EVE 491/591
Toxicology

Lecture #9
1. Haiti: No update today…
2. Chemical-induced mutagenesis
3. Exam #1 Review

DNA and Mutations

- **Mutation**: a permanent change in the DNA
  - Mutagenesis – the process by which a mutation occurs
- **DNA**: our blueprint; it carries the genetic information that makes us unique
  - Human DNA is packaged in 23 pairs of chromosomes
    - Each chromosome is composed of a DNA molecule that is complexed with numerous proteins.
  - Regulates the enzymes that are critical for biotransformation of toxins (recall Lecture #8)
  - Must be able to replicate and maintain its integrity from replication to replication.

DNA Composition
DNA and Mutations

- Four nucleotides (structural DNA molecules):
  - Adenine (A)
  - Thymine (T)
  - Guanine (G)
  - Cytosine (C)
- Nucleotides exist in specific pairs ("base pairs")
  - A/T and G/C
- Incorrect base pairing may result in the alteration of information; normal physiology interrupted
  - Examples:
    - An altered enzyme (metabolic deficiency)
    - An abnormal protein (decreased muscular/skeletal function)

DNA and Mutations

- Damage to DNA can be:
  - Spontaneous (a replication "mistake")
  - The result of environmental exposures
- Mutated DNA can be:
  - Recognized
  - Repaired
- DNA is:
  - Perhaps the only biological macromolecule that can be repaired

Mutations

- Mutations may be:
  - Induced as a result of exposure of the DNA to environmental mutagens
  - Spontaneous as a result of "normal" cellular processes
  - Acquired (i.e., somatic) some time during the life of an individual; usually not passed to offspring
  - Hereditary (i.e., germline) acquired from a "parent" and can be present in all the cells of the offspring
**Mutations and Apoptosis**

- Recall *apoptosis*: planned or programmed cell death
  - It is a normal process that occurs
    - during embryological development
    - as part of normal cellular replacement
    - in response to physical, biological, or chemical stressors
  - Cell turnover occurs without necrosis and inflammation
  - Apoptosis is also an important way that genetically altered cells can be removed from the body if DNA repair does not work/occur
Mutations and Apoptosis

• The triggering of apoptosis is complex
  – Involves the cell receiving chemical messages
to “turn on” those genes involved in the self-
destruction process
• If these genes become mutated and
apoptosis is compromised, then the cell is
at greater risk of becoming one that may
transform into a cancerous cell.

Tests for DNA Damage and
Mutagenicity

• A number of toxicological tests can
evaluate the effects of a chemical agent as
being deleterious to DNA:
  – the Ames test (a biological assay)
  – tests for chromosome aberrations (e.g.,
amniocentesis)
  – exchanges in populations of proliferating cells
  – DNA repair studies
  – others that detect “changes” in the DNA.

Mutagen ≠ Carcinogen

<table>
<thead>
<tr>
<th>Known Human Carcinogens</th>
<th>Mutagens</th>
<th>Suspected Human Carcinogens</th>
<th>Mutagens</th>
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<tbody>
<tr>
<td>Aflatoxins</td>
<td>Acrylamide</td>
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<tr>
<td>Arsenic and arsenic compounds</td>
<td>Benz(a)anthracene</td>
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<tr>
<td>Asbestos</td>
<td>Benz(a)pyrene</td>
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<td>Anilines</td>
<td>Cerulene</td>
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<td>Benzene</td>
<td>Chloroform</td>
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<td>Benzenes</td>
<td>Ethylene dibromide</td>
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<td>Cadmium compounds</td>
<td>Quinol</td>
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<td>Chromium (VI) compounds</td>
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<td>Spermen 7,8 oxide</td>
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<td>Diethylstilbestrol</td>
<td>Tamoxifen</td>
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<td>Ethylene oxide</td>
<td>Benzofuran</td>
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<td>Formaldehyde</td>
<td>Tris(2,3-diaminopropyl) phosphate</td>
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<td>Gallium arsenate</td>
<td>Vinyl chloride</td>
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<tr>
<td>Vinyl chloride</td>
<td>Vinyl fluoride</td>
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Examples of Chemical Mutagens

- Some chemical mutagens directly react to disrupt the base pairing within the DNA macromolecule.
  - Nitrous acid (N₂O, “laughing gas”) can deaminate (remove the amino group) certain bases.
  - Other chemicals such as methyl or ethyl methanesulfonate, mustard gas, and nitrosoguanidine, can add methyl or ethyl groups onto the bases.

Exam #1 Topical Review

- Chapter 1
  - What is toxicology?
  - Toxicant vs. toxin vs. poison vs. xenobiotic
  - Toxicology in antiquity
  - Dose-response concept
- Chapter 2
  - Atoms, elements, compounds
    - Within and foreign to the body
  - Mixtures, suspensions, and aerosols

Exam #1 Topical Review (2)

- Chapter 2, continued
  - Physical properties of chemicals
    - pH, solubility, octanol-to-water partition coefficient, boiling point, melting point, vapor pressure…
- Chapter 3
  - Manifestations and adverse effects of toxicity
    - Very minor → necrosis → death
  - Factors that modify toxicity
    - Age, gender, disease, etc.
Exam #1 Topical Review (3)

- Chapter 4
  - Biological poisons
    - Bacteria, fungi, algae, plants, animals
    - Venom vs. poison
  - Chapter 5
    - Fate of pollutants and ecotoxicology
    - DDT
      - Positive and negative attributes
    - Organic mercury

Exam #1 Topical Review (4)

- Chapter 5, continued
  - Pollutant vs. contaminant
  - Ecosystems and compartments
    - Atmosphere, hydrosphere, biosphere, soils
  - Toxicity in a population
  - Chapter 6
    - Dose-response
      - The fundamental principle of toxicology
      - Doses
        - Administered, absorbed, internal, delivered

Exam #1 Topical Review (5)

- Chapter 6, continued
  - Effect levels and dose-response curves
    - NOAEL, LOAEL, threshold, LD_{50}
    - Slope, potency
  - Individual responses to a dose
    - Hyporesponsive, hyperresponsive
    - Body weight standardization
  - Toxicity rating
  - Dose of an inhaled aerosol
Exam #1 Topical Review (6)

• Chapter 7
  – Toxicant entry into the body
    • Barriers to absorption
      – Respiratory system
        » Rapid absorption and quick distribution
      – Digestive system
        » Liver is key
      – Skin
        » Vulnerable to lipophilic chemicals
      – Other routes
        » Intravenous, intramuscular,
    – Disposition modeling

Exam #1 Topical Review (7)

• Chapters 8 and 9
  – Toxicant distribution
    • Compartments: plasma, interstitial, intercellular
  – Toxicant storage
    • Fat, bones
    • Liver/kidneys – particularly efficient storage
  – Toxicant elimination
    • Renal, fecal, pulmonary, others
  – Toxicant biotransformation (i.e., metabolism)
    • Bioaccumulation, bioavailability, bioconcentration
    • Key: enzymes