Principles of Environmental Toxicology

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Principles of Environmental Toxicology

- **Fundamental principles of toxicology**
  - Toxicological paradigm
  - Toxicokinetics
    - Absorption
    - Distribution
    - Metabolism
    - Excretion
    - Storage
  - Toxicodynamics
Toxicology is...

...the study of the adverse effects of chemical, physical, or biological agents on living organisms and the ecosystem, including the prevention and mitigation of such adverse effects.

Pharmacology uses many of the same principles, but in the therapeutic realm.
All substances are poisons; there is **NONE** which is not a poison. The right dose differentiates a poison from a remedy.

-Paracelsus (1493-1541)
**Fundamental Principles of Toxicology**

- **Principle I**
  Toxic action of a substance is a consequence of the physical/chemical interaction of the *active form* of that substance with a *molecular target* within the living organism.

- **Principle II**
  Magnitude of toxic effect is a function of the *concentration of altered molecular targets*, which in turn is related to the concentration of the active form of the toxicant at the site where the molecular targets are located.
Fundamental Principles of Toxicology

- **Toxicokinetics** - what the **body** does to the agent
  - Absorption
  - Distribution
  - Metabolism
  - Excretion
  - Storage
- **Toxicodynamics** - what the **agent** does to the body
  - The active form of the agent at the sensitive target

Big picture of Toxicokinetics (TK) and Toxicodynamics (TD)

![Diagram](Image)

TK/TD affected by:
- Other drugs/xenobiotics
- Genetic polymorphisms
- Infection/GI flora
- Age, weight, diet

Adapted from Pete Dedon and John Essigmann

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Processes Associated with the Toxicokinetics of Agents

- Absorption
- Distribution
- Metabolism
- Excretion
- Storage

Absorption and distribution

- Route of administration determines TKs
  - **Enteral**
    - oral
    - sublingual
    - rectal
  - **Parenteral**
    - intravenous (i.v.)
    - intramuscular (i.m.)
    - subcutaneous (s.c.)
  - **Other routes**
    - inhalation
    - topical
    - transdermal

Adapted from Pete Dedon and John Essigmann
Absorption (1)

- Common feature of all routes of administration (except IV): epithelial barriers
  - Epithelial cells line our body cavities and surfaces (e.g., skin)

- Uptake of compounds from GI tract, lungs, or skin must cross epithelial cell barriers to gain access to systemic circulation

Absorption (2)

- Epithelial tissues as barriers to absorption
  - Sheets of cells lining all body surfaces and cavities
  - Varying thickness: Single-cell (gut, lungs) to multilayer (skin)
  - Cell-cell junctions prevent movement around cells
  - Drugs must cross lipid bilayers

- Physicochemical factors that affect kinetics of absorption:
  - pH, blood flow, gastric emptying, bowel transit
  - Surface area: lungs – up to 100 m²; GI tract - 300 m²; skin - 1.5-2 m²

Adapted from Pete Dedon, MIT

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## Route of Exposure and the Extent of Toxicity

### Variation in Toxicity by Route of Exposure

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Species/Sex</th>
<th>Route</th>
<th>LD50/(mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-Methyl-N-(1-naphthyl) fluoroacetamide</td>
<td>Mouse/M</td>
<td>Oral, dermal, subcutaneous</td>
<td>371, 402, 250</td>
</tr>
<tr>
<td>N-Methyl-N-(1-naphthyl) fluoroacetamide</td>
<td>Rat/M</td>
<td>Oral, dermal, subcutaneous</td>
<td>115, 300, 78</td>
</tr>
<tr>
<td>Chlordane</td>
<td>Rat/M</td>
<td>Oral, dermal</td>
<td>335, 840</td>
</tr>
<tr>
<td>Endrin</td>
<td>Rat/M</td>
<td>Oral, dermal</td>
<td>18</td>
</tr>
</tbody>
</table>


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## Toxicology of gasoline

<table>
<thead>
<tr>
<th>Route of exposure</th>
<th>Experimental (LD_{50})</th>
<th>Lethal dose for 10kg child</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI Tract</td>
<td>Large (19mg/kg)</td>
<td>300/soft-drink bottle</td>
</tr>
<tr>
<td>Lung</td>
<td>Small (0.2 ml)</td>
<td>2.5/teaspoon</td>
</tr>
</tbody>
</table>

*Environmental Health Perspectives: 101: 115-131, 1993*
Major Differences between General (Non-neuronal) and Brain Capillary

- Capillary endothelial cells in CNS
  - Tightly joined
  - Contain ATP-dependent transporter (efflux pump)
- Capillaries in CNS are to large extent surrounded by glial cells
- Low protein content of interstitial fluid in brain limits movement of water-insoluble molecules by paracellular transport

Blood-Brain Barrier is Less Permeable to Toxicants (Deeper Data)
Processes Associated with the Toxicokinetics of Agents

- Absorption
- Distribution
- Metabolism
- Excretion
- Storage

BIOTRANSFORMATION (Metabolism)

- Purpose:
  - to convert xenobiotics to water soluble forms so that they can be excreted in breath, feces and urine
  - Lung, skin, GI, bladder
Organs Involved in Biotransformation

- **LIVER**
- Lung
- Kidney
- Intestine
- Skin
- Gonads
Example of a Phase 1 Reaction
(Exposing a Functional Group)

Example of a Phase 1 Reaction
(Introducing a Functional Group)
Biotransformation & Bioactivation

- Many xenobiotics (foreign - and potentially toxic - compounds) are lipophilic (fat soluble).
- The body readily excretes water soluble compounds.
- So, the body transforms (chemically alters) xenobiotics (via Phase 1 and Phase 2 reactions) to make them more water soluble.
- Sometimes, these transformations make the resulting compound more toxic (the compound is bioactivated).

The Truck-Hitch-Trailer Paradigm of Xenobiotic Metabolism

Foreign Chemical (xenobiotic)

TRUCK

- lipophilic
- not charged
- not water soluble
- poorly excretable
The Truck-Hitch-Trailer Paradigm of Xenobiotic Metabolism

Foreign Chemical (xenobiotic) → Phase 1 enzymes → Phase 2 enzymes

TRUCK
- lipophilic
- not charged
- not water soluble
- poorly excretable

HITCH
- still lipophilic
- possibly reactive
- poorly water soluble
- poorly excretable
- catalyzed by P450s

TRAILER
- not lipophilic
- usually not reactive
- water soluble products
- excretable
- catalyzed by transferases
  - sugars, amino acids, sulfates, acetyl groups

* endogenous molecules

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Phase 1 reactions create the HITCH. Phase 2 reactions add on the TRAILER.

Example of a Phase I Reaction
(Exposing a Functional Group)

\[ \text{OCH}_3 \quad \xrightarrow{\text{OCH}_2\text{OH}} \quad \text{OH} + \text{HCHO} \]

\[ \text{NO}_2 \quad \xrightarrow{\text{NO}_2} \quad \text{NO}_2 \]

\( p \)-Nitroanisole \( p \)-Nitrophenol

The functional group is the HITCH.
The TRAILER gets "conjugated" (attached) to the HITCH.
Example of a Phase I Reaction
(Introducing a Functional Group)

Phase 1 Reactions

- Primary enzyme is *cytochrome P-450* (also referred to as mixed function oxidase)
  - Can metabolize many xenobiotics
  - Also metabolize endogenous substrates
  - Can catalyze many type of reactions (broad substrate specificity)
  - Widely distributed amongst tissues
- *Very cool enzymes*: Splits molecular oxygen (O₂) into one atom that oxidizes compounds and one atom reduced to H₂O
Phase 2 Reaction Enzymes
(Four Primary Enzymes)

These 4 primary enzymes attach these TRAILERs to the HITCH:

- **Glucuronyltransferase** → Glucuronic acid
- **Sulfotransferase** → Sulfate
- **Glutathione-S-Transferase** → Glutathione (GSH)
- **Acetyltransferase** → AcetylCoA

(genesis for these enzymes can be polymorphic too)
Excretion Pathways

- **Respiratory excretion**
  - Mucociliary clearance
  - Gas exchange

- **Gastrointestinal excretion**
  - Biliary excretion
  - Entero-hepatic circulation

- **Urinary excretion**
  - Glomerular filtration
  - Trans-tubular secretion
Other Routes of Excretion

- Milk
- Sweat
- Hair
- Nails
- Saliva

Processes Associated with the Toxicokinetics of Agents

- Absorption
- Distribution
- Metabolism
- Excretion
- Storage
Biological Half Life

- The *biological half-life* ($T_{1/2}$) is the time required for some measure of the amount of a chemical in the body (for example, body burden, tissue concentration) to decrease to 1/2 its current value.
Examples of half-lives

- **Short half life**
  - rapidly cleared from body (minutes to hours)
  - usually metabolized to water soluble derivative
  - e.g., ethanol

- **Long half life**
  - persists in body for months to years
  - typically lipophilic and poorly metabolized
  - e.g., POPs (persistent organic pollutants), dioxin
    Pb in bone, DDT in body fat

**Toxicological Endpoints**

- Cell death
- Cellular/organ dysfunction
- Teratology (birth defect)
- Genetic changes (e.g., mutation)
- Cancer
Key Points - 1

- Toxicology includes the processes of toxicokinetics and toxicodynamics.
- Toxicokinetics includes absorption, distribution, metabolism, excretion, and storage (ADMES) processes.
- The toxicity of a compound can be expressed as the LD50 – the lethal dose to 50% of the test population. A lower LD50 means a more toxic compound. However, LD50 is no longer the major metric of toxicity.
- The route of exposure can affect toxicity of a compound.

Key Points - 2

- Transport mechanisms include diffusion, filtration/bulk flow, endocytosis, and passive or active transport.
- A typical uptake and clearance curve is governed by a half-life for washout.
- The first pass effect refers to the biliary excretion route for xenobiotics (foreign compounds).
- The blood-brain-barrier prevents many compounds from entering the brain.
Phase 1 and Phase 2 reactions represent biotransformations whose purpose is to increase excretability of xenobiotics. Sometimes, these reactions activate toxins.

- Phase 1 reactions add or expose functional groups; the primary enzyme is cytochrome P-450 ("mixed function oxidase"). There are multiple forms of P-450s in tissues.
- Phase 2 reactions conjugate compounds with other molecules; there are 4 primary Phase 2 enzymes (glucuronosyltransferase, sulfotransferase, glutathione-S-transferase, acetyltransferase).

The first principle of toxicology is that the toxic action of a compound is a consequence of the physical/chemical interaction of the active form of the compound with a sensitive molecular target within the living organism.

- The second principle of toxicology is that the magnitude of the toxic effect is a function of the concentration of the active form of the compound, and its duration, at the sensitive molecular target.
- Reactive intermediates of chemicals can be electrophiles or free radicals and are known as “ultimate toxicants”. They often react with target molecules leading to toxicity.
Biomarkers reflecting the toxicokinetics of a compound reflect “internal dose” and “biologically effective dose”, while those reflecting toxicodynamic processes are “early biological effects” and “altered structure/function”.

Important susceptibility factors that influence inter-individual differences in toxicokinetics include DNA repair capacity and biotransformation, and when coupled with exposure, provide examples of gene-environment interactions.