Update on PBTK model-based derivation of HBM-1 values for ethylene glycol monoethyl ether (acetate)
Outline

1. Application scenarios of PBTK modeling
2. Example: Ethylene glycol ethyl ether (EGEE)
   • Points to be discussed
     – Generic PBTK model
     – Pregnancy and the definition of HBM values
     – Non-linear relationship between external exposure and internal exposure
   • Proposal for HBM-1 value for EGEE, EGEEA and EGME (revisited)
Application of PBTK modeling in the derivation of HBM values

- *Inter-species extrapolation for TK*
  - e.g., NO(A)EL, TDI, ...
  - by prediction of systemic/target tissue exposure (dose, AUC, Cpeak)

- Prediction of the *concentration in urine*
- Prediction of *intra-species UF(kinetic)*
  - inter-individual variability
- Assessment of *critical subpopulations*
  - children, pregnant women

- General insight by analyzing *what-if scenarios*
Example: Ethylene glycol ethyl ether (EGEE)

Based on the PBTK model by Gargas et al, (2000) and intra-species UF of Sweeney et al (2001)
Ethylene glycol ethyl ether (EGEE)

- CAS No 110-80-5, IUPAC name: 2-ethoxyethanol

- metabolized to 2-ethoxy-acetic acid (2-EAA) and EG

- rat
  - critical study: Doe 1984, developmental effects
  - NOEL 50 ppm (6h/day on GD 6-15)

- human
    - NAEL = 25 ppm (consequently, PBTK-based inter-species UF(TK) = 2)
    - OEL = 2 ppm

- Only inhalation considered, no dermal absorption

Model structure almost surely not consistent with implementation by Gargas et al.!
Validation on human data (Groeseneken et al, Br J Ind Med 1986)

- EGEE administered to group 1

Exposure protocol:
4 repeated exposures of EGEE (50min exposure, 10min break) in male volunteers

![Diagram showing urinary excretion of ethoxyacetic acid during and after exposure to EGEE at rest. Data are means ± SD for five subjects. Shaded area indicates exposure period.]

**Table 1  General characteristics of the subjects**

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>23 ± 4</td>
<td>21 ± 2</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>70.7 ± 10.1</td>
<td>66.1 ± 7.6</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>181.4 ± 3.7</td>
<td>178.4 ± 3.8</td>
</tr>
<tr>
<td>% Body fat</td>
<td>11.7 ± 3.5</td>
<td>8.9 ± 2.8</td>
</tr>
</tbody>
</table>

Fig 1  Urinary excretion of ethoxyacetic acid during and after exposure to EGEE at rest. Data are means ± SD for five subjects. Shaded area indicates exposure period.
Exposure of a female (58.6kg, Q_{alv}=5.4 L/min) to EGEE

NOEL=25ppm

intermittent exposure 25ppm (8h/d,5d/w)

\[ \text{fac} = \frac{8}{24} \cdot \frac{5}{7} = \frac{5}{21} \]

constant 6ppm (24h/d)

point for discussion: intra-individual variability and its consequences for HBM values

predictions based on original Gargas model
Exposure of a female (58.6 kg, $Q_{alv}=5.4$ L/min) to EGEE

NOEL = 25 ppm

intermittent exposure
25 ppm (8h/d, 5d/w)

constant 6 ppm (24h/d)

$\text{fac} = \frac{8}{24} \cdot \frac{5}{7} = \frac{5}{21}$

renal excretion: 73 mg EAA/day

predictions based on original Gargas model

PBTK-model based prediction
Uncertainty factors (Sweeney et al 2001)

- **AF toxicodynamic**
  - inter-species = 2.5 (default)
  - intra-species = 3.2 (default)
- **AF toxicokinetic**
  - inter-species: not needed, since based on PBTK extrapolation rat-to-human
  - intra-species = 1.8 (PBTK-based Monte Carlo analysis)
- **Further AF (to be discussed).**

- **total AF = 14.4 = 2.5 * 3.2 * 1.8**

**Note:**
- default inter-species AF for TK = 4 vs. 2 = PBTK-based inter-species extrapolation factor (extrapolation of rat NOEL=50ppm to human NOAL=25ppm, Sweeney 2001)
- default intra-species AF for TK = 3.2 vs. 1.8 = PBTK-based intra-species UF for TK
- overall: default TK-AF = 4 * 3.2 = 12.8 vs 3.6 = 2 * 1.8 = PBTK-based UF
Derivation of HBM values (1\textsuperscript{st} proposal)

- intermittent exposure (8h/d, 5d/w): 25ppm
- constant exposure (24h/d): 6ppm

- resulting renal excretion of EAA: 73mg EAA/day
- total AF = 14.4 (Sweeney 2001)

- resulting HBM-1 value = renal excretion/UF = \textbf{5.1} mg EAA/day (in urine)

- HBM-1 value corresponds to 6ppm/14.4 = 0.4 ppm (24h/d)
- OEL according to Sweeney et al (2001) 25ppm/14 = 2 ppm (8h/d, 5d/w)
Some points for discussion
Some points for discussion

- Generic PBTK model
- Pregnancy and the definition of HBM values
- Non-linear relationship between external exposure and internal exposure
Generic PBTK model

- Make use of established, more physiological representation in PK

Parameter values (human)

<table>
<thead>
<tr>
<th>Percentage of body weight</th>
<th>Day 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>2.4</td>
</tr>
<tr>
<td>Fat</td>
<td>27.6</td>
</tr>
<tr>
<td>Slowly perfused</td>
<td>48.7</td>
</tr>
<tr>
<td>Richly perfused</td>
<td>3.7</td>
</tr>
<tr>
<td>Blood</td>
<td>5.9</td>
</tr>
</tbody>
</table>

Flows

- Cardiac output (liters/h/kg^{0.74})
- Alveolar ventilation (liters/h/kg^{0.74})

- Sum = 88.3%
- No difference between sex

ICRP: %Fat 32 (f) vs. 20 (m)
Proposal:
- use this established generic PBPK model
- choose \{hea, kid, spl, gut\} = richly perfused, \{mus, ski, bon\} = slowly perfused

Generic PBPK model

reference values (adult/children, m/f)
Generic PBTK prediction

- Allows to take into account details of study population for model validation
- Ex: exposure of EGME to 7 male volunteers (Groeseneken et al, 1989)

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (years)</th>
<th>Weight (kg)</th>
<th>Height (cm)</th>
<th>Pulmonary ventilation (l/min)</th>
<th>Oxygen consumption (l/min)</th>
<th>Respiratory frequency (min⁻¹)</th>
<th>Heart rate (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>24</td>
<td>72</td>
<td>187.5</td>
<td>8.2 ± 0.9</td>
<td>0.31 ± 0.04</td>
<td>13.7 ± 1.8</td>
<td>73 ± 4</td>
</tr>
<tr>
<td>2</td>
<td>31</td>
<td>80</td>
<td>185</td>
<td>8.2 ± 0.4</td>
<td>0.30 ± 0.05</td>
<td>11.0 ± 1.3</td>
<td>59 ± 5</td>
</tr>
<tr>
<td>3</td>
<td>27</td>
<td>78</td>
<td>181</td>
<td>7.3 ± 0.5</td>
<td>0.30 ± 0.04</td>
<td>11.4 ± 0.4</td>
<td>56 ± 4</td>
</tr>
<tr>
<td>4</td>
<td>26</td>
<td>85.5</td>
<td>182.5</td>
<td>8.4 ± 0.4</td>
<td>0.33 ± 0.04</td>
<td>11.6 ± 1.7</td>
<td>65 ± 5</td>
</tr>
<tr>
<td>5</td>
<td>25</td>
<td>85</td>
<td>190</td>
<td>7.0 ± 0.4</td>
<td>0.26 ± 0.05</td>
<td>11.6 ± 2.2</td>
<td>50 ± 4</td>
</tr>
<tr>
<td>6</td>
<td>24</td>
<td>78</td>
<td>189</td>
<td>9.8 ± 0.5</td>
<td>0.34 ± 0.06</td>
<td>14.1 ± 0.8</td>
<td>64 ± 4</td>
</tr>
<tr>
<td>7</td>
<td>23</td>
<td>63</td>
<td>172</td>
<td>7.5 ± 0.8</td>
<td>0.26 ± 0.04</td>
<td>11.6 ± 1.2</td>
<td>66 ± 4</td>
</tr>
<tr>
<td>Mean</td>
<td>26 ± 3</td>
<td>77 ± 8</td>
<td>184 ± 6</td>
<td>8.0 ± 0.6</td>
<td>0.30 ± 0.05</td>
<td>12.1 ± 1.3</td>
<td>62 ± 6</td>
</tr>
</tbody>
</table>
Generic PBTK prediction for EGME (Groeseneken et al, 1989)

Exposure protocol:
4 repeated exposures of EGME
(50min exposure, 10min break)
in male volunteers

Generic PBTK prediction for EGME (Groeseneken et al, 1989)

Exposure protocol:
4 repeated exposures of EGME (50min exposure, 10min break) in male volunteers

Kmet_MAA as in Gargas (4.9)
Kmet_MAA changed (4.9→20)
Kmet_MAA changed (4.9→20)

Pregnancy and the definition of HBM values
Pregnancy and the definition of HBM values

- How to deal with pregnancy within the concept of HBM values (in general lifelong exposition)?

- How to account for physiological changes during pregnancy?

**respiratory function**

ICRP report No 89 (2002), p. 236

**renal function**

ICRP report No 89 (2002), p. 238
Non-linear relationship between external and internal exposure
Increased conversion of EGEEA → EGEE at higher concentrations

Exposure protocol:
4 repeated exposures of EGEEA (50min exposure, 10min break) in male volunteers

The observation that retention increased when exposure concentration was higher is rather unusual. Depending on the degree of saturation of the metabolic clearance mechanisms, retention is expected at most to remain constant or to decrease. Since the first step in EGEE-Ac metabolism is the conversion to EGEE by (plasma) esterases, the absorbed EGEE-Ac has to compete for these enzymes with their normal substrates. With increasing plasma concentrations, EGEE-Ac may compete more favourably for the available esterase. As a consequence, EGEE-Ac may be cleared from the blood at a higher rate resulting in a higher alveolocapillary concentration gradient.

Generic PBTK prediction for EGEEA (Groeseneken et al, 1987)

Exposure protocol:
4 repeated exposures of EGEEA
(50min exposure, 10min break)
in male volunteers

- original Gargas parameters and individual covariates as in Groeseneken
- no nonlinearity metabolism

14 mg/m3
28 mg/m3
50 mg/m3
Resulting HBM-1 values for EGEE, EGEEA and EGME (revisited)

based on rat NOELs and AF accounting for inter- and intra-species differences
Generic PBTK prediction for **EGEE**: female (60kg, Qalv=5.5 L/min)

- Intermittent exposure: 25ppm (8h/d, 5d/w)
- Constant 6 ppm (24h/d)

Renal excretion: 76 mg EAA/day

\[ \text{HBM-1 (EGEE)} = 5.2 \text{ mg EAA/day (in urine)} \]

\[ \text{UF 14.4} \]

\[ \text{1.2 L/day urine} \]

\[ \text{HBM-1 (EGEE)} = 4.3 \text{ mg EAA/L (in urine)} \]

(Note: slight difference to renal excretion of 73mg EAA/day on p.7 due to different PBTK model)
Ethylene glycol ethyl ether acetate (EGEEA)

- CAS No 111-15-9, IUPAC name: 2-Ethoxyethylacetat

\[
\text{CH}_3\text{CH}_2\text{O} - \text{O} - \text{CH}_2\text{CH}_2\text{OH}
\]

- metabolized to EGEE via plasma esterases
  \[\rightarrow \text{HBM-1 value for joint exposure to EGEEA and EGEE reasonable}\]
- rat
  - critical study: Doe 1984, developmental effects
  - NOEL 50 ppm (6h/day on GD 6-15)
- human
  - extrapolation from rat to human (Gargas et al, Tox Appl Pharmacol 165, 2000)
    - NOAL = 25 ppm (blood AUC) or NOAL 40 ppm (Cmax blood)
    - OEL = 2 ppm, based on NOEL=25ppm
Generic PBTK prediction for **EGEEA**: female (60kg, Qalv=5.5 L/min)

intermittent exposure 25ppm (8h/d,5d/w)

constant 6 ppm (24h/d)

renal excretion: 76 mg EAA/day

\[ \text{HBM-1 (EGEEA)} = 5.2 \text{ mg EAA/day (in urine)} \]

\[ \text{UF 14.4} \]

1.2 L/day urine

\[ \text{HBM-1 (EGEEA)} = 4.3 \text{ mg EAA/L (in urine)} \]

\[ \rightarrow \text{cumulative HBM-1 for exposure EGEEA+EGEE} = 4.3 \text{ mg EAA/L (in urine)} \]
Ethylene glycol monomethyl ether (EGME)

- CAS No 109-86-4, IUPAC name: 2-Methoxyethanol

- metabolized to 2-methoxy-acetic acid (2-MAA) and EG

- rat
  - critical study: Hanley et al EHP 1984, developmental effects
  - NOEL 10 ppm (6h/day on GD 6-15)

- human
    - NAEL = 12 ppm
    - OEL = 0.9 ppm
Generic PBTK prediction for **EGME**: female (60kg, Qalv=5.5 L/min)

- **Kmet_MAA changed** (4.9→20)
- **Intermittent exposure** 12ppm (8h/d, 5d/w)
- **Constant** 2.9 ppm (24h/d)

**Kmet_MAA as in Gargas (4.9)**

**Renal excretion:** 63 mg MAA/day

- **UF 13.6**
- **1.2 L/day urine**

**HBM-1 (EGME) = 4.6 mg MAA/day (in urine)**

- **HBM-1 (EGME) = 3.8 mg MAA/L (in urine)**

(Note: for Kmet_MAA as in Gargas (4.9), all values have to be divided by 1.05)
<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Studientyp</td>
<td>Inhalation s.c.</td>
<td>Inhalation s.c.</td>
<td>Inhalation (Gestation)</td>
<td>Inhalation s.c</td>
</tr>
<tr>
<td>Spezies</td>
<td>Kaninchen</td>
<td>Kaninchen</td>
<td>Ratte</td>
<td>Kaninchen</td>
</tr>
<tr>
<td>Dosis EGME</td>
<td>0, 30, 100, 300 ppm</td>
<td>0, 30, 100, 300 ppm</td>
<td>0, 3, 10, 50 ppm</td>
<td>0, 30, 100, 300 ppm</td>
</tr>
<tr>
<td>Dosierung</td>
<td>6 h/d, 5 d/w, 13 Wochen</td>
<td>6 h/d, 5 d/w, 13 Wochen</td>
<td>Für 6 h/d an den Tagen 6–15 der Gestation</td>
<td>6 h/d, 5 d/w, 13 Wochen</td>
</tr>
<tr>
<td>POD</td>
<td>NOAEL 30 ppm Hodentoxizität</td>
<td>NOAEL 30 ppm Hodentoxizität</td>
<td>NOAEL 10 ppm Reproduktions-</td>
<td>LOAEL 30 ppm =95 mg/m³ Hodentoxizität</td>
</tr>
<tr>
<td>Extrapolationen (Assessmentfaktoren, AF)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Datenqualität + Studiendauer</td>
<td>10</td>
<td>10</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Expositionszeit</td>
<td>5,6 [24/6×7/5] (5,4 ppm ~17 mg/m³)</td>
<td>5,6 [24/6×7/5] (5,4 ppm ~17 mg/m³)</td>
<td>PBPK von MAA 12 ppm [8 h/d, 5 d/w über 8 Wochen]</td>
<td>5,6 [24/6×7/5]</td>
</tr>
<tr>
<td>Interspezies</td>
<td>10</td>
<td>3</td>
<td>2,5</td>
<td>2,5</td>
</tr>
<tr>
<td>Intraspezies</td>
<td>10</td>
<td>10</td>
<td>3,2 (Dynamik)</td>
<td>10</td>
</tr>
<tr>
<td>Gesamtfaktor</td>
<td>1000</td>
<td>300</td>
<td>14</td>
<td>580</td>
</tr>
<tr>
<td>Ergebnis (mg EGME/m³)</td>
<td>0,02 mg/m³</td>
<td>0,06 mg/m³</td>
<td>3 mg/m³ (0,9 ppm)</td>
<td>0,2 mg/m³ (RW II) (gerundet) (95/560=0,17)/10 [\rightarrow 0,02 \text{ mg/m}³ \text{(RW I)}]</td>
</tr>
</tbody>
</table>
END
Comments

EGEEA/EGEE (Gargas et al 2000)

- conversion of EGEEA to EGEE by blood esterases stated in Table 1 on p. 66 as Keec (L blood/h) = 2.3. This value does not allow to reproduce the results of Fig. 4 in human and is in contrast to the description of the PBTK model in the method section on p.65, left column (‘For human, this rate was scaled by body weight to the 0.74 power’).
- In the PBTK model, we extrapolated the rate with blood volume from rat to human, i.e., Keec(human) = 2.3 \* Vblood(human)/Vblood(rat), since this appears to be more physiological. Scaling with BW gives the same values of 76 mg EAA/day.

EGME (simulations presented March 22\textsuperscript{nd}, 2010)

- Simulations could only be reproduced for a male, 77kg and an average Qalv = 19 L/h/kg BW\(^{0.75}\), i.e, Qalv = 8.23, in addition to correctly account for the difference in MW between EGME and MAA. Prediction, however, were sought for a female (60kg) with Qalv = 15.3 L/h/kg BW\(^{0.75}\), i.e, Qalv = 5.5.