Human Health Concerns

Health Effects of Hazardous Materials

Toxicology

• Study of the nature, effects, and detection of poisons in organisms
  – Humans are obvious focal point
  – Other species and ecosystem function also
• Study of the relative toxicity of materials
  – A relatively new science
    – Evolved into another environmental technology
    – Heavy in the use of scientific principles and disciplines
    – Numerous technologies invented to support research

Toxicity

• Degree to which a chemical substance has a harmful effect on living things

• Quality or condition of being toxic; degree to which a poison is toxic (Amer. Heritage dictionary)

• “Every chemical is toxic, only the dose…” (Paracelsus, 16th century ‘scientist’)

• One of several possible hazards a chemical may pose…consider flammability
Exposure and Absorption

Exposure may result in absorption

Absorption leads to dose

Exposure routes:
• Inhalation
• Dermal Contact
• Ingestion
• Injection

Exposure by Inhalation

Intake:
• Upper and lower respiratory tracts
• Lung tissue

Uptake: Interface with circulatory system
• Absorption
• Diffusion of substance from alveoli to blood

Local and systemic effects
• Direct damage to lung tissue or passages
• Effects at tissues away from lungs

What can be inhaled:
• gases, vapors of volatile liquids, dusts (solids), aerosols (liquids), fumes (sublimed [vaporized] solids)

Considerations:
• Respiratory membrane built for rapid and efficient absorption
• Factors influencing absorption include
  – toxicant-related factors like particle size (solids), solubility (gases & vapors)
  – organism-related factors like respiration rate, physical conditioning, general health
• Particulates may remain deep in lung, migrate to adjacent tissues
• Immediate or delayed response
Exposure by Dermal Contact

• Layers: epidermis, dermis, hypodermis
  – Note blood involvement beneath epidermis
• Skin thickness varies: palms/soles vs genitals
• Mucus membranes and eyes

Exposure and Absorption

What can be absorbed through skin:
• gases, liquids, then solids to a lesser extent
• fat-soluble organic compounds rapidly absorbed
  – blood vessels in dermal and subcutaneous layers translocate toxicants
Skin is an effective barrier to solids, polar substances
• Duration of contact a factor

Corrosives damage skin
Flammables present burn and toxicity hazard

Exposure by Ingestion

Human alimentary tract: Oral cavity, esophagus, stomach, sm & lg intestines
Exposure by Ingestion

Layers of alimentary tract: mucosa, submucosa, others
Again, note blood involvement in mucosa and submucosa

Exposure by Ingestion

What can be absorbed through the mucosa: gases (dissolved), liquids, solids

Should not be common route in the workplace
– However bad habits, swallowing of contaminated sputum, swallowing gas-contaminated water
More common outside of workplace with accidental poisonings and contaminated food

Like the respiratory membrane, the alimentary mucosa efficiently absorbs substances

Exposure by Injection

What can be injected: liquids, gases?, solids?
• direct entry into bloodstream of dermis, hypodermis
• exposure and absorption at open wounds
Dose

- Amount exposed to and amount absorbed by a living organism are often different
  - But usually correlated

- Dose definition: quantity of material absorbed during a known period of time adjusted for weight of the organism
  - mg/kg/day is a unit of dose

Factors Affecting the Dose

1. Exposure route
   - Skin can be a barrier to some
   - Inhalation and ingestion: absorptive membrane not much of a barrier

Chemically-protective clothing and devices form a barrier, but not a permanent one

Factors Affecting the Dose

2. Duration Of Exposure
   - Short, long, continuous
   - Typically longer exposures lead to higher doses

3. Concentration Of The Chemical
   - Typically higher concentrations lead to higher doses given the same duration
   - Air, water, soil, waste, product

4. Form of the substance, as noted previously
Consequences of Dose

Human tissues consist of cells
A cell’s structure and metabolism is complex
• consists of many substances and chemical reactions
• Humans have about 70-100 trillion cells

Consequences of Dose

Substances introduced may participate in chemical reactions either positively, neutrally, or negatively
– Disrupt the cell’s membrane
– Disrupt the cell’s metabolism
  • Destroy needed substances like enzymes
  • Inhibit cellular respiration
– Mutate the cell's DNA

Toxicity

Rate of damage (or magnitude of impairment) exceeds rate of repair
• Cells
• Tissues

Damage to tissue, organs
• Initiation of malfunction (illness)
• Initiation of cancer
• Death
Acute Toxicity
Immediate effects resulting from a brief exposure to acutely-toxic concentrations

Acute Effects
• occur a short time after the initial exposure/absorption
• are sometimes reversible if the exposure ends and dose decreases (loss or transformation of substance)
• typically noticeable, observable

Chronic Toxicity
Effects occurring after
• long-term, constant exposure or
• Intermittent, repeated exposures
to less-than-acute concentrations

Chronic effects
• Initially only subtle or unnoticeable effects
• Damage often not reversible even if exposure ceases
• Difficult to prevent since effects are not noticed at the time of exposure

Chronic Toxicity
Latency Period
• the state or period of living or developing in a host without producing effects
• the interval between dose and response

Chronic toxicity is technologically difficult to study in the laboratory
Other Effects

Carcinogenicity
• Initiation of cancer
• Generally considered to result from chronic exposures/absorptions

Mutagenicity
• Causing a permanent genetic change in a cell other than that which occurs during normal growth

Teratogenicity
• relating to, or causing developmental malformations

Efforts to Identify the Dose-Response Relationship for a Single Substance

• Essential element of the science of toxicology
• Needed to answer question:
  – Are there safe levels for toxicants in the workplace? (re ecological effects)
  – in an environmental medium? (re ecological effects)
  – or in air or drinking water? (re human health effects)
• Typical dose-response for a single substance: increasing dose increases effects

Sources Of Information On Dose-Response and other Toxic Effects

• Epidemiological studies including accidental exposures
• Animal studies
• Structure-Activity Relationships
  – elements and/or chemical structures present

Are clinical trials (pharmaceuticals) dose-response studies?
Determining Dose-Response Relationships For Single Chemical Exposures

Simple laboratory study
• 3 to 5 increasing concentrations (inhalation) or doses (oral) of a substance and a (no dose) control group
• One time exposure or continuous exposure
• Repeated observation of test organisms during a specified time period
• Data collection: death, sublethal effects
• Plot response at each test level on Y axis and concentration/dose at each level on X axis
• Draw line to connect points or use computerized statistics to analyze data
• Determine the dose or concentration that kills 50% of the test organisms
• Determine a "threshold" dose, if one exists

Rat Inhalation Study

Preliminary vs definitive studies

Threshold Model

Dose/Response Curve for Non-Carcinogen

% individuals Responding

0 10 20 30 40 50 60 70 80 90 100

0 100 200 300 400 500 600 700 800 900 1000 1100 1200

Dose (mg/kg body weight)

LD50

threshold

Live damage

Developmental toxicity

Mortality
Dose-Response

- In many acute toxicity tests, lethality or death is considered the “response”

- If death used as the observed effect, then increasing dose leads to increasing number of deaths

Linear No-Threshold

Other Dose Responses: Essential Nutrients

Example: selenium
Effect of Multiple Chemical Exposures on Local and Systemic Effects

- Synergistic Effect (2+2=6)
- Potentiation (0+2=10)
- Antagonism (4+6=8)
- Additive Effect (2+2=4)

- Effects of multiple chemical exposures are not well understood

Acute Dose-Response Endpoints

- LD\(_{50}\)
  - the median lethal dose
  - dose that kills 50% of the population exposed
  - given orally, by injection, dermally, in eye
- LC\(_{50}\)
- ED\(_{50}\)
- TD\(_{50}\)

Acute Dose-Response Endpoints

- NOAEL and LOAEL
  - concentrations or doses in toxicity tests
  - no observable adverse effects level means no effects were seen in this group
  - may be considered an "acute" safe level
  - Alternately: NOEC and LOEC
- expressed as mg/kg (oral and dermal dose), OR ppm, ppb (both air concentrations), mg/l (water concentration)
Acute Dose-Response Terms

• The lower the LD or LC the more toxic the chemical
• Can be used to compare the toxicity of chemicals

Acute Dose-Response Endpoints

• Classes of Toxic Doses - based on LD$_{50}$ values
  – used to classify substances for consumer product labeling
  – Table based on single oral dose

<table>
<thead>
<tr>
<th>Toxicity Level</th>
<th>LD$_{50}$ Value</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 1 g/kg</td>
<td>Extremely Toxic</td>
<td>More than a Quart</td>
</tr>
<tr>
<td>0.5 - 1 g/kg</td>
<td>Moderate Toxic</td>
<td>A Pint (500 ml)</td>
</tr>
<tr>
<td>0.1 - 0.5 g/kg</td>
<td>Slight Toxic</td>
<td>A Quart (1:2)</td>
</tr>
<tr>
<td>&lt; 0.1 g/kg</td>
<td>Low Toxic</td>
<td>A Teaspoon (5-10 ml)</td>
</tr>
<tr>
<td>&lt; 0.01 g/kg</td>
<td>Almost Inapp.</td>
<td>Almost Inapp.</td>
</tr>
</tbody>
</table>

Chronic Dose-Response Endpoints

Hypothesis testing using statistical methods
  – chronic endpoint like tumor incidence, reproductive impairment, growth impairment, etc. selected and enumerated during and after testing
  – experimental groups compared to control group for similarity or significant difference
  – concentrations or doses significantly different from the control are not safe

• LC$_{50}$/LD$_{50}$ don't apply to chronic exposures
• NOAEL and LOAEL applicable
What is Cancer?

A Failure to Control Tissue Growth

• Cell reproduction usually be controlled by various regulatory pathways
  – If not, malignant tumors result
• Fast growing, abnormal cells typically begin to invade healthy tissue or spread to other parts of the body

Cancer

Adverse effects

• Competition with normal tissue
  – Angiogenesis
  – Crowding
• Secondary infections
• Secondary tumors
• Production of substances in abnormal amounts

Possible Causes Of Cancer

• Carcinogens - not all carcinogens are the result of industrial activities
• Carcinogens are listed based on evidence from exposure to humans (known carcinogens) or laboratory animals (suspected carcinogens)
  – Radiation - Ionizing and perhaps non-ionizing
  – Virus
    • Hepatitis B virus
    • Type 2 Herpes simplex
    • Human papilloma virus
  – Genetic predisposition
  – Stress effect on immune system?
**DNA Damage & Repair**

**The Mechanism Of Cancer**

- **Oncogene Initiation**
  - Oncogenes are derived from the genes that control cell growth and development which are present in every cell
  - Proto-oncogene can become an oncogene as a result of a single mutation leading to activation

- **Oncogene may produce abnormal protein product, or...**
  - abnormally high levels of normal product (like a growth factor), or...
  - cause changes in surface proteins simulating the presence of a growth factor
  - all lead to abnormal growth

The 'One-Hit' Theory or "No-Threshold"