HBM4EU project

Basic principles of biokinetics

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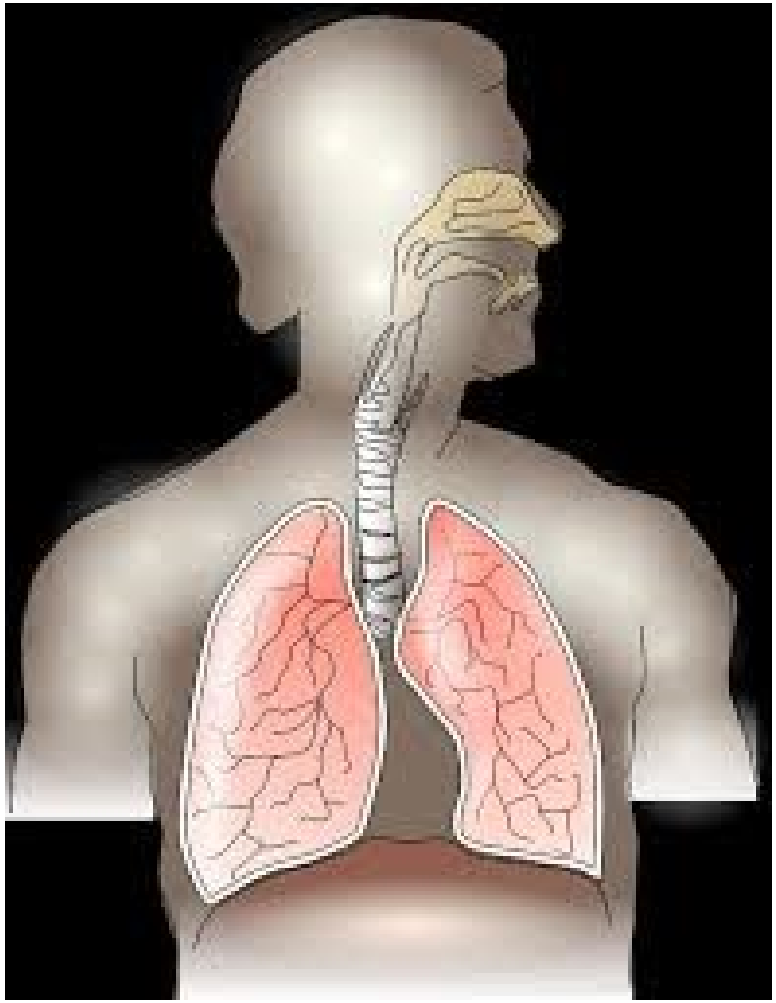
Toxicology is divided in two main 'chapters':

Toxicokinetics – what does the body to the substance

Toxicodynamics – what does the substance to the body

Toxicokinetics can be subdivided in four processes (ADME):

1. *Absorption*
2. *Distribution*
3. *Metabolism*
4. *Excretion*



Principles of biokinetics

ADME

Absorption

- *Inhalation (relative fast kinetics)*
- *Oral (relative fast kinetics and first pass effect)*
- *Dermal (much slower for most substances)*

Distribution

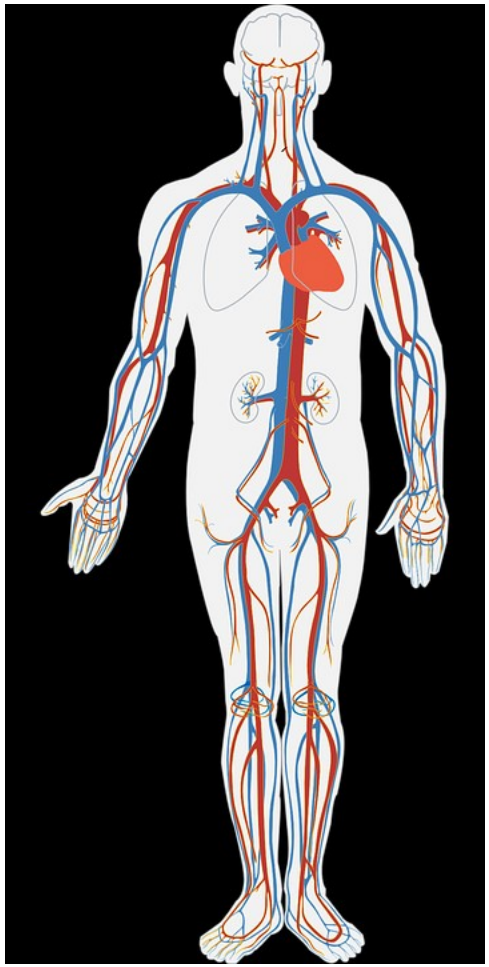
- *Protein-binding in the circulation*
- *Accumulation in adipose tissue*
- *Translocations (blood-brain, blood placenta)*

Metabolism

- *Activation and deactivation by enzymes*
- *Genetic polymorphisms*

Elimination

- *Lungs/Urine/feces*



Absorption by ingestion

First pass effect - Xenobiotics taken up through the gastrointestinal tract are absorbed in the intestine and will reach the liver through the vena porta. They will be metabolized before distributing to other organs.

Absorption by skin absorption or inhalation

Xenobiotics can reach target tissues before being metabolized (e.g. inhaled neurotoxic substances can reach the brain before detoxification in the liver)

Free in plasma vs. protein binding

A reduction of protein binding from 99 to 95 % results in a fivefold increase of the plasma concentration (from 1 to 5 %). E.g. role of metallothionine proteins regulate plasma concentration of metals

Translocations to circulation and targets

Lung lumen to lung tissue and circulation (e.g.ultrafine particles)

Blood to brain (e.g. neurotoxic substances)

Blood to placenta (e.g. reproduction toxic substances)

Storage in adipose tissue

Distribution of a substance between blood and adipose tissue, e.g. persons with a low BMI exposed to organic solvents are likely to have higher plasma peak levels compared to their colleagues with a high BMI

Metabolic deactivation and metabolic activation

Most substances have less toxic metabolites. Polycyclic aromatic hydrocarbons, n-hexane, amines, methylene chloride are examples of substances activated by metabolism

Limitations to enzyme capacity

High exposures (peak exposures) may lead to saturation of metabolic pathways and (enzymes) depletion of protective biomolecules (e.g. glutathion)

Genetic polymorphisms

Genetic makeup may lead attenuation of enzyme activity, e.g. alcohol dehydrogenase in ethnic Asians

Competitive inhibition

If two substrates depend on one enzyme for their metabolism competition may lead to a lower conversion rate. Note that in reality xenobiotics use alternative pathways for their metabolism

Induction of enzyme activity

High exposures over a longer time may lead to an adaptive higher activity of an enzyme. This may be related to the use of medication, alcohol but also environmental exposures, e.g. PCBs and dioxines are well known to induce CYP through the Ah receptor

Lungs

Most gases and volatile liquids are quickly cleared via the lungs (bring the victim into fresh air; support breathing using a non-rebreathing mask)

Most gases and volatile liquids have a short elimination half-life

Kidney

Substances can be made more water soluble by metabolism

Elimination can be boosted by certain drugs (e.g. Metals can be removed from the circulation by nonspecific chelator substances such as EDTA, DMPS)

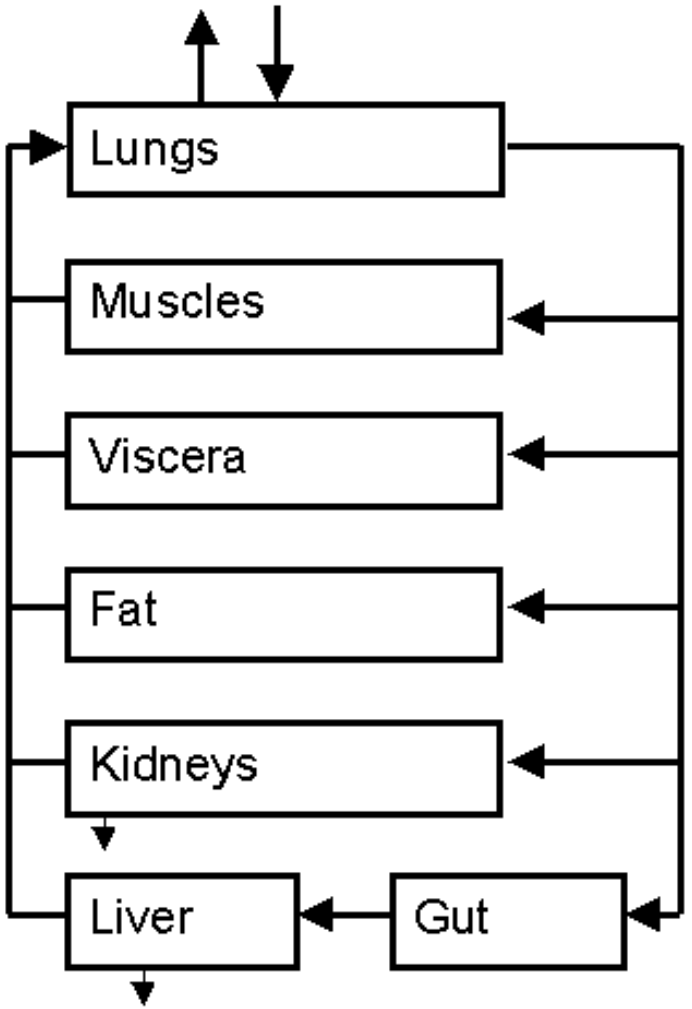
Biokinetic modelling

1. Toxicokinetic (TK) models

Mathematical equations describing the concentration time pattern of the parent and/or a metabolite

2. Physiology-Based Pharmaco-Kinetic (PBTK) models

A schematic representation of the circulation is used to describe the concentration time pattern of the parent and/or a metabolite



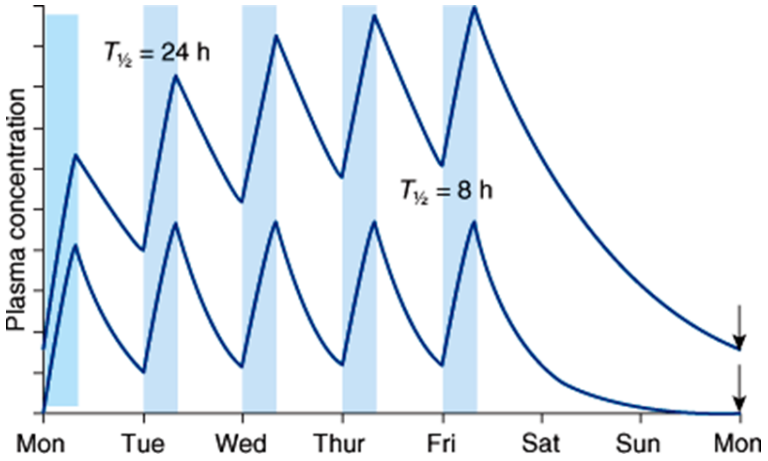
Applications of kinetic models

1. Calculation of target dose

Prediction of the concentration in a target tissue (target dose)

2. Retrospective dosimetry

Use a conversion factor to estimate the exposure from a dose estimate (e.g. biomarker value)



Take home

Kinetics change the fate of a xenobiotic (what the body does to a substance).

Biokinetic modelling supports interpretation of outcomes of HBM

Contacts

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Speaker's information

Paul T.J. Scheepers PhD works as associate professor at the Radboudumc, Nijmegen, The Netherlands. He received training in toxicology and occupational hygiene. In HBM4EU he is responsible for training activities as task leader in WP2. He is a member of the ethics board in WP1.

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