What is Toxicokinetics?

Toxicokinetics Defined

Toxicokinetics is essentially the study of "how a substance gets into the body and what happens to it in the body." Before this term was used, the study of the kinetics (movement) of chemicals was originally conducted with pharmaceuticals and the term pharmacokinetics became commonly used. Similarly, toxicology studies were initially conducted with drugs. Toxicokinetics deals with what the body does with a drug when given a relatively high dose relative to the therapeutic dose. Read more about **differences between pharmacokinetics and toxicokinetics**.

Processes

Four processes are involved in toxicokinetics:

1. **Absorption** — the substance enters the body.
2. **Distribution** — the substance moves from the site of entry to other areas of the body.
3. **Biotransformation** — the body changes (transforms) the substance into new chemicals (metabolites).
4. **Excretion** — the substance or its metabolites leave the body.

The science of toxicology has evolved to include environmental and occupational chemicals as well as drugs. Toxicokinetics is thus the appropriate term for the study of the kinetics of all substances at toxic dose/exposure levels.

Frequently the terms toxicokinetics, pharmacokinetics, or disposition have the same meaning. Disposition is often used in place of toxicokinetics to describe the movement of chemicals through the body over the course of time, that is, how the body disposes of a xenobiotic.

Figure 9.1.1. Processes of toxicokinetics
(Image Source: Adapted from iStock Photos, ©)

Factors Determining the Severity of Toxicity

The disposition of a toxicant and its biological reactivity are the factors that determine the severity of toxicity that results when a xenobiotic enters the body. The most important aspects of disposition include:

- **Duration and concentration** of a substance at the portal of entry.
- **Rate and amount** of the substance that can be absorbed.
- **Distribution** in the body and **concentration** of the substance at specific body sites.
- **Efficiency** of biotransformation and nature of the metabolites.
- **Ability** of the substance or its metabolites **to pass through cell membranes** and come into contact with specific cell components (for example, DNA).
- **Amount and duration of storage** of the substance (or its metabolites) in body tissues.
- **Rate and sites of excretion** of the substance.
- **Age and health status** of the person exposed.

Here are some examples of how toxicokinetics of a substance can influence its toxicity:

- **Absorption** — A highly toxic substance that is poorly absorbed may be no more hazardous than a substance of low toxicity that is highly absorbed.
- **Biotransformation** — Two substances with equal toxicity and absorption may differ in how hazardous they are depending on the nature of their biotransformation. A substance that is biotransformed into a more toxic metabolite (bioactivated) is a greater

hazard than a substance that is biotransformed into a less toxic metabolite (detoxified).

Inter-Related Processes of Absorption, Distribution, Biotransformation, and Elimination

Absorption, distribution, biotransformation, and elimination are inter-related processes as illustrated in Figure 2 below. After the substance is absorbed, it is distributed through the blood, lymph circulation, and extracellular fluids into organs or other storage sites and may be metabolized. Then, the substance or its metabolites are eliminated through the body's waste products.

Figure (\PageIndex{2}\). Absorption, Distribution, Metabolism, and Elimination
(Image Source: NLM)

What are Transporters?

Transporters, also called transporter proteins, play an important role in the processes of absorption, distribution, metabolism, and elimination (ADME). They are important to pharmacological, toxicological, clinical, and physiological applications. For example:

- In the **liver** — transmembrane transporters, together with drug metabolizing enzymes, are important in drug metabolism and drug clearance by the liver. Xenobiotics, endogenous metabolites, bile salts, and cytokines affect the levels (or "expression") of these transporters in the liver. Adverse reactions in the liver to a xenobiotic such as a drug could be caused by genetic or disease-induced variations of transporter expression or drug-drug interactions at the level of these transporters.
- In the **kidneys** — renal proximal tubules are targets for toxicity partly because of the expression of transporters that mediate the secretion and reabsorption of xenobiotics. Changes in transporter expression and/or function could enhance the accumulation of toxicants and make the kidneys more susceptible to injury, for example, when xenobiotic uptake by carrier proteins is increased or the efflux of toxicants and their metabolites is reduced. The list of nephrotoxic chemicals is a long one and includes:
  - Environmental contaminants such as some hydrocarbon solvents, some heavy metals, and the fungal toxin ochratoxin.
  - Some antibiotics.
  - Some antiviral drugs.
  - Some chemotherapeutic drugs.

The competition of xenobiotics for transporter-related excretion and genetic polymorphisms affecting transporter function affect the likelihood of nephrotoxicity.
Because of concerns that such changes to transporter expression and function can adversely affect clinical outcomes and physiological regulation, increased drug transporter activity is important to study and understand. There is clinical and laboratory research including *in vitro*, *ex vivo*, and *in vivo* studies that shows how powerful drug-drug interactions can be.
For example, drugs might compete with each other for binding to a transporter, which can lead to changes in serum and tissue drug levels and possible side effects.

- This is one possible explanation for the rare occurrence of potentially severe toxicity when the drug methotrexate and nonsteroidal anti-inflammatory drugs are given at the same time.
- The drug probenecid, which competitively inhibits some transporters, has been used to increase the half-life of antibiotics such as penicillin and antiviral drugs and improve their therapeutic value.

Pharmacokinetics and Toxicokinetics: Now and in the Future

Current research priorities suggest that we can anticipate important strides in the following areas of pharmacokinetics and toxicokinetics:

- An increased understanding of human variability of pharmacokinetics and pharmacodynamics in the population.
- Further exploration of mode of action hypotheses (**MoA**).

- Is a MoA the same as a MOA? No. A **mode of action (MoA)** describes a functional or anatomical change, at the cellular level, resulting from exposure to a substance. A **mechanism of action (MOA)** describes changes at the molecular level.

- Further application of biological modeling in the risk assessment of individual chemicals and chemical mixtures.
- Further identification and discussion of uncertainties in the modeling process.
- Further use of "Reverse Toxicokinetics," also called **"IVIVE" (*In vitro* to *in vivo* extrapolation)**. IVIVE *in vitro* data to estimate exposures that could be associated with adverse effects *in vivo*.
