Toxicology
The Science of Poisons
or
The science that deals with the adverse effects of chemicals on living organisms and assesses the probability of their occurrence

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Outline

• History of Toxicology
• Dose Response
• Types of Toxicants
• Potency
• The Complexities of Environmental Toxicology
Historical Perspective

"...the appearance of disease in human populations is influenced by the quality of air, water, and food; the topography of the land; and general living habits."

The ancient-Greek physician Hippocrates in his treatise Air, Water and Places 400 BC
All substances are poisons; there is none that is not a poison. The right *dose* differentiates a poison and a remedy.

Paracelsus (1493-1541)
The Father of Modern Toxicology
Spanish physician Orfila (1815) established toxicology as a distinct scientific discipline.
Toxicology Today

**Mechanistic toxicology:** The study of how a chemical causes toxic effects by investigating its absorption, distribution, and excretion.

**Descriptive toxicology:** The toxic properties of chemical agents are systematically studied for various endpoints using a variety of different organisms.

**Clinical toxicology:** They study of toxic effects of various drugs in the body, and are also concerned with the treatment and prevention of drug toxicity in the population.
Forensic toxicology: A branch of medicine that focuses on medical evidence of poisoning, and tries to establish the extent to which poisons were involved in human deaths.

Environmental toxicology: The study of the effects of pollutants on organisms, populations, ecosystems, and the biosphere.

Regulatory toxicology: The use scientific data to decide how to protect humans and animals from excessive risk. Public or Private Sector.
Dose

The amount of chemical entering the body
This is usually given as
mg of chemical/kg of body weight = mg/kg

The dose is dependent upon
* The concentration
* The properties of the toxicant
* The timing and frequency of exposure
* The length of exposure
* The exposure pathway
What is a Response?

The degree of responses depend upon the dose and the organism

• Change from normal state
  – could be on the molecular, cellular, organ, or organism level--the symptoms

• Local vs. Systemic

• Reversible vs. Irreversible

• Immediate vs. Delayed
CHEMICALS: Major Types of Toxicity

- Acute toxicity: It involves lethal concentrations and short-term exposures.
- The end point is usually death.
- An $LD_{50}$ is a dose of a toxic chemical that kills half of the population.
- $LD_{50}$ is obtained by plotting, for a given dose the proportion of the population that responded to that dose and all lower doses.
Dose Response

![Dose Response Graph]

- Response (Percent)
- Dose (mg)
- LD50
- Data Point

The graph illustrates the relationship between dose and response, highlighting the LD50 dose level.
CHEMICALS: Major Types of Toxicity

• Chronic toxicity: It involves Sub-lethal concentration and long-term exposure
• Chronic toxicity test is used to derive Effective Dose ($ED_{50}$): Is the dose by which half of the population has been affected
• Effect could be anything but death
• $ED_{50}$ is obtained by plotting, for a given dose the proportion of the population that responded to that dose and all lower doses
CHEMICALS: Major Types of Toxicity

• No Observable Adverse Effect Level (NOAEL) – the threshold where no effects are observed.
• Lowest Observable Adverse Effect Level (LOAEL) – the concentration level where effects are observed.
Potency – concentration to produce an effect.
CHEMICALS: Major Types of Toxicity

• Cancer causing chemicals are assessed by risk since one mutation has an inherent risk. 1:1,000,000 risk is considered acceptable. (note: we can only measure 1:100 in the laboratory and must extrapolate the low risk level).

• Hormesis - biphasic dose response to an environmental agent characterized by a low dose stimulation or beneficial effect and a high dose inhibitory or toxic effect.
Dose Response Curves

- No-Threshold Toxicant
- Essential Nutrient
- Threshold Toxicant
- NOAEL

Increasing adverse effect

Increasing Dose

0
Populations

Average subjects

Sensitive subjects

Insensitive subjects

Number of subjects

Daily intake necessary to produce a predefined level of effect

8 WEEKS LIVE BABY
CHEMICALS: Major Types of Toxicity

• Toxins – biological compounds (Ricin, botulism)
• Carcinogens - may induce cancer or increase its incidence and can affect any cells or tissues (benzene, vinyl chloride, benzo(a)pyrene )
• Mutagen - may induce hereditary genetic defects or increase their incidence and effect on the germ cells (gonads). (radiation, nitrosoamines)
• Teratogens - may induce non-hereditary congenital malformations or increase their incidence and effect on the growing fetus (rubella, thalidomide, PCBs, Dioxins)
• Endocrine disruptor – hormone mimic (PBDE, DDT)
Perceptions About Chemicals

• What drives our perceptions? Are chemicals bad?

HUMAN RISK PERCEPTION... is affected by the degree of pleasure / displeasure associated with the particular risk
<table>
<thead>
<tr>
<th>Agent</th>
<th>LD-50 (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethyl alcohol</td>
<td>10,000</td>
</tr>
<tr>
<td>Salt (sodium chloride)</td>
<td>4,000</td>
</tr>
<tr>
<td>Iron (Ferrous sulfate)</td>
<td>1,500</td>
</tr>
<tr>
<td>Morphine</td>
<td>900</td>
</tr>
<tr>
<td>Mothballs (paradichlorobenzene)</td>
<td>500</td>
</tr>
<tr>
<td>Aspirin</td>
<td>250</td>
</tr>
<tr>
<td>DDT</td>
<td>250</td>
</tr>
<tr>
<td>Cyanide</td>
<td>10</td>
</tr>
<tr>
<td>Nicotine</td>
<td>1</td>
</tr>
<tr>
<td>Tetrodotoxin (from fish)</td>
<td>0.01</td>
</tr>
<tr>
<td>Botulinum Toxin</td>
<td>0.000001</td>
</tr>
</tbody>
</table>
What type of toxic chemical is alcohol?

- Group 1 known Human Carcinogen
- Exhibits hormesis – small amounts are beneficial (cardiovascular system)
- Teratogen - fetal alcohol syndrome

“Of all the substances of abuse (including cocaine, heroin, and marijuana), alcohol produces by far the most serious neurobehavioral effects in the fetus.”

—Institute of Medicine Report to Congress, 1996.
Fetal Alcohol Syndrom Facts

- Alcohol diffuses through placenta
- Concentration in fetal blood is the same as in the mother’s blood within a few minutes
- The fetus is able to metabolize alcohol 10% as fast as the mother
- 1 in 200 individuals are affected by prenatal alcohol exposure.
Sequence of Human Development

Embryonic Development

Developmental Progression & Susceptibility to Teratogens & Fetal Loss

Black - most sensitive
Endocrine disruptors:

• Synthetic or naturally occurring chemicals that affect the Endocrine or hormonal system of animals

• May either:
  • Mimic hormones
  • Block hormone activities
  • Directly stimulate or inhibit the endocrine system
Endocrine Disruptors

Some chemicals, once inside the bloodstream, can “mimic” hormones.

If molecules of the chemical bind to the sites intended for hormone binding, they cause an inappropriate response.

Thus these chemicals disrupt the endocrine (hormone) system.
Examples of Hormonally Active Agents
## Endocrine Disruptor Potency

<table>
<thead>
<tr>
<th>Compound</th>
<th>Potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oestradiol</td>
<td>1</td>
</tr>
<tr>
<td>DES</td>
<td>0.64</td>
</tr>
<tr>
<td>Coumestrol</td>
<td>0.129</td>
</tr>
<tr>
<td>Nonyl phenol</td>
<td>0.0002 (5,000x)</td>
</tr>
<tr>
<td>Bisphenol</td>
<td>0.000007 (15,000)</td>
</tr>
<tr>
<td>Methoxychlor</td>
<td>5x10^-6</td>
</tr>
<tr>
<td>DDT</td>
<td>8x10^-6</td>
</tr>
</tbody>
</table>
Baker and Chandsawangbhuwana 2012
Environmental toxicology is highly interdisciplinary field
Toxicants take many routes through the environment often as mixtures.
Summary

• Toxicology is a complex science based on the principle of dose and response.
• Environmental exposures further adds to this complexity.
• Human perception is key factor.
• Green chemistry can provide solutions!