Principles of toxicology

Chemical safety and risk assessment, introduction to toxicology, acute poisoning, treatment of acute poisoning, example of chronic poisoning
Paracelsus, the grandfather of toxicology

• All things are poison and nothing is without poison, only the dose permits something not to be poisonous.
• The dose makes the poison.
Chemical safety and risk assessment

Definition, significance, important pollutants, risk assessment
Chemical safety

• Chemical safety is achieved by undertaking all activities involving chemicals in such a way as to ensure the safety of human health and the environment.

• It covers *all chemicals*, natural and manufactured, and the full range of *exposure situations* from the natural presence of chemicals in the environment to their extraction or synthesis, industrial production, transport use and disposal.
Significance of chemical safety

• It is estimated that at least 4.9 million deaths (8.3% of all deaths) are due to environmental exposure to selected chemicals each year.

• The largest contributors include indoor smoke from solid fuel use, outdoor air pollution and second-hand smoke, followed by occupational particulates, chemicals involved in acute poisonings, and pesticides involved in self-poisonings.
Ten chemicals of major public health concern

1. Air pollution
2. Arsenic
3. Asbestos
4. Benzene
5. Cadmium
6. Dioxin and dioxin-like substances
7. Inadequate or excess fluoride
8. Lead
9. Mercury
10. Highly hazardous pesticides
Risk assessment

• Risk assessment is the determination of quantitative or qualitative value of risk related to a concrete situation and a recognized threat
Acceptable risk

• Quantitative risk assessment requires calculations of two components of risk (R):
  • the magnitude of the potential loss (L)
  • and the probability (p) that the loss will occur.

• Acceptable risk is a risk that is understood and tolerated usually because the cost or difficulty of implementing an effective countermeasure for the associated vulnerability exceeds the expectation of loss.
In the estimation of risks, three or more steps are involved that require the inputs of different disciplines:

- Hazard identification.
- Dose-response analysis.
- Exposure Quantification.
Hazard identification

• Hazard Identification, aims to determine the qualitative nature of the potential adverse consequences of the contaminant (chemical, radiation, noise, etc.) and the strength of the evidence it can have that effect.

• This is done, for chemical hazards, by drawing from the results of the sciences of toxicology and epidemiology. For other kinds of hazard, engineering or other disciplines are involved.
Dose-Response Analysis

• Dose-Response Analysis is determining the relationship between dose and the probability or the incidence of effect (dose-response assessment).

• The complexity of this step in many contexts derives mainly from the need to extrapolate results from experimental animals (e.g. mouse, rat) to humans, and/or from high to lower doses.

• In addition, the differences between individuals due to genetics or other factors mean that the hazard may be higher for particular groups, called susceptible populations.
Exposure quantification

• Exposure Quantification aims to determine the amount of a contaminant (dose) that individuals and populations will receive.

• This is done by examining the results of the discipline of exposure assessment.

• As different location, lifestyles and other factors likely influence the amount of contaminant that is received, a range or distribution of possible values is generated in this step.

• Particular care is taken to determine the exposure of the susceptible population(s).
There are many resources that provide health risk information. The National Library of Medicine provides risk assessment and regulation information tools for a varied audience. These include:

- TOXNET (databases on hazardous chemicals, environmental health, and toxic releases),[7]
- the Household Products Database (potential health effects of chemicals in over 10,000 common household products),[8]
- TOXMAP (maps of the U.S. Environmental Protection Agency Superfund and Toxics Release Inventory data).

The United States Environmental Protection Agency provides basic information about environmental risk assessments for the public.
Introduction to toxicology

Definitions, quantifying dose and response, toxicodynamics
Definition of toxicology

• The study of the adverse effects of a toxicant on living organisms.

• Adverse effects
  • any change from an organism’s normal state
  • dependent upon the concentration of active compound at the target site for a sufficient time.

• Toxicant
  • any agent capable of producing a deleterious response in a biological system

• Living organism
  • a „sac of water” with target sites, storage depots and enzymes
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 environmental concentration
  - The properties of the toxicant
  - The frequency of exposure
  - The length of exposure
  - The exposure pathway

Responses to different agents (each one represented by a different color) may vary with increasing dose.
Response

• Change from normal state
  • Could be on the molecular, cellular, organ, or organism level.

• The degree and spectra of responses depend upon the dose and the organism.

• Response can be:
  • Local vs. Systemic
  • Reversible vs. Irreversible
  • Immediate vs. Delayed
  • Graded vs. Quantal
    • Degrees of the same damage vs. all or none
**LD$_{50}$**

- Quantal responses can be treated as gradient when data from a population is used.
- The cumulative proportion of the population responding to a certain dose is plotted per dose (10-30 fold variation w/in a population)
- If Mortality is the response, the dose that is lethal to 50% of the population LD$_{50}$ can be generated from the curve
- Different toxicants can be compared (lowest dose is most potent)
### Comparison of toxicants

<table>
<thead>
<tr>
<th>Chemical</th>
<th>LD$_{50}$ (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethyl Alcohol</td>
<td>10,000</td>
</tr>
<tr>
<td>Sodium Chloride</td>
<td>4,000</td>
</tr>
<tr>
<td>Ferrous Sulfate</td>
<td>1,500</td>
</tr>
<tr>
<td>Morphine Sulfate</td>
<td>900</td>
</tr>
<tr>
<td>Strychnine Sulfate</td>
<td>150</td>
</tr>
<tr>
<td>Nicotine</td>
<td>1</td>
</tr>
<tr>
<td>Black Widow</td>
<td>0.55</td>
</tr>
<tr>
<td>Curare</td>
<td>0.50</td>
</tr>
<tr>
<td>Rattle Snake</td>
<td>0.24</td>
</tr>
<tr>
<td>Dioxin (TCDD)</td>
<td>0.001</td>
</tr>
<tr>
<td>Botulinum toxin</td>
<td>0.0001</td>
</tr>
</tbody>
</table>
NOAEL, LOAEL

- NOAEL: No observed adverse effect level
- LOAEL: Lowest observed adverse effect level
Significance of NOAEL

• Results obtained from animal experiments must be corrected in order to be able to use them for humans.
• To account for the fact that humans may be more or less sensitive than the test animal, a 10-fold uncertainty factor is usually applied to the NOAEL. This uncertainty factor is called the "interspecies uncertainty factor".
• An additional 10-fold uncertainty factor, the "intraspecies uncertainty factor" is usually applied to account for the fact that some humans may be substantially more sensitive to the effects of substances than others.
• Additional uncertainty factors may also be applied.
Exposure pathways

• Routes and Sites of Exposure
  • Ingestion (Gastrointestinal Tract)
  • Inhalation (Lungs)
  • Dermal/Topical (Skin)
  • Injection
    • intravenous, intramuscular, intraperitoneal

• Typical Effectiveness of Route of Exposure
  iv > inhale > ip > im > ingest > topical
Exposure: Duration

- Over time, the amount of chemical in the body can build up, it can redistribute, or it can overwhelm repair and removal mechanisms.

<table>
<thead>
<tr>
<th>Effect</th>
<th>Time</th>
<th>Exposure pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td>&lt;24 hours</td>
<td>Usually 1 exposure</td>
</tr>
<tr>
<td>Subacute</td>
<td>1 months</td>
<td>Repeated doses</td>
</tr>
<tr>
<td>Subchronic</td>
<td>1-3 months</td>
<td>Repeated doses</td>
</tr>
<tr>
<td>Chronic</td>
<td>&gt;3 months</td>
<td>Repeated doses</td>
</tr>
</tbody>
</table>
Absorption, Distribution, Metabolism, and Excretion

• Once a living organism has been exposed to a toxicant, the compound must get into the body and to its target site in an active form in order to cause an adverse effect.

• The body has defenses:
  • Membrane barriers
    • passive and facilitated diffusion, active transport
  • Biotransformation enzymes, antioxidants
  • Elimination mechanisms
Absorption

- Inhalation: readily absorb gases into the blood stream via the alveoli. (Large alveolar surface, high blood flow, and proximity of blood to alveolar air)
- Ingestion: absorption through GI tract stomach (acids), small intestine (long contact time, large surface area)
  - 1st Pass Effect (liver can modify)
- Dermal: absorption through epidermis (stratum corneum), then dermis; site and condition of skin
Distribution

• Blood carries the agent to and from its site of action, storage depots, organs of transformation, and organs of elimination

• Rate of distribution (rapid) dependent upon
  • blood flow
  • characteristics of toxicant (affinity for the tissue, and the partition coefficient)

• Distribution may change over time
Storage and Binding

- Storage in Adipose tissue: very lipophylic compounds (DDT) will store in fat. Rapid mobilization of the fat (starvation) can rapidly increase blood concentration.

- Storage in Bone: chemicals analogous to Calcium: Fluoride, Lead, Strontium.

- Binding to Plasma proteins: can displace endogenous compounds.
  - Only free is available for adverse effects or excretion.
Targeted organ

• A systemic toxin is one that affects the entire body or many organs rather than a specific site.
  • Potassium cyanide affects virtually every cell and organ in the body by interfering with the cell’s ability to utilize oxygen.

• Toxins may also affect only specific tissues or organs while not producing damage to the body as a whole.

• These specific sites are known as target organs or target tissues
  • Benzene is a specific organ toxin in that it is primarily toxic to the blood-forming tissues.
  • Lead is also a specific organ toxic, however it has three target organs (CNS, kidney and hematopoietic system).
Target Organs

- Adverse effect is dependent upon the concentration of active compound at the target site for enough time
- Not all organs are affected equally
  - greater susceptibility of the target organ
  - higher concentration of active compound
- Liver: high blood flow, oxidative reactions
- Kidney: high blood flow, concentrates chemicals
- Lung: high blood flow, site of exposure
- Neurons: oxygen dependent, irreversible damage
- Myocardium: oxygen dependent
- Bone marrow, intestinal mucosa: rapid divide
Target Sites

• Adverse effects occur at the level of the molecule, cell.
• Molecularly, chemical can interact with
  • Proteins
  • Lipids
  • DNA
• Cellularly, chemical can
  • interfere with receptor-ligand binding
  • interfere with membrane function
  • interfere with cellular energy production
  • bind to biomolecules
  • perturb homeostasis (Ca)
Excretion

- Toxicants are eliminated from the body by several routes
  - Urinary excretion
    - Water soluble products are filtered out of the blood by the kidney and excreted into the urine
  - Exhalation
    - Volatile compounds are exhaled by breathing
  - Biliary Excretion via Fecal Excretion
    - Compounds can be extracted by the liver and excreted into the bile. The bile drains into the small intestine and is eliminated in the feces.
  - Milk
  - Sweat
  - Saliva
Metabolism

• Metabolism is the process by which the administered chemical (parent compounds) are modified by the organism by enzymatic reactions.

• 1º objective: make chemical agents more water soluble and easier to excrete
  • decrease lipid solubility --> decrease amount at target
  • increase ionization --> increase excretion rate --> decrease toxicity

• Bioactivation: Biotransformation can result in the formation of reactive metabolites
Biotransformation

• Biotransformation can drastically affect the rate of clearance of compounds
• Can occur at any point during the compound’s journey from absorption to excretion.
• Key organs in biotransformation
  • LIVER (high)
  • Lung, Kidney, Intestine (medium)
  • Others (low)
• Biotransformation Pathways
  * Phase I: make the toxicant more water soluble
  * Phase II: Links with a soluble endogenous agent (conjugation)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Without metabolism</th>
<th>With metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanol</td>
<td>4 weeks</td>
<td>10 ml/hour</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>5 months</td>
<td>8 hours</td>
</tr>
<tr>
<td>DDT</td>
<td>infinity</td>
<td>Days to weeks</td>
</tr>
</tbody>
</table>
Individual Susceptibility I.

There can be 10-30 fold difference in response to a toxicant in a population due to:

• Genetic traits, interindividual variations
• Gender (gasoline nephrotoxic in male mice only)
• Age (young)
  • underdeveloped excretory mechanisms
  • underdeveloped biotransformation enzymes
  • underdeveloped blood-brain barrier
Individual Susceptibility II.

- Age (elderly)
  - Changes in excretion and metabolism rates, body fat
- Nutritional status
- Health conditions
- Previous or Concurrent Exposures
  - additive
  - antagonistic
  - synergistic
Effects of acute and chronic poisoning

• Acute toxicity describes the adverse effects of a substance that result either from a single exposure or from multiple exposures in a short space of time (usually less than 24 hours).
  • Symptoms may vary, severity can range from mild to lethal.

• Chronic toxicity is a property of a substance that has toxic effects on a living organism, when that organism is exposed to the substance continuously or repeatedly.
  • Carcinogenic, mutagenic, teratogenic effects can be expected.
# International Agency Research on Cancer (IARC)

<table>
<thead>
<tr>
<th>Groups</th>
<th>Effect</th>
<th>Number of agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>Carcinogenic to humans</td>
<td>113</td>
</tr>
<tr>
<td>Group 2A</td>
<td>Probably carcinogenic to humans</td>
<td>66</td>
</tr>
<tr>
<td>Group 2B</td>
<td>Possibly carcinogenic to humans</td>
<td>285</td>
</tr>
<tr>
<td>Group 3</td>
<td>Not classifiable as to its carcinogenicity to humans</td>
<td>505</td>
</tr>
<tr>
<td>Group 4</td>
<td>Probably not carcinogenic to humans</td>
<td>1</td>
</tr>
</tbody>
</table>
IARC monographs

• http://monographs.iarc.fr/ENG/Classification/index.php
Public health aspects of acute poisoning

Significance, causes, prescription medicine, pesticides, snake-bite
Significance

- Poisoning is a significant global public health problem.
- According to WHO data, in 2004 an estimated 346,000 people died worldwide from unintentional poisoning.
- Of these deaths, 91% occurred in low- and middle-income countries.
- In the same year, unintentional poisoning caused the loss of over 7.4 million years of healthy life (disability adjusted life years, DALYs).
Types of poisoning

• Deliberate:
  • Overdose as self-harm or suicide attempt.
  • Child abuse ± fabricated or induced illness by carers (formerly referred to as Münchhausen's syndrome by proxy).
  • Third party (attempted homicide, terrorist, warfare).

• Accidental:
  • Most episodes of pediatric poisoning.
  • Dosage error:
    • Iatrogenic
    • Patient error
  • Recreational use.

• Environmental:
  • Plants
  • Food
  • Venomous stings/bites

• Industrial exposures
Common causes of poisoning

• The most common type of toxin ingested varies geographically, being prescribed medication in the developed countries and agricultural chemicals, hydrocarbons or traditional medicines in the developing nations.

• The most at-risk groups are children under the age of 5 and females aged 35-54
Prescription drug overdose

- Most common drugs involved:
  - Opioid analgetics
  - BZD
  - Anti-anxiety and insomnia medication
Pesticides

• Self-poisoning with agricultural pesticides represents a major hidden public health problem accounting for approximately one-third of all suicides worldwide.
• It is one of the most common forms of self-injury in the Global South.
• The World Health Organization estimates that 300,000 people die from self-harm each year in the Asia-Pacific region alone.
• Most cases of intentional pesticide poisoning appear to be impulsive acts undertaken during stressful events, and the availability of pesticides strongly influences the incidence of self poisoning.
Snake-bite

• Snake-bite is a largely unrecognized public health problem that presents significant challenges for medical management.

• While reliable data are hard to obtain, it has been estimated that about 5 million snake-bites occur each year, resulting in up to 2.5 million envenomings, at least 100,000 deaths and around three times as many amputations and other permanent disabilities.
Treatment of acute poisoning

Five-finger rule
Five-finger rule

A. Elementary aid
B. Decontamination
C. Antidote therapy
D. Transport
E. Securing of evidence
A. Elementary aid
B. Detoxification

• Vomiting (conscious patient)
  • E.g. Pharmaceuticals (within the first hour).
  • Contraindication: solvents, acids, alkaline solutions.

• Gastric lavage (conscious or unconscious)
  • Adults: 10-20l body temperature water in 0,5-1l doses.
  • Children: Isotonic sodium chloride solution
  • Active charcoal may be administered together with laxatives, through gastric tube.

• Other possibilities: forced diuresis, hemodialysis, hemoperfusion, plasmapheresis
Detoxification

A. Detoxification

- Conscious
  - Vomiting
  - Gastric lavage

- Unconscious
  - Ventilation (intubation, tracheal cuff)
  - Gastric lavage

- Ipecac syrup
- Activated charcoal
- $\text{Na}_2\text{SO}_4$
C. Antidote therapy I.

- Only in certain cases
- Specific
  - Pl. dimetilaminophenol creates methemoglobin with cianide, and enables its elimination
- Less specific
  - Active charcoal binds poisons in the GI and inhibits their absorption.
  - Chelating substances bind heavy metals and enables their elimination
- Can be found in ICU, ambulance
C. Transport

- Patients should be transported to the proper institution as soon as possible.
- Transportation is only possible once circulation has been stabilized and the airway is cleared.
E. Securing evidence

• Critical in diagnosing

• Possible samples
  • Blood in EDTA tube
  • Urine
  • Stool
  • Exhaled air

• Accurate labeling

• Blood and urine samples should be secured before administering antidote.
Example of chronic poisoning

Endocrine disruptors, their effects and prevention
Endocrine disruptors

• Endocrine disruptors are chemicals that, at certain doses, can interfere with the endocrine (or hormone) system in mammals.
  • Direct effect: acting as receptor agonists/antagonists
  • Indirect effect: Interfering with metabolism or regulation of hormones.
Effects of endocrine disruptors

1. Estrogens
   DES, o,p’-DDT, DEHP, bisphenol A
2. Antiestrogens
   hexachloro-4-biphenylol, luteoline
3. Antiandrogens
   p,p’-DDE, vinclozoline
4. Progestogens
   norethindrone, norgestrol
5. Adrenal cortex toxins
   o,p’-DDD,
6. Thyreotoxic
   PCB, goitrine, azoxyglycosids, sztreptozotocines
7. Metals
   Kadmium, ólom, arzén
8. Retinoids
   A vitamin analógok
Antiestrogenic and antiandrogenic effect

**Antiestrogenic effect**
- Antiestrogen
- Estrogen
- Silent gene
- Gene activation

**Antiandrogenic effect**
- Hypothalamus
- Hypophysis
- Testis
- Antiandrogen
- Masculinization
- Fertility
Thyreotoxic effect

- Decreases hormone production of thyroid gland.
- Decreases the activation of thyroid hormones.
- Increases the elimination of thyroid hormones.
Sources of endocrine disruptors I.

- Pharmaceuticals
- Pesticides
- Plasticizers
- Detergents
- Cosmetics
- Flame retardants in electronic devices
Sources of endocrine disruptors II.

800 chemicals are known to be endocrine disruptors. Most of these chemicals are found in products for everyday use and in the air, water, soil, and food as pollutants.
Pharmaceuticals

• Pharmaceuticals containing estrogens (e.g. contraceptive pills)
  • 20% of European women use contraceptive pills
  • In Hungary 40% of women use them.
• NSAID (pl. paracetamol)
• Antiepileptic (pl. valproat)
• Antiparkinson medicines (pl. deprenil)
Endocrine disruptors in the households

- Cleaning supplies
- Cosmetics
- Sunscreen
- Soap, shampoo, perfumes
- Pacifiers, feeding-bottles
- Plastic toys for children
- Other plastic products (e.g. shower curtains)

![Global plastic production graph]
Persistent organic pollutants

DDT and PCB found in organisms

Comparative lists of POPs selected for environmental and toxicological studies

<table>
<thead>
<tr>
<th>POPs selected on the Stockholm Convention (2001)</th>
<th>Organic pollutants (or proposed POPs) with an assigned TEF* or REP**</th>
<th>Emerging POPs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldrin</td>
<td>PCBs, PCDDs/PCDFs</td>
<td>PBDEs, PBDDs/ PBDFs, PBBs</td>
</tr>
</tbody>
</table>
Newer persistent organic pollutants

- Chlordecon – pesticide
- α-Hexachlorocyclohexán – pesticide
- Hexabromodiphenyl éter – pesticide
- Pentachlorobenzén – pesticide
- Endoszulfán – preservation of wood
- Perfluorooctanesulfon sav – electronic appliances
- Tetrabromodiphenyl éter – flame retardants in electronic appliances
- Hexabromocyclododecán – flame retardants in electronic appliances
Risk groups

- Pregnant women
- Fetus
- Infant
- Child, adolescent
  - Higher breathing volumen compared to body surface
  - Different metabolism
  - Typical childhood habits
Effects of endocrine disruptors
Ecological effect of endocrine disruptors
Prevention

• Greener industry
• Recycling
• Selective waste collection
• Zero tolerance against persisting and accumulating pollutants
• Identifying other endocrine disrupting chemicals
• Natural substances in agriculture
• Information dissemination, education
• CHEMICAL SAFETY
Effects of regulation

Effect of DDE ban on contamination of eggs

Effect of lead regulation on blood concentrations

- Year
- DDE (ppm)
- Occupied nests

- Year
- Lead in fuel (tons)
- Lead in gasoline
- Lead in blood
- Blood level (mikrog/dl)
Thank you for your attention!