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

\[ V_{\text{org}} \frac{d}{dt} C_{\text{org}} = Q_{\text{org}} \cdot \left( C_{\text{in}} - \frac{C_{\text{org}}}{P_{i,p}} \right) - CL \cdot C_{\text{org}} \]
The potential

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 \[\xrightarrow{\text{PBTK}}\] systemic exposure (parent + metabolite) \[\xrightarrow{\text{MBTD}}\] 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

\[ \text{concentration of xenobiotic} \]

→ 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

• More recent history in drug discovery and development
  – predominantly since 2000 due to large amount of parameters needed
Biological complexity

Molecular dynamics  Systems biology  Toxicokinetics

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

Mass balance differential equations for each tissues/organ

Well-stirred tissue model:

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

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:

\[ \frac{dC}{dt} = Q_P P_{\text{blo:air}} P_{\text{alveolare ventilation rate}} \]

Blood:air partition coefficient

\[ P_{\text{blo:air}} = \frac{C_{\text{art}}}{C_{\text{out}}} \]

Parameterization and parameters sources
A rich source of data (human: adult and children)
Accounting for inter-individual variability

ORIGINAL ARTICLE

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

W Huisingsa¹, A Solms¹,², L Fronton¹,² and S Pilari²,³,⁴
A rich source of data (animals: mice and rats)
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:

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

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**

**tissue constituents**

- water
- neutral lipids
- phospholipids
- proteins
- etc

“Kunst aufgeräumt” by Ursus Wehrli
More mathematical

- Ansatz based on mass balance equation

\[
A_t = A_{wi} + A_{pr} + A_{wc} + A_{nl} + A_{ph}
\]

\[
= V^i (C_{ui} + C_{pr}) + V^{wc} C_{uc} + V^{nl} C_{nl} + V^{ph} C_{ph}
\]

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

Approximate partition coefficients based on in vitro data

\[
P_{o:w} = \frac{C_{octanol}}{C_w} \approx \frac{C_{nl}}{C_{up}}
\]

in vitro assay
Hepatic metabolism

\[ V_{tis} \frac{d}{dt} C_{tis} = Q_{tis} \cdot \left( C_{in} - \frac{C_{tis}}{K_{tis}} \right) - CL_{int} \cdot C_{tis} \]
Determining hepatic intrinsic clearance from in vitro data

- Hepatocyte assay
  \[ \text{CL}_{\text{int}}(in \text{ vitro}) \text{ in } \left[ \frac{\mu L}{\min} \text{ per } 10^6 \text{ cells} \right] \]

- Microsomal assay
  \[ \text{CL}_{\text{int}}(in \text{ vitro}) \text{ in } \left[ \frac{\mu L}{\min} \text{ per } \mu g \text{ microsomes} \right] \]

- Scaling approach to hepatic intrinsic clearance
  \[ \text{CL}_{\text{int}}(in \text{ vivo}) = OW_{\text{liv}} \cdot SF \cdot \text{CL}_{\text{int}}(in \text{ vitro}) \]

- with scaling factors

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<tr>
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<th>hepato-cellularity</th>
<th>microsomal recovery</th>
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</thead>
<tbody>
<tr>
<td>human</td>
<td>107-120 [10^6 hepatocytes/g liver]</td>
<td>33-52.5 [mg protein/g liver]</td>
</tr>
<tr>
<td>rat</td>
<td>109-135 [10^6 hepatocytes/g liver]</td>
<td>45-60 [mg protein/g liver]</td>
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</tbody>
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Parameterization of PBPK models

Species specific
- blood flows, organ volumes
- tissue composition data

Drug specific
- intrinsic clearance $CL_{int}$
- blood:plasma ratio $B:P$
- fraction unbound $fuP$
- octanol-water coeff $Pow$
- pKa value
- Administration (dose, route, etc)

Rate of change in tissue:

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

Tissue-to-blood partition coefficient:

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

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

Prof. Wilhelm Huisinga
Non-linear relationship between external and systemic exposure

- 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 $Q_p \rightarrow 14\%$ 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 (Tuyet 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 → systemic exposure (parent + metabolite) → exposure at site of action → effect

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

Most critical bottleneck for application: availability of parameter values
Some references

- Poulin & Krishnan/Theil, 1995-2002
- WHO, *Characterization and Application of PBPK models in Risk Assessment*, 2010
- and many more.
Acknowledgement

- U. Gundert-Remy (Berlin)
- K. Abraham, H. Mielke (BfR, Berlin)

- For information:

PhD Program PharMetrX, bridging pharmacy and mathematics at the Freie Universität Berlin and the Universität Potsdam/Germany, supported by