CVEN 4474/5474 Haz Waste
Outline

• Toxicity

Paracelsus: “All substances are poisons. The right dose differentiates a poison and a remedy.”

• Examples

<table>
<thead>
<tr>
<th>Substance</th>
<th>RDA (mg/day)</th>
<th>Toxic Level (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zinc</td>
<td>15</td>
<td>60 (LOAEL)</td>
</tr>
<tr>
<td>Selenium</td>
<td>0.05-0.2</td>
<td>0.8-1.0 RfD</td>
</tr>
<tr>
<td>Chromium</td>
<td>0.05-2 (+3)</td>
<td>70 (+3) RfD</td>
</tr>
</tbody>
</table>

RDA = Recommended Daily Allowance
LOAEL = lowest observed adverse effect level
RfD = reference dose for oral intake by 70 kg person

• Toxicology = study of adverse effects to organisms due to chemical exposure
  – Controlled; lab; animals

• Epidemiology = study of distribution of diseases and causes in humans
  – Avoids extrapolation from animals
  – Observational - correlation but not causation
  – Sensitivity problems - population or dose too small to see effect
  – Months, years, or lifetimes req’d for study

• Few compounds have enough human data to quantitatively determine negative effects
  – Worker exposure
    – Miners, hat makers, manufacturing,…..
  – Accidental catastrophes
    – Bhopal, Sveso Italy, ….

• Most toxicity data based on animal studies

Toxic Effects of Chemicals

• Exposure to chemical
  – 3 routes: skin absorption, inhalation, ingestion
  – Uncertainty: conc in soil, air, water, food; contact time, cumulative over time?

• Dose of chemical
  – Amount in body to target organs
  – Net = input - elimination

• Response to chemical
  – Death, illness, cancer, sensory effects,…..

Response vs Dose

• Non-carcinogenic effects
  – Assume a “threshold” below which no adverse effects

• Definitions
  – ADI = acceptable daily intake
  – LOAEL = lowest observed adverse effect level
  – NOAEL = no observed adverse effect level
  – RfD = Reference Dose; “safe”, ~ ADI
  – NOAEL/UF where UF = uncertainty factor
Extrapolate from lab study with animals to humans

- NOAEL → ADI 1-10x (UF 1-10)
  - Quality of study
- LOAEL → NOAEL 1-10x
- Subchronic animal study → chronic effect 10x
- Chronic ave animal → Ave human 10x
- Ave human → Sensitive human 10x
- Multiple cmpd exposures 1-100x

Example

Data from toxicity study with rabbits and malathion.
50 rabbits per dose group 2 yrs

<table>
<thead>
<tr>
<th>Dose, mg/kg-d</th>
<th># Dead</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>14</td>
<td>17</td>
</tr>
<tr>
<td>23</td>
<td>26</td>
</tr>
</tbody>
</table>

What is LD50 (lethal dose to 50% of population)?
What is NOAEL?
What is LOAEL?
What is safe dose for humans?

Putting it together: Which of the compounds is more toxic?

<table>
<thead>
<tr>
<th>CMPD A</th>
<th>CMPD B</th>
</tr>
</thead>
<tbody>
<tr>
<td>LD50 10 mg/kg</td>
<td>LD50 100 mg/kg</td>
</tr>
<tr>
<td>CPF 10 kg-d/mg</td>
<td>CPF 100 kg-d/mg</td>
</tr>
<tr>
<td>NOAEL 0.1 mg/kg</td>
<td>NOAEL 1 mg/kg</td>
</tr>
</tbody>
</table>

CPF = carcinogenic potency factor

Which interaction is most likely?

- If similar mechanism may be additive
- Synergistic if:
  - affect the same organ in different ways
  - Chemical reactions (nitrites + amines = nitrosamines; carcinogen!)
- Antagonistic if:
  - Chemicals react together (EDTA + metals)
  - Opposite effects of toxins (stimulant vs depressant)
  - Competition for the same enzymes or receptors

ANSWER: Depends on assumptions made!

- Assume ADDITIVE toxicity, then
  - 50% each: LD50 = 18
  - (0.5/LD50₁ + 0.5/LD50₂) = (1/LD50₃)
    - 25A/75B: LD50 = 31
  - Assume SYNERGISTIC toxicity, then
    - 50% each: LD50 < 18
  - ASSUME ANTAGONISTIC toxicity, then
    - 50% each: LD50 > 18

What is the combined toxicity of A and B?

- What is the LD50 if the total dose to which an organism is exposed is 50% A and 50% B by mass?
- What is the LD50 if the total dose to which an organism is exposed is 25% A and 75% B by mass?
However, unfortunately…

- Interactions of mixtures are difficult to predict
- Optimally have data
  - Ex: tobacco smoke & asbestos on lungs
  - Ex: ethanol and CT on liver
- Most often do not have data
  - Too many chemicals and potential combinations!

Further complications…

- Not a single value
  - Ex: LC50 for endosulfan toxicity to fish ranged from 0.68 to 3.30 mg/L in 4 different labs (5x)
- Different organisms respond differently
- Low level effects difficult to detect
  - Ex: 24,000 mice tested, couldn’t detect 1% excess risk (1/100 incidence)
  - $1.5M for rodent sty of 1 chemical @ >5%