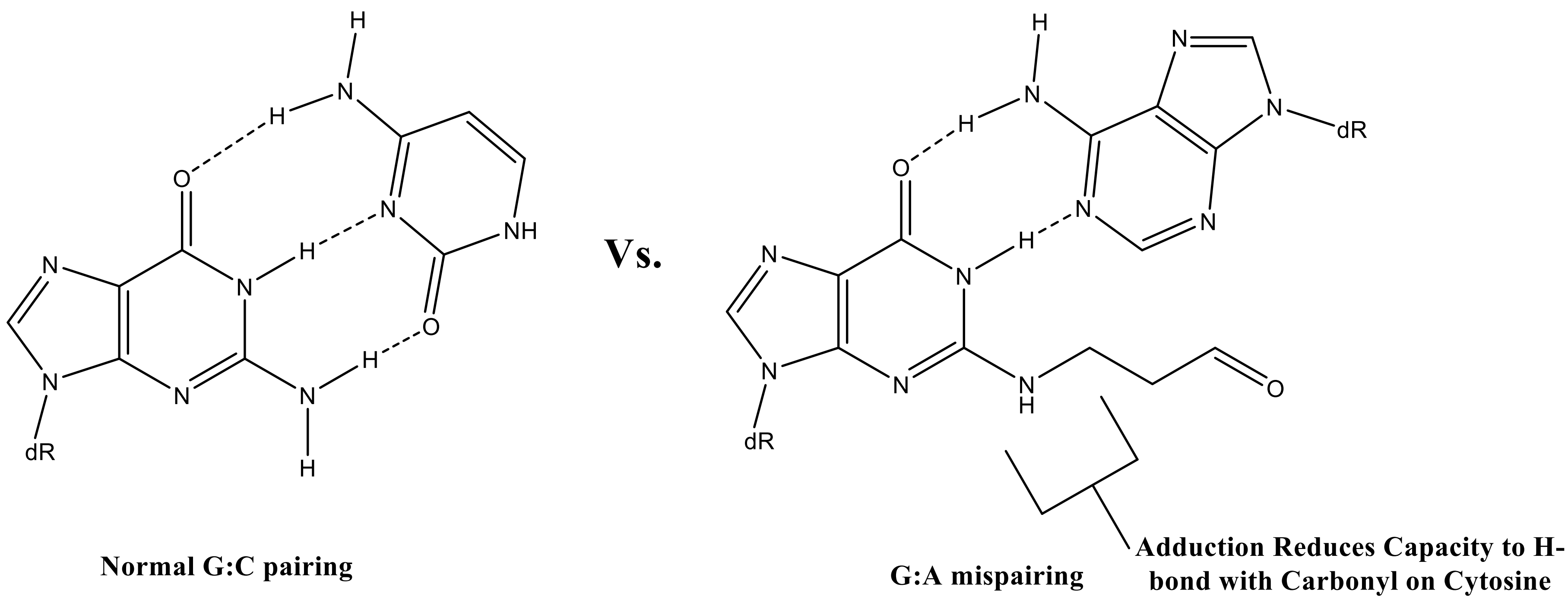
- MDA has shown to form adducts with with dG,dA, and dC bases
- This results in A→G, G →T, and C →T mutations
- If unrepaired this could potentially lead to protein malfunction or cancer
- Above is a proposed mechanism of adduction with Cytosine

Toxicity of lipid peroxidation byproducts: Michael Addition to Acrolein



Toxicity of lipid peroxidation byproducts: DNA Adduction of Acrolein





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.

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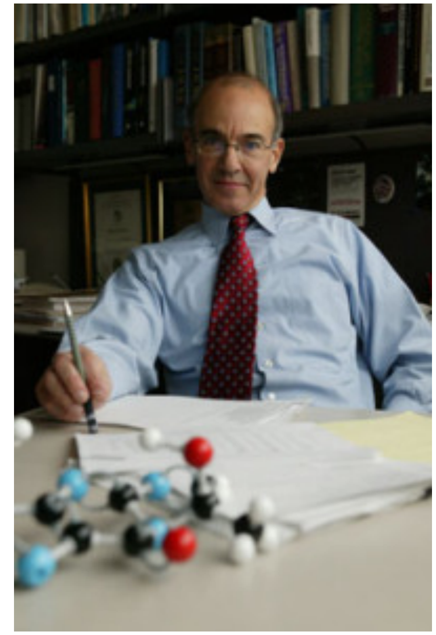
Green chemists make better Chemists



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