Toxicity and Risk Assessment

Part I
Outline

- What is a Toxic Substance?
- Factors that affect Toxicity
- Adverse Effects on young and unborn
- Most dreaded diseases
  - Environmental hormones
  - cancer
Definitions

- **Toxicant or Poison**
  - A substance that can cause adverse effects in a plant, animal and human.
  - It does so by impairing vital metabolic function

- **Toxin:**
  - A Toxicant produced by a living organism such as a microorganism, plant, spider or snake

- **Hazardous Substance:**
  - May be toxic, corrosive, reactive, flammable, radioactive, infectious or a combination of these

- **Xenobiotics:** Toxins produced outside the body
What is a Toxic Substance

- All Substances are toxic
  - A non-toxic substance can be toxic at high doses
  - A toxic substance can be non-toxic at low enough doses
- A chemical’s effect depends on
  - Dose
  - How fast it is given
  - Health, age and gender of the receiver
• Everything is toxic at high enough dose, even drinking water
• As dose increases, the response is positive up to the optimum level after which adverse effect begins to occur which might even lead to death
<table>
<thead>
<tr>
<th>Chemical</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botulinum toxin</td>
<td>Acute chemical toxin, caused many deaths in people eating improperly processed food Treats muscular spasm, used cosmetically to temporarily relax wrinkles</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Synthetic chemical used as rat poison Used to prevent strokes and heart attacks</td>
</tr>
<tr>
<td>Atropine</td>
<td>The deadly nightshade plant makes this super toxin Used as an antidote for nerve gas and pesticide poisoning</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Caused birth defects in 1960s Used to treat leprosy and AIDS</td>
</tr>
<tr>
<td>Curare</td>
<td>Natural poison, used on arrow tips by Amazon tribes Used to promote muscular relaxation during surgery</td>
</tr>
<tr>
<td>Salt</td>
<td>A nutrient essential to life Causes retention of body fluid, high blood pressure, stomach cancer, death in small children</td>
</tr>
<tr>
<td>Nickel and Chromium</td>
<td>Nutrient Can cause cancer in high doses</td>
</tr>
<tr>
<td>Nitric Oxide</td>
<td>Neurotransmitter produced within body Ambient air pollutant</td>
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</table>
Acute and Chronic Toxicity

- **Acute Toxicity:**
  - Adverse effect seen soon after one-time exposure to a chemical
  - Can be vomiting, diarrhea, irregular heartbeat, unconsciousness
  - Can be caused by overdosing of drugs, farm worker exposed to pesticide, sniffing glue or gasoline etc.

- **Chronic Toxicity**
  - Results from long-term exposure to lower doses of a chemical
  - Long term can be few weeks to tens of years
  - Examples: Lung cancer from cigarette smoke, cancer, leukemia from long term exposure to Benzene
  - Substance that does not cause acute effect can cause chronic effect and *vice versa*.
    - A one-time exposure to mercury vs long term exposure
    - H2S gas (acute but not chronic)
    - Cigarette Smoke (chronic but not acute)
Comparing Toxicity of chemicals

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>LD_{50} (mg/kg body weight)</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slightly toxic</td>
<td>500-5000</td>
<td>Aspirin, vitamin, salt</td>
</tr>
<tr>
<td>Moderately toxic</td>
<td>50-500</td>
<td>Caffeine, nicotine</td>
</tr>
<tr>
<td>Highly toxic</td>
<td>1-50</td>
<td>Sodium cyanide, Vitamin D</td>
</tr>
<tr>
<td>Supertoxic</td>
<td>&lt; 0.01</td>
<td>Atropine, nerve poisons</td>
</tr>
<tr>
<td>Biotoxins</td>
<td>&lt;&lt;0.01</td>
<td>Botulinum ricin</td>
</tr>
</tbody>
</table>

LD_{50} : Dose which kills 50% of the animals exposed to it

- The period over which the dose is consumed is important:
- An aspirin a day for 100 day may be beneficial but 100 aspirins at one time can be deadly
- Timing of exposure can be important: embryo may suffer during the first eight weeks of pregnancy but may not be affected late in pregnancy
Exposure to multiple chemicals

- Additive (most common effect)
- Synergism: combined effect of multiple chemicals more than the sum total of each.
  - e.g., lung cancer can be caused by radons but the risk gets magnified in smokers
  - Alcohol and barbituates
- Potentiation:
  - Chemical 1 is harmless but chemical 2 is. Adding 1 makes exposure to 2 more toxic
    - Phenergan(R), an antihistamine, when given with a painkilling narcotic such as Demerol(R) intensifies its effect, thereby cutting down on the amount of the narcotic needed.
- Antagonism:
  - One chemical interferes with the other: antidote e.g., ipecac to induce vomiting to poisoning victims
  - Two chemicals react to form less toxic product e.g., dimecarpol binds to metal ions to combat metal poisoning
Systemic and Local Effects

- **Systemic Effects**: occurs at a point distant from where a chemical enters the body
  - Potassium Cyanide
- **Local Effect**: occurs at a point where a chemical enters the body
  - Acid
- A chemical can have both systemic and local effects.
Chemical Pathways in the Body

- Absorption
- Distribution
- Metabolism
- Excretion
Absorption

- **Ingestion:**
  - taken by drinking or eating
  - Absorbed in the blood stream in small intestine
  - Liver is the most affected organ

- **Inhalation:**
  - Fastest
  - Absorbed through lungs

- **Skin absorption**
  - Some skins (stomach, scrotum) more permeable
  - Larger the area exposed and Longer the contact, the greater the absorption
  - Acid, alkalis or metals have local effect – need not be absorbed
**Distribution**
- After absorption a chemical is distributed by the blood stream
- Can have greater effect on one organ compared to other. To be toxic the chemical must reach the target organ at high enough doses.
- Nervous system is a major target of lead and mercury, Benzene
- Often substances are stored in the body and do not show toxic effect

**Metabolism**
- Liver and Kidney transforms xenobiotics in forms that can be excreted. Sometimes this biotransformation can produce even more harmful chemicals e.g., benzene is transformed into benzene oxide in the liver

**Excretion**
- Water soluble chemicals are mostly excreted through urine
- If not, body try to **biotransform** it to water soluble chemical
- Volatile chemicals can be excreted in breath
- Milk of nursing mother can be a pathway out of the body and might harm the nursing infant
- Sweat
Other important Concepts

- **Bioavailability**
  - **Physical Factor**
    - Chemicals such as Dioxin, PCB binds to soil and often trapped in a particle’s interior.
    - Largely inaccessible and are not bioavailable
  - **Chemical Factor**
    - Toxins that are fat or water insoluble are passed into feces and are not absorbed, e.g., elemental mercury
    - However, mercury compounds can be highly absorbent
    - Barium metal is toxic but barium sulfate is not bioavailable hence used in X-ray diagnosis

- **Bioaccumulation:**
  - when a pollutant concentrates in the body at a level higher than the environment:
    - PCB, dioxin in fat; Lead in bones; metals in liver and kidney
Important concepts (contd)

- **Storage:**
  - Body might store some chemicals for short or long periods and then gradually works it out of the system once the exposure to the chemical is reduced or eliminated. As long as these chemicals are remain bound such as in blood proteins, they do not do harm. However sometimes these chemicals are released rapidly causing problems:
  - Lead is ordinarily released slowly over many years. However, during pregnancy, mother’s bone releases calcium for the fetus along which lead is also released and carried into the fetus
  - Fat soluble chemicals remain stored in fat and can be released rapidly when the body needs to use up fat as in the case of low food availability. DDT is a good example
• When a pollutant reached progressively higher concentration as it moves through the food web, it is said to ‘biomagnify’
• PCBs, methylmercury, DDT
Factors affecting Toxicity

- **Species**
  - Guinea pigs more sensitive to dioxins than humans
  - Mules not susceptible to silicosis

- **Gender, age and nutrition**
  - Women more affected by alcohol
  - Babies and small children more affected
  - Elderly population more susceptible
  - Good nutrition provides better protection
  - Alcoholics, Obese people more susceptible; Obese people have a greater risk of cardiovascular diseases and certain types of cancer
Dreaded Diseases

1. Environmental Hormones
   - Hormones: important for reproduction, sexual identity, development and metabolism
   - Environmental Hormones: pollutants that mimic hormones
     - Also known as endocrine disrupters, hormonally active agents
     - Can be industrial chemicals, pharmaceutical, plant products
     - DES (diethylstilbestrol) prescribed to prevent miscarriage produced vaginal cancer in offsprings 15 – 25 yrs later
     - Only animals (?) have suffered harm from environmental hormones:
       - DDT: thinning of eggshells, long persistence
       - Spill of pesticide dicofol, only % of alligator eggs hatching, many died within weeks: traced to DDT in dicofol
       - Estrogens from birth control pills:
       - Plant estrogens in soy based products
       - Androgens, thyroid hormones
   - NRC did not find any conclusive evidence that environmental hormones are unsafe to humans
100 industrial pollutants are known to be environmental hormones
  - Pesticides, metals, phthalate (used in plastics), arsenic

US Congress has ordered EPA to screen 87,000 commercial chemicals

12 persistent organic pollutant has been banned or restricted worldwide by international treaty
Cancer

- Tobacco: cause of 30% of all cancers
- Diet: cause of another 30%.
  - too much fat, too much salt, too little fiber
- Alcohol: liver, colon and breast cancer
- Sunlight: skin cancer
- X-ray: leukemia
- Viral, Bacterial Infection: liver, stomach cancer
- Sexual habits: HPV $\rightarrow$ cervical cancer
- Occupational pollutants: benzene $\rightarrow$ Leukemia. PVC $\rightarrow$ Liver cancer
- Environmental pollutants: smoke, radon, fine particles $\rightarrow$ lung cancer
- Age: by the age 85% almost $\frac{1}{3}$rd of people will have cancer
Risk

- Risk: Probability of suffering harm from a hazard
- Hazard: source of the risk

Risk = Hazard X Exposure

- A hazard can be
  - Chemical substance, pathogen, infectious disease organism, radiation, hot water
- Risk has a probability of 0 to 1
Risk Assessment

- Provides answers to questions like:
  - What is the risk to my child’s health of drinking water containing 3 ppb of Atrazine
  - What is the risk if I eat meat containing 1 ppm of benzopyrene
  - How much dioxin can be safely left in the soil after the clean-up of a hazardous waste site
  - What should be the standard of Arsenic in drinking water
Comparative Risk Assessment

- What is the risk of ozone depletion to the risk of acid rain?
  - Both the environmental risks involve chemicals
- Evaluating the risk of a hazardous waste site
  - Many chemicals
  - Assessments done on indicator chemicals: the ones that pose the most risk to the population
When to do Risk Assessment

- Is there an exposure to chemical?
  - No – no need to risk assessment
  - Yes – focus on chemicals which are most toxic or have the highest exposure
    - Pesticide: meant to kill, will affect many species so we do risk assessment on any new pesticide
    - Food additives are ingested so risk assessment is carried out on all new additives
- Risk assessment is never precise – it compensates for a lack of information. It is a set of decision tools
- Two categories; Cancer and Non-Cancer
Non-Cancer Risk Assessment

1. Hazard Assessment: Why is the substance considered a hazard?

2. Calculate exposure to the chemical

3. Dose-response assessment: what doses are toxic to lab animals

4. Risk Characterization: Takes into all the info from steps 1 to 3 and calculate a safe limit for human exposure
Step 1: Hazard Identification

- Collect and analyze all the available information from literature
- What effect it has on lab animals? Does it harm the nervous system, cause birth defects, interferes with respiration or suppresses immune system?
- How does the exposure occur? Inhalation, ingestion, skin absorption?

Step 2: Dose–response Assessment

- Expose different groups of animals with progressively increasing doses
- The highest dose that the animals tolerate without showing any ill-effect is called “No Observed Adverse Effect Level (NOAEL)”
- Determine a safety factor: assume humans are 10X sensitive than the animal, assume some humans are 10X more sensitive than others, assume children are even more sensitive
- Determine the Reference Dose (RfD)
  - Reference dose (RfD) = NOAEL / Safety factor. Smaller RfD = more toxic chemical
Step 3: Exposure Assessment:

- **Source:** industry?
  - Auto exhaust? Waste dump?

- **Route of exposure:**
  - Drinking water? Food? Soil? Air?
  - What is the concentration in each and how much is ingested or inhaled?
  - How long does the exposure continue?

- **Most highly exposed population:**
  - Some native Indians eat a large amount of fish and have high exposure to chemicals concentrated in fish (PCB, methylmercury)
  - Children are likely to eat soil, or paint
  - Urban people drinking chlorinated water – exposed to disinfectant products
  - Rural people drink well water: radon, arsenic, nitrate
  - People living near hazardous waste sites are more exposed to chemicals emanating from the site
• Step 4: Risk Characterization: Brings all info together to calculate the risk or the “hazard quotient”
• Multiple Chemicals: hazard quotients are added
• Multiple Pathways: Hazard quotients are added
• RfD is the dose considered safe over the lifetime of exposure. If the Hazard quotient is less than rfD, it is considered safe.
Cancer risk assessment

- Step 1: Hazard Identification for possible carcinogens
  - why is it suspected to be a carcinogen?
    - Lab animals study?
    - Epidemiological Study?
    - Is it produced in large quantity
    - Are large number of people exposed to it?

- Step 2: Exposure assessment
  - Done the same way as non-carcinogens
Dose–response assessments for possible carcinogens

- Uses a special protocol
- Rats and mice are typical test species; additional species can be tested for potent carcinogens
- Exposure begins immediately after weaning and continues every day for 18 months to 2 years (lifetime studies).
- Control Group: receives no chemical
- Second Group: receives Maximum Tolerated Dose (MTD); dose that does not kill the animal from non-cancer causes
- Third Group: receives 1/2 MTD
- Sometimes a 4th group with lower dose
- There is no NOAEL for carcinogens
- If a significant number of tumors develop in test animals, a cancer potency factor is calculated. Higher CPF, more potent the carcinogen
## Cancer Potency factor of some chemicals

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Cancer Potency Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,3,7,8-TCDD (dioxin)</td>
<td>100 000</td>
</tr>
<tr>
<td>Arsenic</td>
<td>15</td>
</tr>
<tr>
<td>Cadmium</td>
<td>6.1</td>
</tr>
<tr>
<td>PCBs</td>
<td>4.34</td>
</tr>
<tr>
<td>DDT</td>
<td>0.34</td>
</tr>
<tr>
<td>Benzene</td>
<td>0.029</td>
</tr>
</tbody>
</table>
Risk Characterization

- Expressed as probability that a given exposure will result in cancer
- Calculated for exposure over a 70 year lifetime
  - Arsenic: every 2 μg/l of arsenic in drinking water increases risk by 1 in 100,000
  - Tetrachloroethylene: every 2.4 μg/l of arsenic in drinking water increases risk by 1 in 10,000,000
- Upper bound of plausible risk and not likely to underestimate the risk. Actual risk may be much lower or even zero.
- Risk < 1 in million is considered safe
Risk Management

- Government regulation
  - Clean water act, emission trading, take-back laws
- Non-regulatory tools:
  - Educate the public
  - Govt-industry partnership:
    - 1150 companies voluntarily reduced emissions of 17 chemicals by 50%
    - Pollution Prevention (P²) saves money
    - Develop safer chemicals
    - Develop environmental safer products: e.g., hybrid cars
  - Voluntary action by industry
  - NGO
  - Research support by the society
- Information as Risk-management tool:
  - 500 US companies are evaluating 2800 high production chemicals (Production >1 million lbs/yr)
  - US, Japan, EU: evaluating all 87,000 chemicals in commercial production
• Reducing risk to children:
  • Determine tolerance levels of pesticide residue even for non-cancer effects
  • EPA citing risk to fetus will lower mercury emissions of coal burning plants
  • Companies voluntarily evaluating 20 chemicals the children are most exposed to

• Reducing risk to wildlife
  • Effect of DDT in thinning of bird eggs
  • Acid rain affects aquatic life and forests
  • CFC causing Ozone hole
  • Nutrient, algal bloom, anoxia
  • Polluted run-of and industrial discharges
  • Effluents should be tested for toxin levels for aquatic life, hazardous waste sites should be cleaned up limiting exposure to surrounding wild life
  • Laws requiring clean air and water helps animals too