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Grundlagen und Anwendungen der Physiologie-basierten Toxikokinetik-Modellierung

47. Sitzung der HBM Komission
24./25. März 2014, Berlin

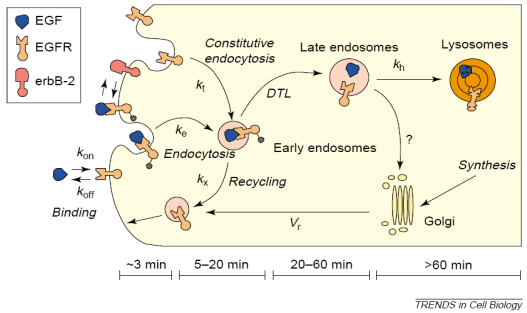
Outline

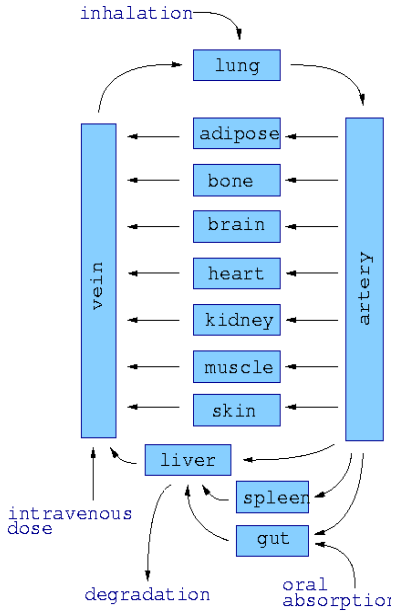
1. The potential
2. The structure of physiologically-based toxicokinetic models
3. Parameterization (incl. underlying model assumptions) and parameter sources
4. Example
5. Summary & References

The use of the term model in different contexts

- Model organisms
  - mouse as a model for human
  - yeast as a simple eukaryote

- Biological model:
  - interaction network
  - cartoon





- Mathematical model:
  - representation of biological model in terms of mathematical language
  - in our context deterministic differential or algebraic equations

$$V_{org}\frac{d}{dt}C_{org} = Q_{org}\cdot\left(C_{in} - \frac{C_{org}}{P^{t:p}}\right) - \mathrm{CL}\cdot C_{org}$$

The potential

external exposure

PBTK

systemic exposure (parent + metabolite)

exposure at site of action

MBTD

effect

PBTK modeling offers a way to

- integrate data from various sources
- study ‘what-if’ scenarios
- quantify the impact of variability and uncertainty
- identify critical parameters
- …

(PBTK= physiologically-based toxicokinetics, MBTD = mechanism-based toxicodynamics)

The potential

external exposure

PBTK

systemic exposure (parent + metabolite)

exposure at site of action

MBTD

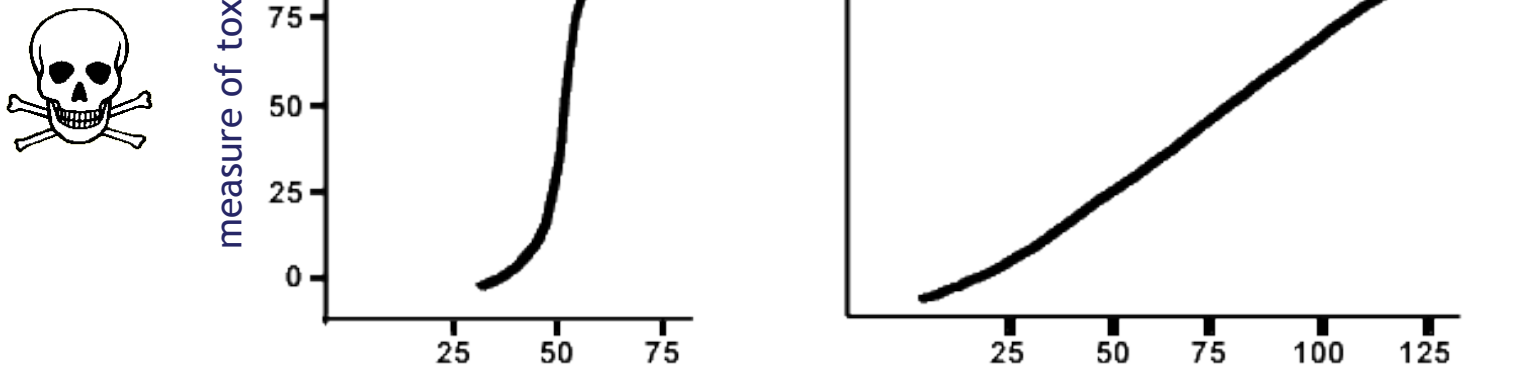
effect

Important to consider
- variability
- uncertainty
- species differences
- in vitro-in vivo differences

Most critical bottleneck for application: availability of parameter values

Toxicity measured in in vitro assays

- Cell-culture in vitro assay data



→ Conclusions for toxicological risk assessment?

- Link from external exposure to systemic concentration and/or concentration at target site?
- Measure of exposure: Cmax, AUC, ...? Parent compound or metabolite?

The structure of physiologically-based toxicokinetic models

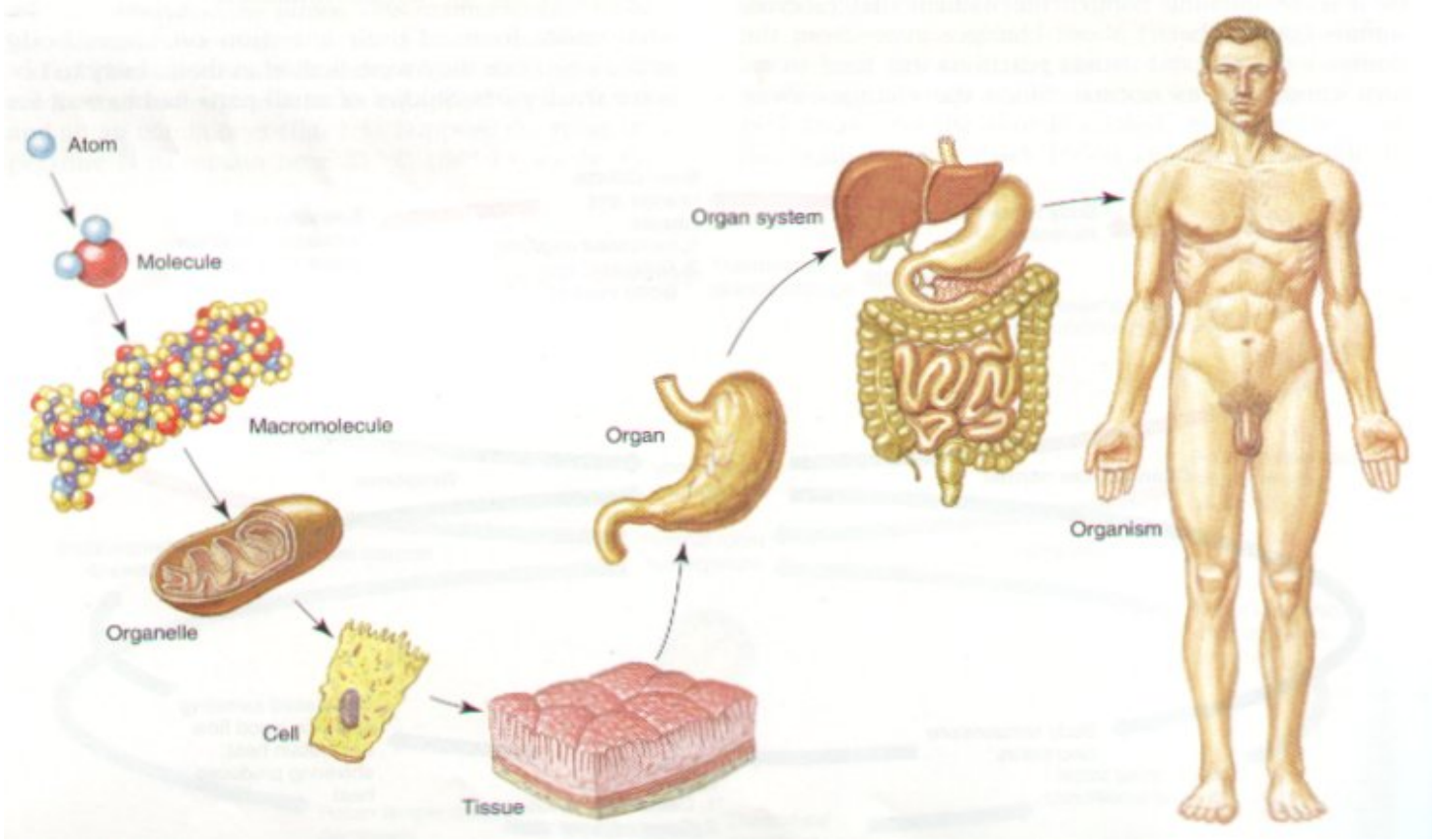
PBTK modelling

- Main features:
  - mechanistic model of principal ADME processes:
    (Absorption, Distribution, Metabolism, and Excretion)
  - compartments have anatomical interpretation
  - parameterized by physiological, anatomical and compound-specific data

- Long history in toxicokinetics
  - Teorell (1937) first PBPK model of therapeutically important, non-volatile chemical
  - Review: Gerlowski & Jain, *PBPK modelling: Principles and applications*, J Pharm Sci 72 (10), 1983

- More recent history in drug discovery and development
  - predominantly since 2000 due to large amount of parameters needed
  - breakthrough with seminal papers by Poulin&Theil, J Pharm Science (2000-2002)

Biological complexity



http:www.sirinet.net/~jgjohnson/intro.html

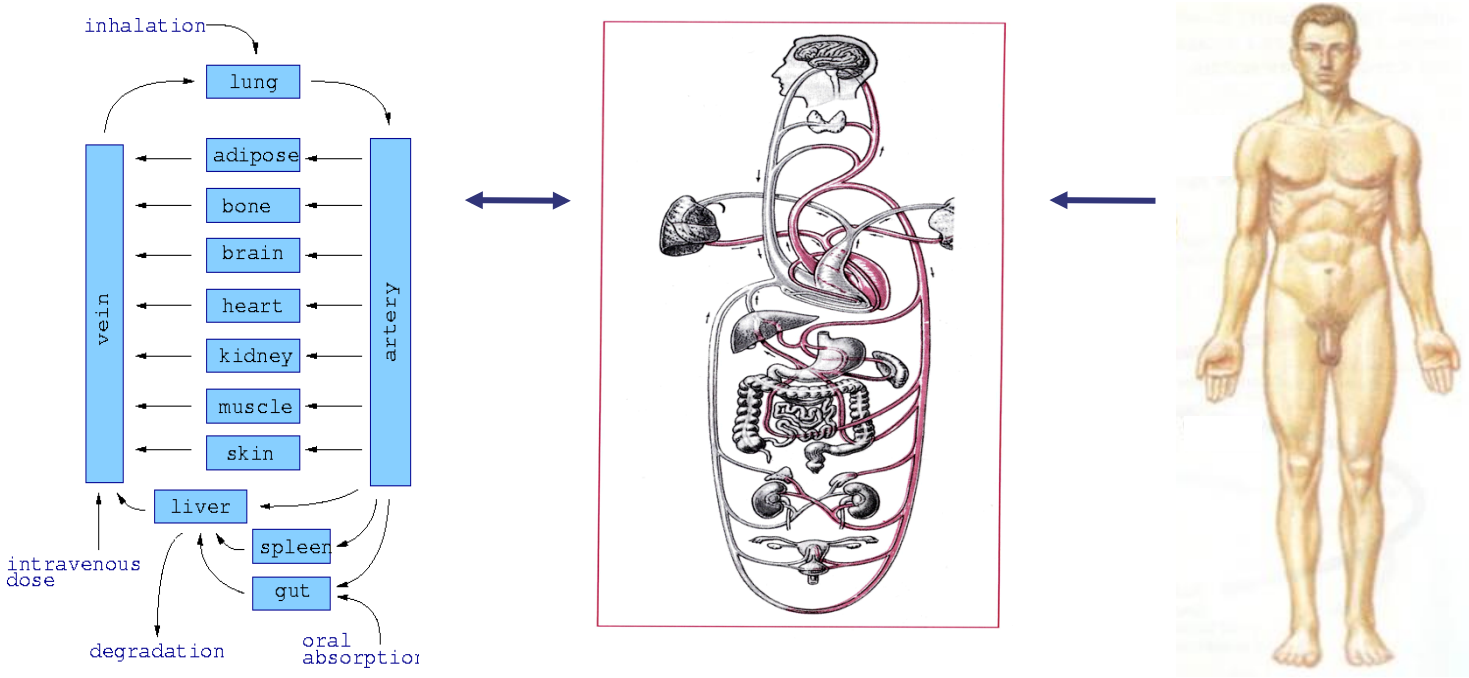
Molecular dynamics

Systems biology

Toxicokinetics

Physiologically based pharmacokinetic models

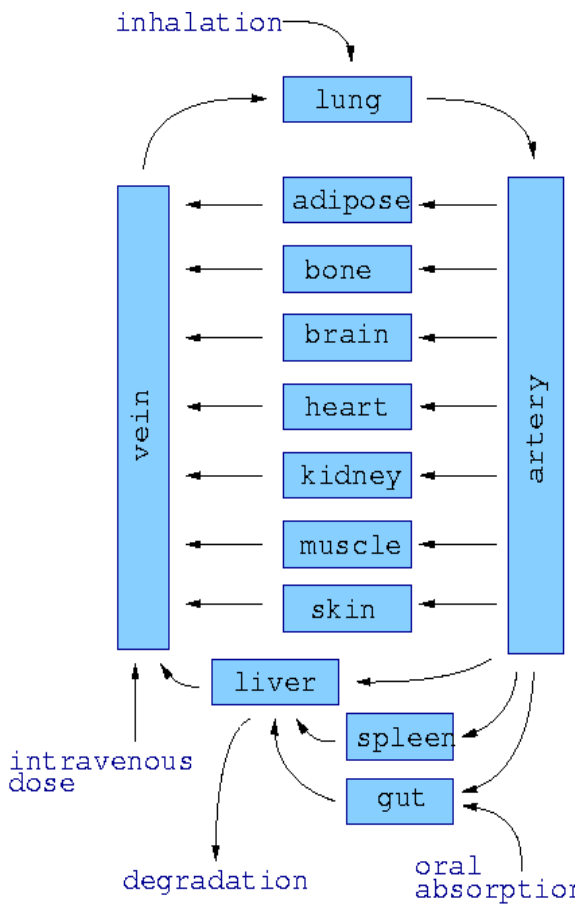
- **Top down approach**
  - organs, tissue and other spaces, interconnected by the blood flow



  - Mass balance equations (ODEs) for concentrations in tissues/organs

Poulin & Theil, J Pharm Sci. (2002); Luepfert & Reichel, Chem Biodiv, (2005);
Von Kleist, & Huisinga, J Pharmacokinet Pharmacodyn (2007)

Mass balance differential equations for each tissues/organ



Well-stirred tissue model:

$$V_{tis}\frac{d}{dt}C_{tis} = Q_{tis}\cdot\left(C_{in} - \frac{C_{tis}}{K_{tis}}\right) - CL_{\text{int}}\cdot C_{tis}$$

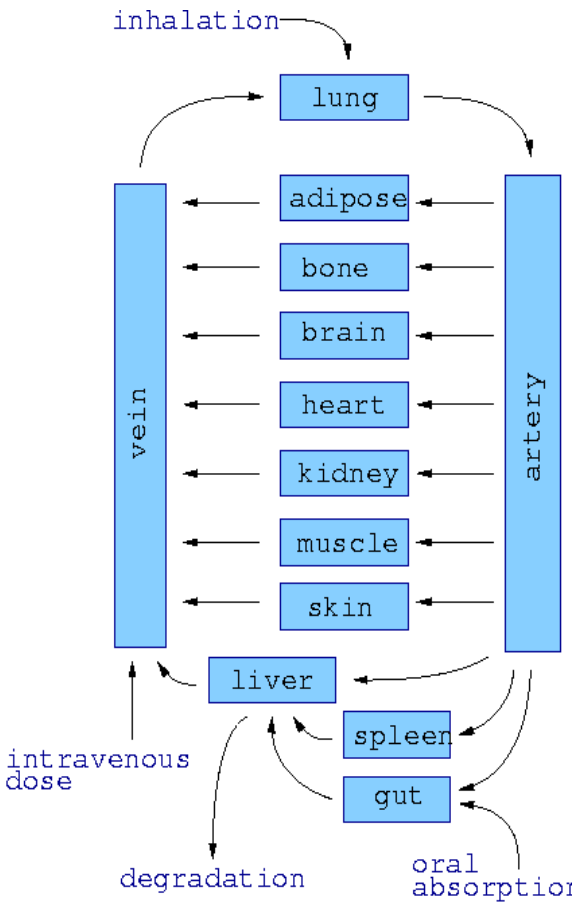
inflowing blood conc.

out-flowing blood conc.

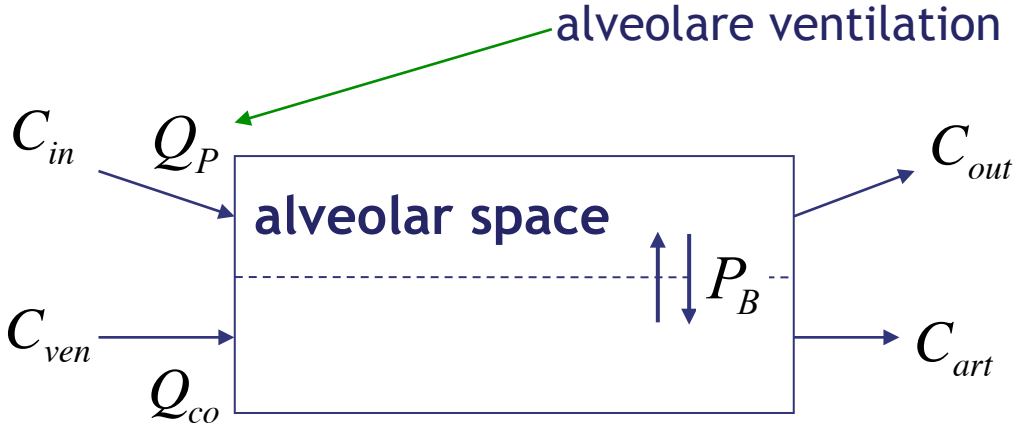
Steady-state tissue-to-blood partition coefficient:

$$K_{tis} = \frac{C_{tis,ss}}{C_{blood,ss}}$$

Mass balance differential equations for lung



Rate of change in lung:



Blood:air partition coefficient

$$P_{blo:air} = \frac{C_{art}}{C_{out}}$$

Poulin & Krishnan, Toxicol Appl Pharmacol (1996)

Parameterization and parameters sources

A rich source of data (human: adult and children)

Annals of the ICRP

ICRP PUBLICATION 89

Basic Anatomical and Physiological Data for Use in Radiological Protection: Reference Values

Editor
J. VALENTIN

PUBLISHED FOR

The International Commission on Radiological Protection

By

PERGAMON

Accounting for inter-individual variability

Citation: CPT: Pharmacometrics & Systems Pharmacology (2012) 1, e4;

www.nature.com/psp

ORIGINAL ARTICLE

Modeling Interindividual Variability in Physiologically Based Pharmacokinetics and Its Link to Mechanistic Covariate Modeling

W Huisinga[1], A Solms[1,2], L Fronton[1,2] and S Pilari[2,3,4]

A rich source of data (animals: mice and rats)

Toxicology and Industrial Health, Vol. 13, No. 4, 1997

PHYSIOLOGICAL PARAMETER VALUES FOR PHYSIOLOGICALLY BASED PHARMACOKINETIC MODELS

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Harvard School of Public Health
Boston, Massachusetts

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U.S. Environmental Protection Agency
Washington, DC

Parameterization of PBPK models

Species specific

- blood flows, organ volumes

Drug specific

- intrinsic clearance (CLint)
- tissue-to-blood partition coefficients

- Administration (dose, route, etc)

Rate of change in tissue:

$$V_{tis}\frac{d}{dt}C_{tis} = Q_{tis}\cdot\left(C_{in} - \frac{C_{tis}}{K_{tis}}\right) - CL_{\text{int}}\cdot C_{tis}$$

inflowing blood conc.

out-flowing blood conc.

Tissue-to-blood partition coefficient:

$$K_{tis} = \frac{C_{tis,ss}}{C_{blood,ss}}$$

A-priori prediction of partition coefficients

- Idea: Consider tissue as composition of constituents important for xenobiotic distribution

tissue

Kandinskys *Roten Fleck* aufräumen

“Kunst aufgeräumt“ by Ursus Wehrli

tissue constituents

More mathematical

- Ansatz based on mass balance equation

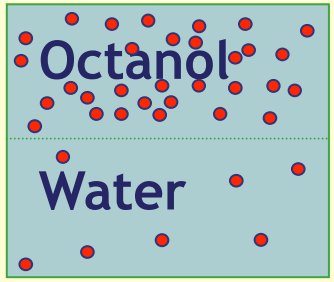
interstitial water
binding proteins
cellular water
neutral lipids
phospholipids

$$A_\mathrm{t} = A_\mathrm{wi} + A_\mathrm{pr} + A_\mathrm{wc} + A_\mathrm{nl} + A_\mathrm{ph}$$

$$= V^i\,(C_\mathrm{ui} + C_\mathrm{pr}) + V^\mathrm{wc} C_\mathrm{uc} + V^\mathrm{nl} C_\mathrm{nl} + V^\mathrm{ph} C_\mathrm{ph}$$

$$\frac{C_\mathrm{t}}{C_\mathrm{up}} = V^{i:\mathrm{t}}\left(1 + \frac{C_\mathrm{pr}}{C_\mathrm{up}}\right) + V^{\mathrm{wc}:\mathrm{t}}\left(1 + V^{\mathrm{nl}:\mathrm{t}}\frac{C_\mathrm{nl}}{C_\mathrm{up}} + V^{\mathrm{ph}:\mathrm{t}}\frac{C_\mathrm{ph}}{C_\mathrm{up}}\right)$$

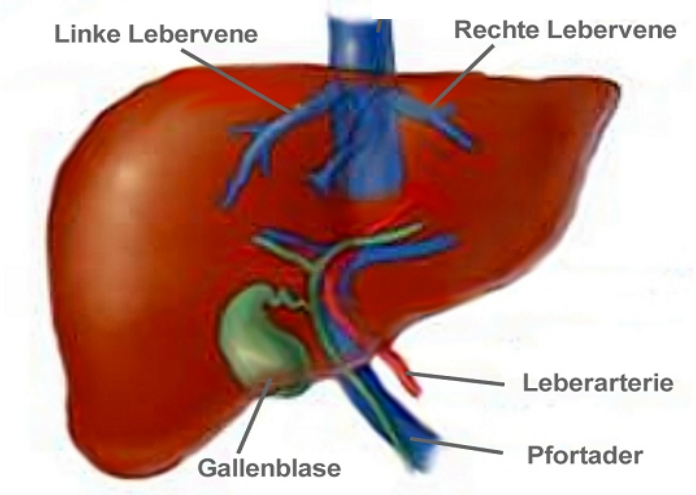
Approximate partition coefficients based on *in vitro* data

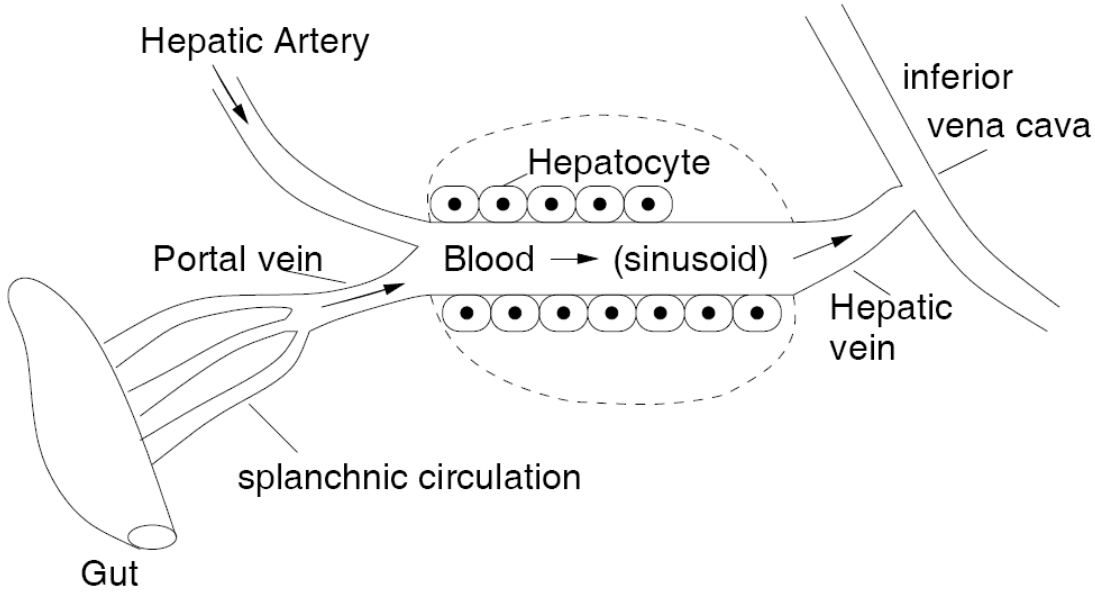


***in vitro* assay**

$$P_{o:w} = \frac{C_\mathrm{octanol}}{C_w} \approx \frac{C_\mathrm{nl}}{C_\mathrm{up}}$$

Hepatic metabolism





intrinsic hetpatic clearance
(potentially also saturable)

$$V_{tis}\frac{d}{dt}C_{tis} = Q_{tis}\cdot\left(C_{in} - \frac{C_{tis}}{K_{tis}}\right) - CL_{\text{int}}\cdot C_{tis}$$

Determining hepatic intrinsic clearance from in vitro data

- Hepatocyte assay

$$\mathrm{CL_{int}}(in\ vitro) \quad \text{in} \quad \left[\frac{\mu L}{\min} \text{ per } 10^6 \text{ cells}\right]$$

- Microsomal assay

$$\mathrm{CL_{int}}(in\ vitro) \quad \text{in} \quad \left[\frac{\mu L}{\min} \text{ per } \mu g \text{ microsomes}\right]$$

- Scaling approach to hepatic intrinsic clearance

$$\mathrm{CL_{int}}(in\ vivo) \quad = \quad \mathrm{OW_{liv}} \cdot \mathrm{SF} \cdot \mathrm{CL_{int}}(in\ vitro)$$

- with scaling factors

	hepato-cellularity	microsomal recovery
human	107-120 [10^6 hepatocytes/g liver]	33-52.5 [mg protein/g liver]
rat	109-135 [10^6 hepatocytes/g liver]	45-60 [mg protein/g liver]

Parameterization of PBPK models

Species specific

- blood flows, organ volumes
- tissue composition data

Drug specific

- intrinsic clearance CLint
- blood:plasma ratio B:P
- fraction unbound fuP
- octanol-water coeff Pow
- pKa value

- Administration (dose, route, etc)

Rate of change in tissue:

$$V_{tis}\frac{d}{dt}C_{tis} = Q_{tis}\cdot\left(C_{in} - \frac{C_{tis}}{K_{tis}}\right) - CL_{\text{int}}\cdot C_{tis}$$

Tissue-to-blood partition coefficient:

$$K_{tis} = \frac{C_{tis,ss}}{C_{blood,ss}}$$

Poulin/Theil (2000), Rodgers/Rowland (2005), Schmidt (2008)

Example

Example

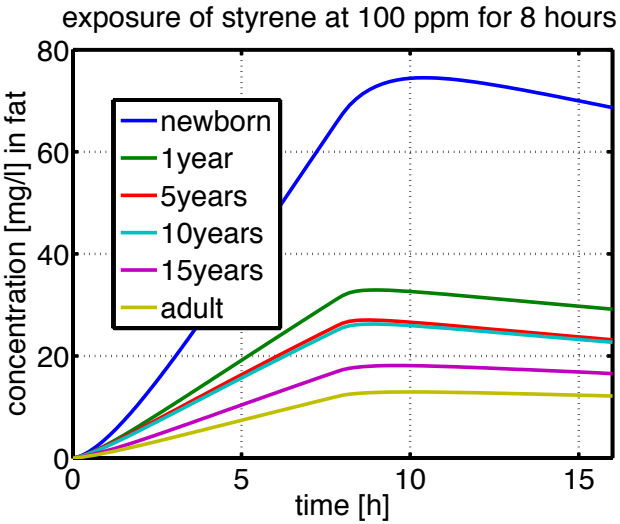
Arch Toxicol (2005) 79: 63–73
DOI 10.1007/s00204-004-0599-3

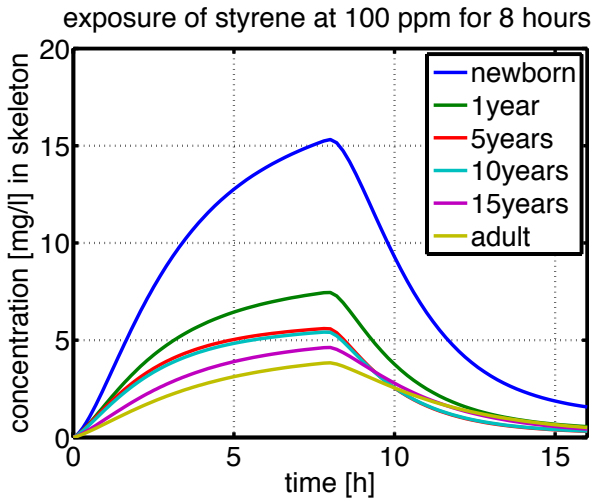
TOXICOKINETICS AND METABOLISM

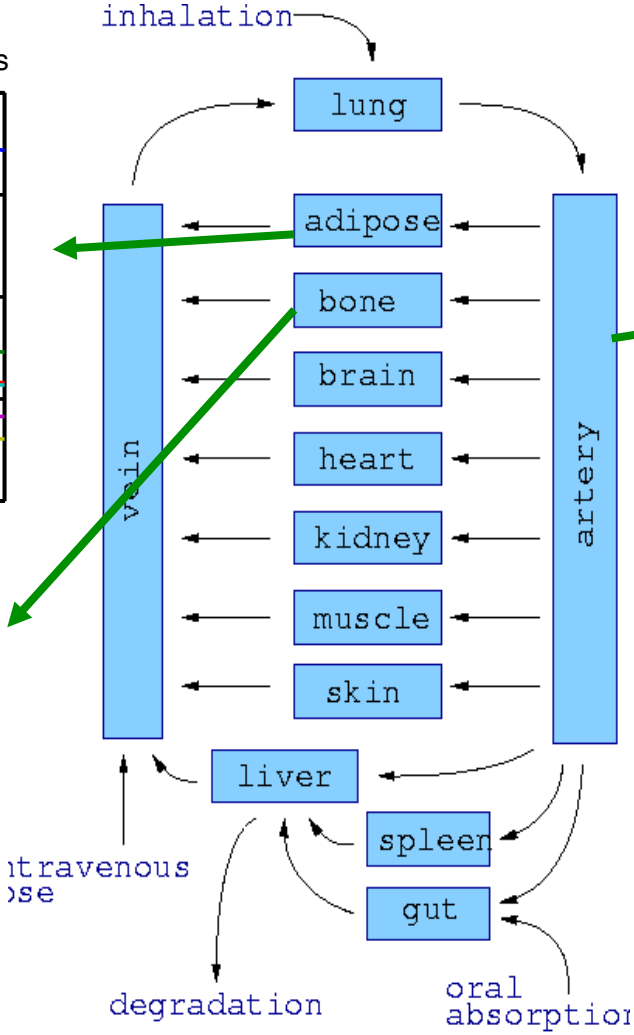
Klaus Abraham · Hans Mielke · Wilhelm Huisinga
Ursula Gundert-Remy

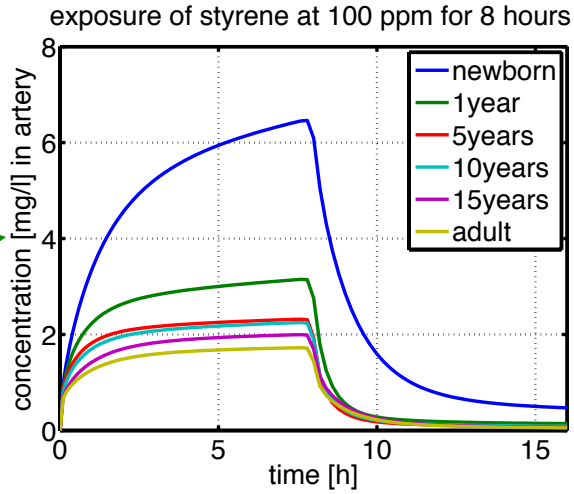
Elevated internal exposure of children in simulated acute inhalation of volatile organic compounds: effects of concentration and duration

Example: exposure of styrene at 100 ppm for 8h





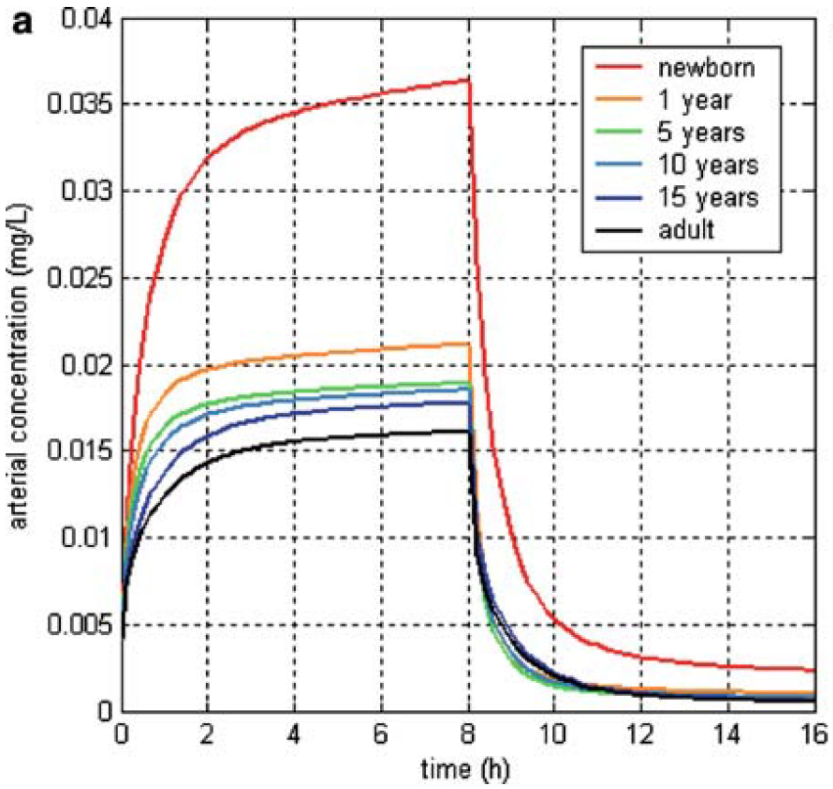




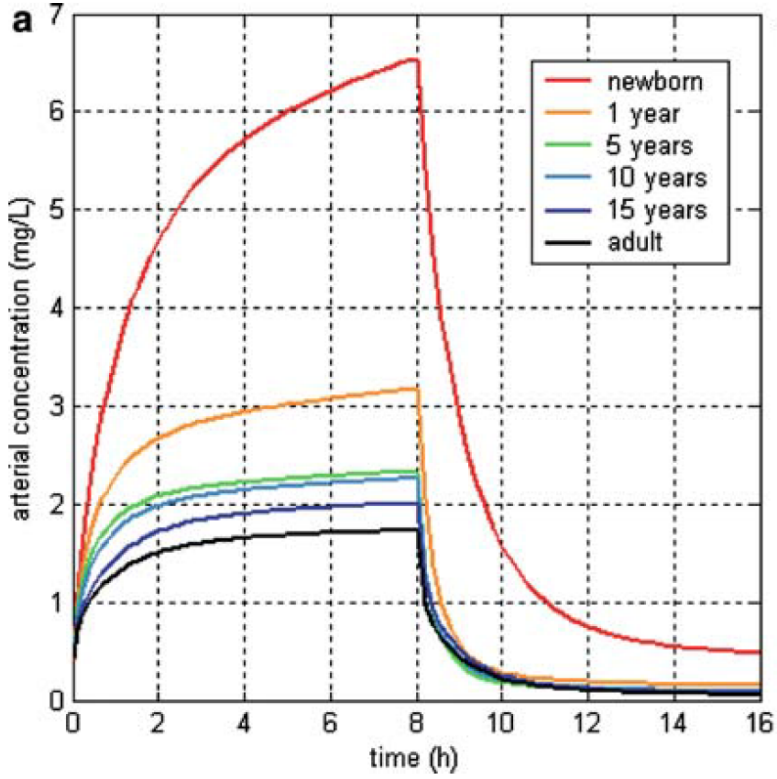
→ different concentrations and profiles in different tissues/organs

Non-linear relationship between external and systemic exposure

1 ppm

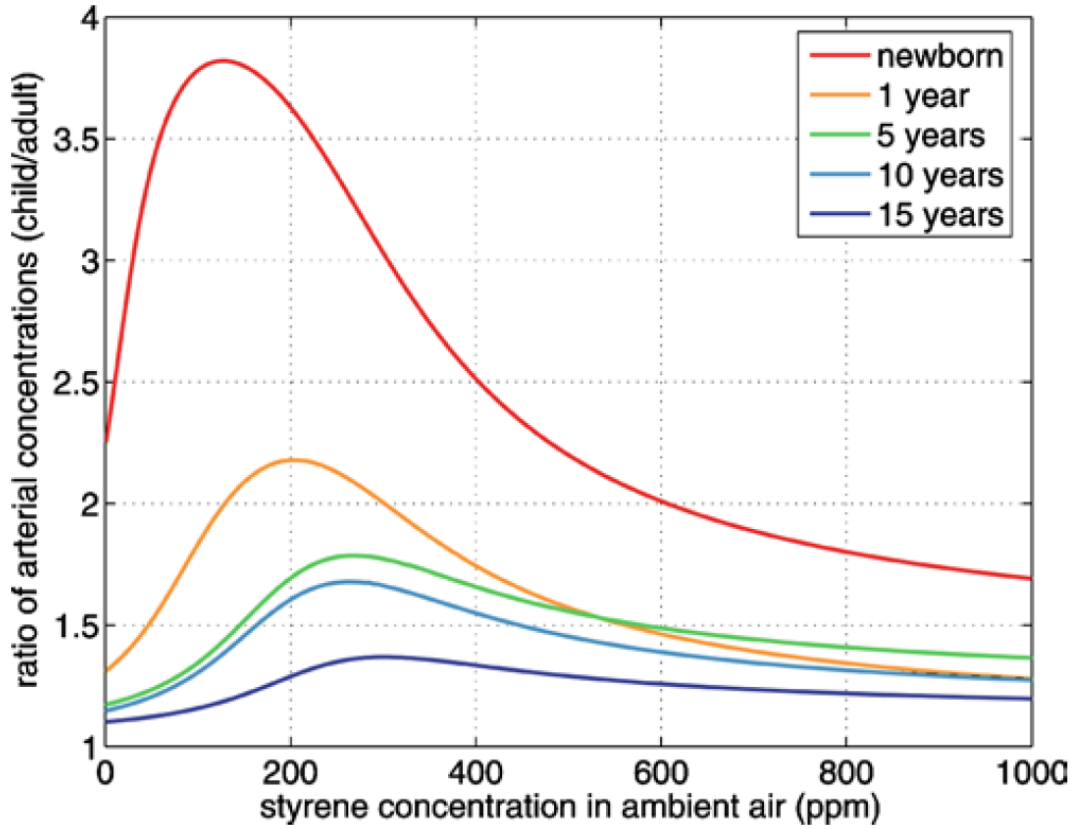


100 ppm



- Underlying reason: saturable metabolism

Exposure ratio Child:Adult depending on external exposure (at 8h)



- exposure ratios also depend on time.
- Sensitivity analysis showed that predictions are most sensitive to alveolar ventilation rate with 20% change of Q_p → 14% change in ratio(newborn)

Further examples

There are also a large number of good examples of PBPK models which describe the kinetics of important environmental contaminants, including methylene chloride (Andersen *et al.*, 1987a, 1991, 1994), trichloroethylene (Fisher *et al.*, 1991; Fisher and Allen, 1993; Allen and Fisher, 1993), chloroform (Corley *et al.*, 1990; Reitz *et al.*, 1990), 2-butoxyethanol (Johanson, 1986), kepone (Bungay *et al.*, 1981), polybrominated biphenyls (Tuey and Matthews, 1980), polychlorinated biphenyls (Lutz *et al.*, 1984) and dibenzofurans (King *et al.*, 1983), dioxins (Leung *et al.*, 1988; Kohn et al., 1993; Andersen *et al.*, 1997), lead (O'Flaherty, 1991a,b,c,1993,1995b), arsenic (Mann *et al.*, 1996a,b), and methylmercury (Farris *et al.*, 1993).

Gentry, Clewell, Anderson, ENVIRON, manuscript

The potential

external exposure

PBTK

systemic exposure (parent + metabolite)

exposure at site of action

MBTD

effect

Important to consider
- variability
- uncertainty
- species differences
- in vitro-in vivo differences

Most critical bottleneck for application: availability of parameter values

Some references

- Gerlowski & Jain, *PBPK modelling: Principles and applications*, J Pharm Sci 72 (10), 1983
- Poulin & Krishnan/Theil, 1995-2002
- K. Abraham, H. Mielke, W. Huisinga and U. Gundert-Remy, *Elevated Internal Exposure of Children in Simulated Acute Inhalation of Volatile Organic Compounds: Effects of Concentration and Duration*, Arch Toxicol 79 (2005)
- M. Reddy et al, *Physiologically-based Pharmacokinetic Modeling*, Wiley 2005
- WHO, *Characterization and Application of PBPK models in Risk Assessment*, 2010
- H. Mielke, U. Gundert-Remy, Physiologically Based Toxicokinetic Modelling as a Tool to Support Risk Assessment: Three Case Studies, J Toxicology, 2012
- and many more.

Acknowledgement

- U. Gundert-Remy (Berlin)
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- For information:

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