Lesson Overview

- What is Toxicology?
- Basic Principles that determine toxic responses to chemicals in our environment
- Chemicals and Cancer

Lesson Objectives

- Explain how scientific information is collected and used to identify and eliminate human health hazards from chemicals in the environment
- Discuss the major causes of cancer, and how chemicals contribute to cancer risk
Basic Concepts

Types of information used to determine chemical risks to humans
- Human Epidemiology data
- Laboratory Animal Data
- Chemical Structure Analysis

Fundamental Rules

1. "The Dose Makes the Poison"

"All substances are poisons. There are none that are not. The dose separates the remedy from the poison."

Paracelsus
(Theophrastus Bombastus von Hohenheim, 1493-1541)

2. Exposure must occur for the chemical to present a risk

3. The magnitude of risks is proportional to both the potency of the chemical and the extent of exposure

Risk = Hazard × Exposure
**Routes of Exposure**

1. Direct Exposure (through Use and/or Accident)
   a) Ingestion (children; intentional)
   b) Skin contact (e.g., acids, solvents, pesticides)
   c) Inhalation (e.g., paints, pesticides)

2. Indirect Exposure
   a) Contamination of drinking water
   b) Contamination of soil / house dust
   c) Contamination of indoor air

**Dose-Response Relationship**

The “individual”, or continuous, dose-response curve
Dose-Response Relationship

Potency & Dose-Response

LD$_{50}$ of Representative Substances

<table>
<thead>
<tr>
<th>TOXIC AGENT</th>
<th>LD$_{50}$</th>
<th>TOXICITY RATING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanol</td>
<td>10,000</td>
<td>Slightly Toxic</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>4,000</td>
<td>Moderately Toxic</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>150</td>
<td>Very Toxic</td>
</tr>
<tr>
<td>DDT</td>
<td>100</td>
<td>Very Toxic</td>
</tr>
<tr>
<td>Parathion</td>
<td>7</td>
<td>Extremely Toxic</td>
</tr>
<tr>
<td>Nicotine</td>
<td>1</td>
<td>Super Toxic</td>
</tr>
<tr>
<td>Curare</td>
<td>0.05</td>
<td>Super Toxic</td>
</tr>
<tr>
<td>Dioxin (TCDD)</td>
<td>0.001</td>
<td>Super Toxic</td>
</tr>
<tr>
<td>Botulinum Toxin</td>
<td>.00001</td>
<td>Super Toxic</td>
</tr>
</tbody>
</table>
Chemical Interactions

- Additive: $2 + 3 = 5$
- Synergistic: $2 + 3 = 20$
- Potentiation: $0 + 2 = 10$
- Antagonism: $4 + 6 = 8$
  $4 + (-4) = 0$
  $4 + 0 = 1$

**NOAEL**
(No Observed Adverse Effect Level)

- Determined from repeated dose experiments
- Identify highest dose used (of 4-6 groups) that produces no evidence of adverse effect
- Used by regulatory agencies to establish “acceptable” doses (e.g., FDA’s “ADI”)
- Safety Factors (or Uncertainty Factors) are used to adjust animal NOAEL to Human dose

Setting the Safe Dose

![Graph showing % animals with tumors vs. dose for various chemicals: Vinyl Chloride, Aflatoxin, Nitrilotriacetic acid, Dimethylnitrosamine)]
Lesson 6: Toxicology & Risk

Setting the Safe Dose

Cancer

- Cancer refers to a chronic disease process characterized by the uncontrolled growth of cells (tumors), that may spread (metastasize) throughout the body, ultimately causing death.
- Cancer arises when the DNA in a cell is altered -- a process called “mutation”

Who gets Cancer?

- 1 out of 3 people living today will get cancer in their lifetime; 1 out of 4 will die from it.
- In the US, nearly 500,000 people will die from cancer this year; 2nd leading cause of death.
- Cancer is largely a disease of “old age”
- Cancer is a disease process affecting different organs; not a single disease.
Lesson 6: Toxicology & Risk

Cancer Deaths

Age Adjusted Death Rates in Males

- Lung
- Stomach
- Prostate
- Liver
- Pancreas

Cancer Deaths

Age Adjusted Death Rates in Females

- Lung
- Breast
- Colon & Rectum
- Ovary
- Pancreas

Smoking & Cancer

CIGARETTE CONSUMPTION

MORTALITY RATES

- Male Death Rate
- Female Death Rate

ENV 150: Intro. to Environmental Health
The Multi-step Process of Cancer

- **Initial Mutation:** Pre-cancerous cell
- **Slow Clonal Expansion:** Blood, lymph
- **Additional Mutations:** Metastasis
- **Rapid Growth:** "Progression"
- **Tobacco**
- **Alcohol**
- **Diet**
- **Food additives**
- **Reproductive/sexual behavior**
- **Occupation**
- **Pollution**
- **Industrial Products**
- **Medicines/medical procedures**
- **Geophysical factors (e.g., radon)**
- **Infection**

Cancer Risk Factors

<table>
<thead>
<tr>
<th>FACTORS</th>
<th>BEST ESTIMATE (%)</th>
<th>RANGE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco</td>
<td>30</td>
<td>25 - 40</td>
</tr>
<tr>
<td>Alcohol</td>
<td>3</td>
<td>2 - 4</td>
</tr>
<tr>
<td>Diet</td>
<td>35</td>
<td>10 - 70</td>
</tr>
<tr>
<td>Food additives</td>
<td>&lt; 1</td>
<td>5 - 2</td>
</tr>
<tr>
<td>Reproductive/sexual behavior</td>
<td>7</td>
<td>1 - 13</td>
</tr>
<tr>
<td>Occupation</td>
<td>4</td>
<td>2 - 8</td>
</tr>
<tr>
<td>Pollution</td>
<td>2</td>
<td>&lt;1 - 5</td>
</tr>
<tr>
<td>Industrial Products</td>
<td>&lt;1</td>
<td>&lt;1 - 2</td>
</tr>
<tr>
<td>Medicines/medical procedures</td>
<td>1</td>
<td>0.5 - 3</td>
</tr>
<tr>
<td>Geophysical factors (e.g., radon)</td>
<td>3</td>
<td>2 - 4</td>
</tr>
<tr>
<td>Infection</td>
<td>10?</td>
<td>1 - ?</td>
</tr>
</tbody>
</table>

What Can You Do To Reduce Your Cancer Risk?

- Don’t smoke
- Eat diets high in fruits and vegetables
- Don’t smoke
- Drink only in moderation
- Don’t smoke
- Learn about workplace hazards and use proper precautions/protective equipment
- Be a ‘good citizen’ of the environment
Lesson 6: Toxicology & Risk

**Summary**

Toxicology is the study of the adverse effects of chemical agents

1. **Dose-Response Relationship**
2. **Risk = Potency \times Exposure**
3. **Acute vs. Chronic Responses**
4. **Cancers**

**Questions**

- [ ]
- [ ]
- [ ]
- [ ]

**For Additional Study**

- **Web sites:**
  - National Toxicology Program - http://ntp-server.niehs.nih.gov/
  - Society for Toxicology - http://ntp-server.niehs.nih.gov/

- **Readings:**
Lesson 6. Toxicology & Risk

Part II. Risk: Assessment and Management

April 20, 2006
Chuck Treser
Dept. of Environmental & Occupational Health Sciences
University of Washington

Uncertainties in Life

“One of the brightest gems in the New England weather is the dazzling uncertainty of it.”

... Mark Twain

Objectives

- Understand perceptions of risk vary
- What is a risk assessment and what are the components of a risk assessment?
- Risk assessment approaches
Why do Risk Assessments?

- We know that
  \[ \text{Risk} = \text{Hazard} \times \text{Exposure} \]
- We use a risk assessment to quantitatively and qualitatively define an exposure that may lead to an adverse effect and use this information to minimize accident or illness.

Understanding Risks

- Hazard identification
- Dose-response assessment
- Exposure assessment
- Risk Characterization
- Risk Management
- Risk Communications

Translation

- Is there a potential problem?
- What is the problem?
- Who has the problem?
- How bad is the problem?
- What should we do about it?
- Who and what do we tell?
Comparing Risks

- Probability
- Expected Value
- Exposure
- Outrage
- Experts
- Avoidance

Comparative Risks

<table>
<thead>
<tr>
<th>Event</th>
<th>Annual Risk</th>
<th>Lifetime Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Car injury</td>
<td>1:100</td>
<td></td>
</tr>
<tr>
<td>Killed hang gliding</td>
<td>1:1,000</td>
<td></td>
</tr>
<tr>
<td>Killed mountain climbing</td>
<td>1:1,585</td>
<td></td>
</tr>
<tr>
<td>Cancer: 1 diet cola/day</td>
<td>1:10,000</td>
<td></td>
</tr>
<tr>
<td>Cancer: 4 tbsp. peanut butter/day</td>
<td>1:100,000</td>
<td></td>
</tr>
<tr>
<td>Hit by Lightning</td>
<td>1:631,000</td>
<td></td>
</tr>
<tr>
<td>Cancer: drinking chlorinated water</td>
<td>1:1,000,000</td>
<td></td>
</tr>
<tr>
<td>Win state lottery grand prize</td>
<td>1:10,000,000</td>
<td></td>
</tr>
<tr>
<td>Win Readers Digest sweepstake</td>
<td>1:250,000,000</td>
<td></td>
</tr>
</tbody>
</table>
Comparing Risks

- Activities that increase annual risk by 1:1,000,000
  - Smoke 1.4 cigarettes
  - Drink 0.5 liters of wine
  - Live 2 days in New York or Boston
  - Live 2 months with a cigarette smoker
  - Live 150 years within 5 miles of a nuclear power plant

Comparing Risks

- Voluntary vs. Involuntary Risks
- Immediate vs. Delayed Effects
- Common vs. Rare (Dread) Events
- Affects Everyone vs. Special Groups
- Reversible vs. Irreversible Effects

Risk Vectors

- Observable
  - Unknown to those Exposed
  - Effects Delayed
  - New Risk
- Risk Unknown to Science

- Observable
  - Known to those Exposed
  - Effects Immediate
  - Old Risk
- Risk known to Science

- Controllable
  - Not Dreaded,
  - Not Global/Catastrophic
  - Not Fatal
  - Equitable
  - Low Risk to Future Generations
  - Easily Reduced
  - Decreasing Risk

- Uncontrollable
  - Dreaded
  - Global/Catastrophic
  - Consequences Fatal
  - Not Equitable
  - High Risk to Future Generations
  - Not Easily Reduced
  - Increasing Risk
Changing Risks

- Understand the risks
- Understand who is at risk
- Characterize the risk
- Consider the alternatives
- Consider “protective” measures
- ACT!!!

Risk Assessment Approaches

- Cost-benefit analysis
- Revealed preference
- Expressed preference
- Natural standards

Cost-Benefit Analysis

Definition: A systematic attempt to compare the costs with the anticipated benefits of a technology, product, substance or process.
### Cost-Benefit Analysis

- List adverse consequences
  - assign probabilities
  - estimate cost of consequences
- List Benefits
  - assign probabilities
  - estimate gains/value of benefits
- Probability X Cost or Gain = Sum
- Compare cost versus benefits

### “Veg-E-Wax”

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Anticipated Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Storage loss prevented</td>
<td>1,000,000</td>
</tr>
<tr>
<td>Nutritive value preserved</td>
<td>800,000</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>$1,800,000</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Costs</th>
<th>Anticipated Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Application costs</td>
<td>100,000</td>
</tr>
<tr>
<td>Cancer in workers</td>
<td>100,000</td>
</tr>
<tr>
<td>Cancer in consumers</td>
<td>100,000</td>
</tr>
<tr>
<td>Unappealing appearance</td>
<td>1,600,000</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>$1,900,000</strong></td>
</tr>
</tbody>
</table>

### Cost-Benefit Analysis

- **Advantages**
  - Flexible
  - Easily scrutinized
- **Disadvantages**
  - Unrealistic assumptions
  - All consequences can not be anticipated
  - Probabilities are often unknown
  - Assigning price tags is difficult
### Cost-Benefit Analysis

**Examples of Regulations Evaluated by Cost per Life Saved**

<table>
<thead>
<tr>
<th>Regulation &amp; Year</th>
<th>Status &amp; Year</th>
<th>Annual Risk &amp; Estimate</th>
<th>Lives Saved Annually</th>
<th>Cost per Life Saved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asbestos Final 1972</td>
<td>4 in 10$^{-5}$</td>
<td>296</td>
<td>$7,400</td>
<td></td>
</tr>
<tr>
<td>Benzene Final 1984</td>
<td>9 in 10$^{-6}$</td>
<td>4</td>
<td>$17,100</td>
<td></td>
</tr>
<tr>
<td>Asbestos Final 1978</td>
<td>2 in 10$^{-3}$</td>
<td>12</td>
<td>$92,500</td>
<td></td>
</tr>
<tr>
<td>Formaldehyde Prop. 1983</td>
<td>7 in 10$^{-7}$</td>
<td>&lt;1</td>
<td>$72,000,000</td>
<td></td>
</tr>
</tbody>
</table>

### Revealed Preferences

**Definition:** The acceptable risk for a new technology is the level of safety associated with ongoing activities having similar benefits to society.

### Revealed Preferences

**Consistent Features of Revealed Preferences Approach**

- Positive correlation between risk and benefits
- Voluntary risks always riskier for the same amount of benefit
Revealed Preferences

Important Drawbacks of Revealed Preferences Approach

- Assumes past behavior is valid indication of present preferences
- Politically conservative
- Ignores distribution of risks & benefits
- May under weigh risks to which the market is sluggish

Expressed Preferences

Definition: If people say it is safe, then it is safe enough.

Expressed Preferences

- Advantages
  - Elicits current preferences
  - Citizen involvement
  - Considers all aspects of risk and benefits
- Disadvantages
  - Complex issues for general population
  - Well articulated preferences for new and complex issues may not be available
**Natural Standards**

**Definition:** A technology is safe if its risk are no greater than those accompanying the development of the human species.

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**Advantages**
- Avoids need to convert risks to dollars
- Compatible with people’s natural thinking
- Avoids referring to small probabilities

**Disadvantages**
- New exposures are in addition to background levels
- No historical tolerance to new chemicals
- Limited use

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**Regulation Philosophies**

- Count the bodies
- Engineering solutions (BAT)
- Uniform Risk/Equal Rights
- Cost-Benefit
- Delaney Approach
Current Federal Issues

- Risk and Regulation
- Cost-Benefit Analysis

Uncertainties in Life

“Remember to change your underwear — you never know when you’ll be in an accident.”

Your Mother

Questions