CVEN 4474/5474 Haz Waste Outline

• Carcinogens
  – How they work
  – Dose:Response
• Endocrine Disruptors
  – How do they work
  – Examples

Carcinogens = ?

• Chemical (or radiation) which induces formation of tumors (aka “cancer”)
  – 4 in 10 Americans will develop cancer in lifetime
  – 2 in 10 Americans will die from cancer
• 90% of cancers attributable to exposure to carcinogens (via lifestyle or involuntary)
  10% of cancers attributable to genes/DNA
• No threshold …even minute quantities can cause cancers
• Hard to quantify due to: latent period, low level effects, multiple exposures in daily life

Mechanistic Carcinogen Models
One Hit

\[ \text{normal cell} \rightarrow \text{tumor cell} \]

Multi-Hit, Single Target

\[ \text{normal cell} \rightarrow \text{tumor cell} \rightarrow \text{tumor cell} \]

Multi-stage

\[ \text{normal cell} \rightarrow \text{tumor cell} \rightarrow \text{tumor cell} \rightarrow \text{tumor cell} \]

Finding chemicals that cause cancer

• Look at low incidences / high concs
• Tests:
  – Ames Test: bacteria, short-term gene mutation
    – Cheap, fast, easy
  – Mammalian assays: tissue samples, gene mutation
    – Short term animal studies (rats, mice, rabbits)
• Sensitivity: true carcinogens found?
• Specificity: inc. non-carcinogens?
• Predictive value: if test Y, does it?

How does cancer form?

Exposure \( \Rightarrow \) Initiation \( \Rightarrow \) Promotion \( \Rightarrow \) Progression

\[ \begin{align*}
\text{normal cell} & \quad \downarrow \\
\text{DNA mutation} & \quad \downarrow \\
\text{chemical signal} & \quad \downarrow \\
\text{mutated cell} & \quad \downarrow \\
\text{TUMOR} & \quad \downarrow \\
\text{more DNA mutations pile up, can spread to other areas} & \quad \downarrow \\
\text{CANCER} & \quad \downarrow
\end{align*} \]

1 chemical can play ALL roles, or only 1 step

Risk or probability of cancer =

\[ \text{Chronic daily intake} \times \text{carcinogenic potency factor} \]

\[ I, \text{mg/kg-d} \times CPF, \text{kg-d/mg} \]

The CPF is a slope factor

– slope of probability vs Dose graph

Usually ADD effect of mixtures of chemicals if they target the same organs in the body
Example: “Mega Mouse” Study
• 2400 mice tested
• 8 doses of DDT in diet
• Looked for incidence of liver cancer

Excess Risk, #/300

Dose causing 1 in a million risk? Need to extrapolate!

Extrapolated dose

<table>
<thead>
<tr>
<th>Model</th>
<th>mg DDT/kg-d causing 1 in a million excess liver cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>single hit</td>
<td>0.00021</td>
</tr>
<tr>
<td>multi-hit</td>
<td>0.013</td>
</tr>
<tr>
<td>multi-stage</td>
<td>0.00025</td>
</tr>
<tr>
<td>log-normal</td>
<td>0.68</td>
</tr>
<tr>
<td>log-log</td>
<td>0.0066</td>
</tr>
<tr>
<td>Weibul</td>
<td>0.05</td>
</tr>
</tbody>
</table>

All models similar fit to data, ...
~3 orders of magnitude difference in low dose estimation

More uncertainty....
• What is “safe” for a mouse?
• What is “safe” for a human?

EPA Carcinogen Classifications
• A = human carcinogen
  – sufficient human epidemiological studies
• B1 = highly probable human carcinogen
  – limited human data, strong animal data
• B2 = low probable human carcinogen
  – inadequate human data, sufficient animal data
• C = possible human carcinogen
  – No human data, limited animal data
• D = not classified (inadequate data)
• E = non-carcinogen for humans
  – negative animal &/or human studies

Few “Class A” Carcinogens
• Arsenic
• Asbestos
• Aflatoxin B
• Benzene
• Benzidine
• Bis(chloromethyl)ether
• Chloromethyl methyl ether
• Chromium VI
• Nickel

• Arsenic
• 2378-TCDD (dioxin)
• Vinyl Chloride
• Env. Tobacco Smoke (ETS)

Cancer registries in U.S. track new diagnoses of cancers
– 1995 1.2M people in US diagnosed with cancer
– ↑ # of cancer, but also ↑ pop. & ↑ older Amer.
– Can age adjust and population normalize
• # of ≥ “possible” carcinogens in environment
  – 40 in drinking water
  – 60 released by industry into air (TRI)
  – 60 routinely used as pesticides
Where to find carcinogen data

- WEB-SITES
  - EPA’s IRIS (www.epa.gov/iris)
  - ATSDR (www.atsdr.cdc.gov)
  - EXTOXNET (pesticides)
  - DOE (radionuclides)

use these sources to find data on chemical toxicity for your risk assessment projects

Example data for radionuclides

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Lung clear class</th>
<th>GI Abs Factor</th>
<th>Ingest risk/pCi</th>
<th>Inhale risk/pCi</th>
<th>Extern risk/yr per pCi/g soil</th>
</tr>
</thead>
<tbody>
<tr>
<td>U235</td>
<td>Yt</td>
<td>0.05</td>
<td>4.5 E-11</td>
<td>1.3E-8</td>
<td>2.6E-7</td>
</tr>
<tr>
<td>Rn 220</td>
<td>(gas)</td>
<td>--</td>
<td>--</td>
<td>1.9 E-13</td>
<td>1.9E-9</td>
</tr>
<tr>
<td>P32</td>
<td>D</td>
<td>0.8</td>
<td>6.1 E-12</td>
<td>2.9 E-12</td>
<td>0</td>
</tr>
</tbody>
</table>

Endocrine Disruptors

- Chemical disrupts hormone levels in the body or mimics hormones in the body
- “Our Stolen Future” Colburn, et al.
- Hormones regulate brain development, reproductive organs, blood sugar, etc.
- Example: estrogen mimics (PCBs, pesticides)
  - Decrease immune system
  - Change male/female characteristics
  - Decrease sperm counts/activity in humans
  - Cause cancer in reproductive organs
  - Linked to hyperactivity, clinical depression

Endocrine Disruptors (cont.)

- Dose:Response effect often a “bell curve”
  - Easy to have large errors in predicted effects if all doses of interest not tested
- VERY low doses (nanograms/L) can cause the adverse effects
- Effects may be manifested as carcinogenic and/or non-carcinogenic effects