Toxicology of High Priority Substances

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Part 1: Principles

Part 2: Metals

Part 3: Dioxin and TCE

Toxicology

“Science of poisons”
- Toxin = Poison
- Toxin = Chemical that has an adverse effect on a living system.
- Mechanism & Effects
  - Potency
  - Control
  - Treatment

“Dose Makes the Poison”

- The amount of a chemical to which a living system is exposed is critical to the expressed toxic response.
- Each chemical has its own “dose-response” relationship.
- Potency is not defined by any particular response, but by the amount required to produce a specific toxic response.

"Dose Makes the Poison"

Variable % of response

More potent

Less potent

Dose

0%

100%
Dose-Response Curve
- "Sigmoid" curve
- Defined in term of a specific response
- Requires a specific effect to look for...
- Terminology
  - No Observed Effect Level (NOEL)
  - No Observed Adverse Effect Level (NOAEL)
  - LD50/ED50
- Often little or no human data

Toxic Response - Factors
- Dose
- Specific effect(s)
  - Mechanism
  - Target cells/tissues
  - Route of exposure
- Duration
- Individual susceptibility
  - Age, genetics, other exposures, illness, etc.

Important Point
- What we see and what the person feels are effects at the level of function of an whole organ or system, not the specific toxic response at the level of the cell or tissue.

Toxic Responses - Mechanism
- Cytotoxic (cell injury)
- "Physiologic" (disrupt normal functions)
- Allergenic (asthma, dermatitis)
- Mutagenic
  - Carcinogenic
  - Teratogenic
- Toxins often act through more than one mechanism

Cytotoxic Responses: Cell Injury
Cells Can’t Just Stop

- Important to remember that active cell processes are required to maintain the cells in a functional state.
- If the processes fall below a critical level, the cell will enter a period of functional decline and eventually reach a state from which they cannot recover.
- In the most active cells, this state can be reached in a few minutes.

**Spectrum of Cell Injury**

<table>
<thead>
<tr>
<th>Dose</th>
<th>Acute</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Acute severe illness</td>
<td>Fibrosis and progressive loss of function</td>
<td></td>
</tr>
<tr>
<td>Acute moderate-severe illness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild-moderate reversible illness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>Reduced function</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

**Physiologic Responses**

- **Acute toxic exposure**
  - Presents as acute symptoms
  - Carcinogenesis unusual
  - Full recovery possible

- **Chronic toxic exposure**
  - Insidious
  - Presents as chronic, irreversible injury
    - Cirrhosis, emphysema, cancer

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**Duration of Exposure**

- **Acute**
  - Presents as acute symptoms
  - Carcinogenesis unusual
  - Full recovery possible

- **Chronic**
  - Insidious
  - Presents as chronic, irreversible injury
    - Cirrhosis, emphysema, cancer
Carcinogenic Responses

- Normal Cell
- First Mutation
- Second Mutation
- Third Mutation
- Fourth or Later Mutation
- Malignant Cell

Teratogenic Responses

- Human Development

- Critical Stages

Target Cells and Tissues

- Direct contact: lungs, skin
- Active sites of metabolism and biotransformation: liver
- Concentration and excretion: liver, kidney
- Critical susceptibility: brain, heart
Common Chemical Health Effects

- Eye irritation
- Skin irritation and rash
- Respiratory irritation and cough
  - Reactive airways disease
  - Allergic reactions (requires more than one exposure)

Sources of Exposure

- >100,000 commercial chemicals
- Several thousand new each year
- Limited data on almost all
  - Know very little about mixtures (e.g., smoke).
  - We know most about acute effects of common chemicals at high doses.
- Drugs are most extensively tested.

How Do We Know Something is Toxic?

- The association of exposure and illness must be recognized (and accepted).
- May cause acute illness on exposure
- Exposure markedly increases the risk of something unique and rare
- Illness consistent with experimental data

Things that get in the way

- Exposure increases the risk of a common illness.
- Limited opportunity to make associations
  - Structure of the medical industry
  - Mobile workforce
  - Complex exposure histories
  - Resistance to the recognition of compensable illnesses
Break