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

49th Sitzung der HBM-Kommission
March 5th+6th, 2015, UBA/Berlin

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

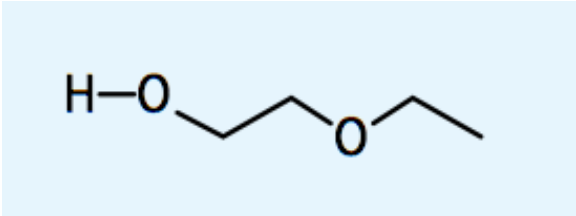
- General insight by analyzing *what-if scenarios*

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)

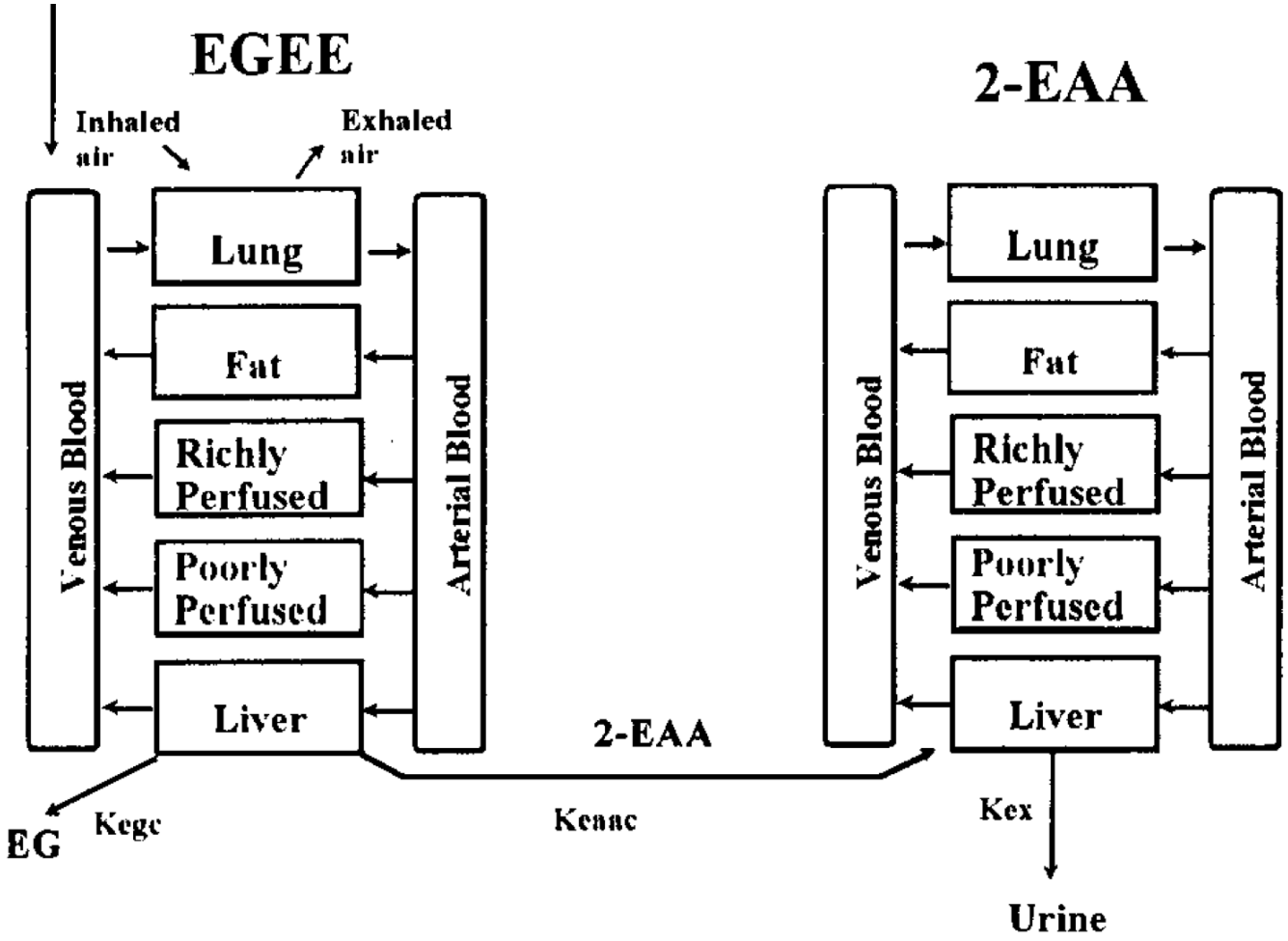
- CAS No 110-80-5, IUPAC name: 2-ethoxyethanol



- 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
  - exposure data: Groeseneken et al, Br J Ind Med 1986;43:615-619
  - extrapolation from rat to human (Sweeney et al Tox Sci 62 (2001), based on Gargas et al, Tox Appl Pharmacol 165, 2000)
    NAEL = 25 ppm (consequently, PBTK-based inter-species UF(TK) = 2)
    OEL = 2 ppm

Gargas et al (2000)

- Only inhalation considered, no dermal absorption



Gargas et al, Toxicol Appl. Pharmacol 165, 53-62 (2000)

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

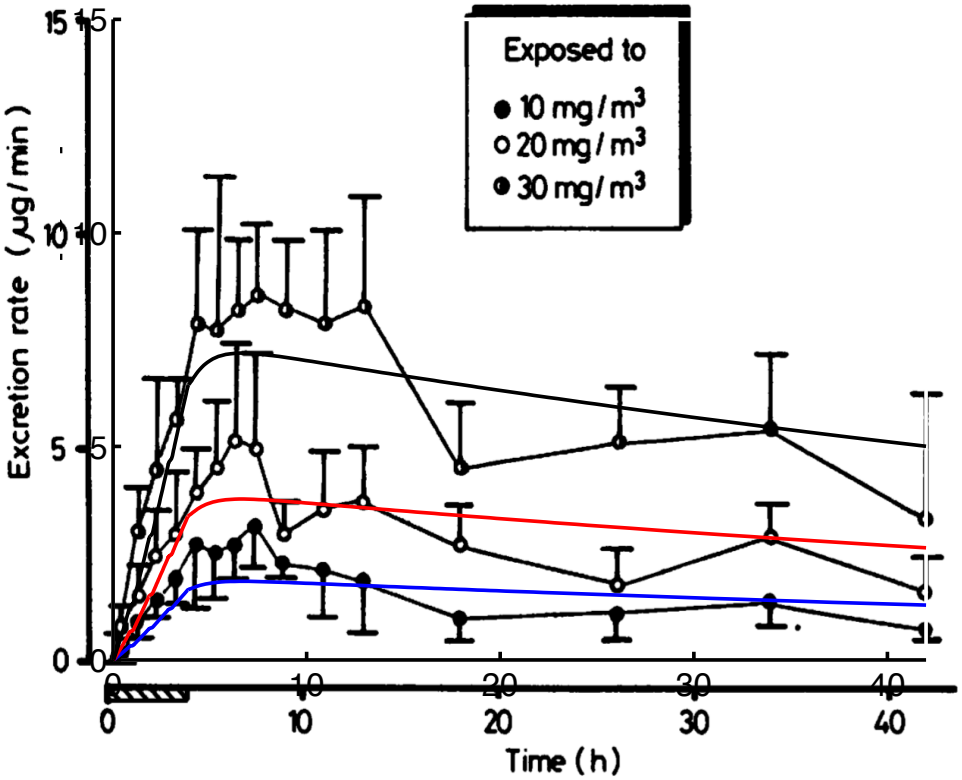


Fig 1 *Urinary excretion of ethoxyacetic acid during and after exposure to EGEE at rest. Data are means ± SD for five subjects. Shaded area indicates exposure period.*

Table 1 *General characteristics of the subjects*

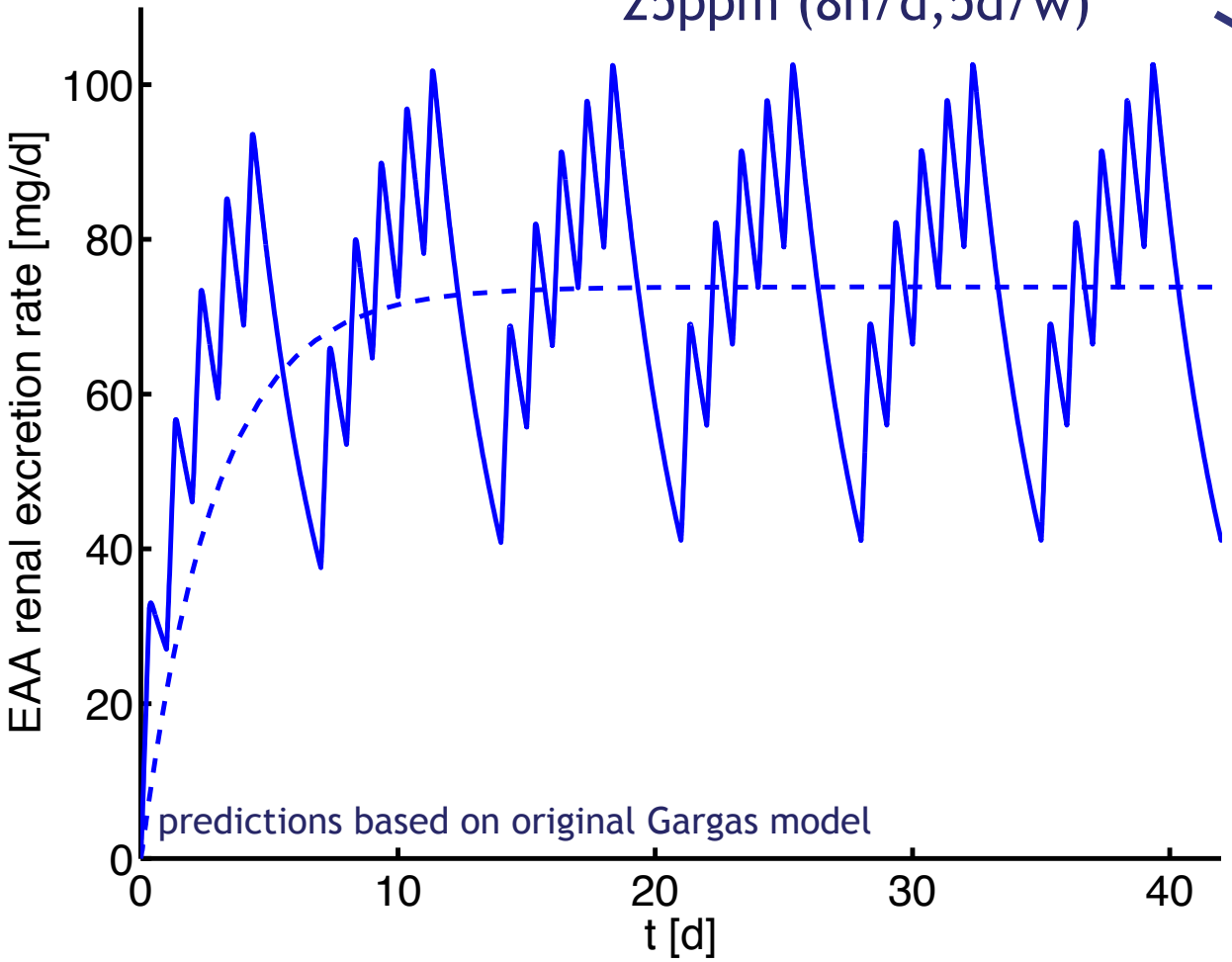
	Group 1 (*n* = 5)	*Group 2* (*n* = 5)
Age (years)	23 ± 4	21 ± 2
Weight (kg)	70·7 ± 10·1	66·1 ± 7·6
Height (cm)	181·4 ± 3·7	178·4 ± 3·8
% Body fat	11·7 ± 3·5	8·9 ± 2·8

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

Exposure of a female (58.6kg, Q_alv=5.4 L/min) to EGEE

NOEL=25ppm

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



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

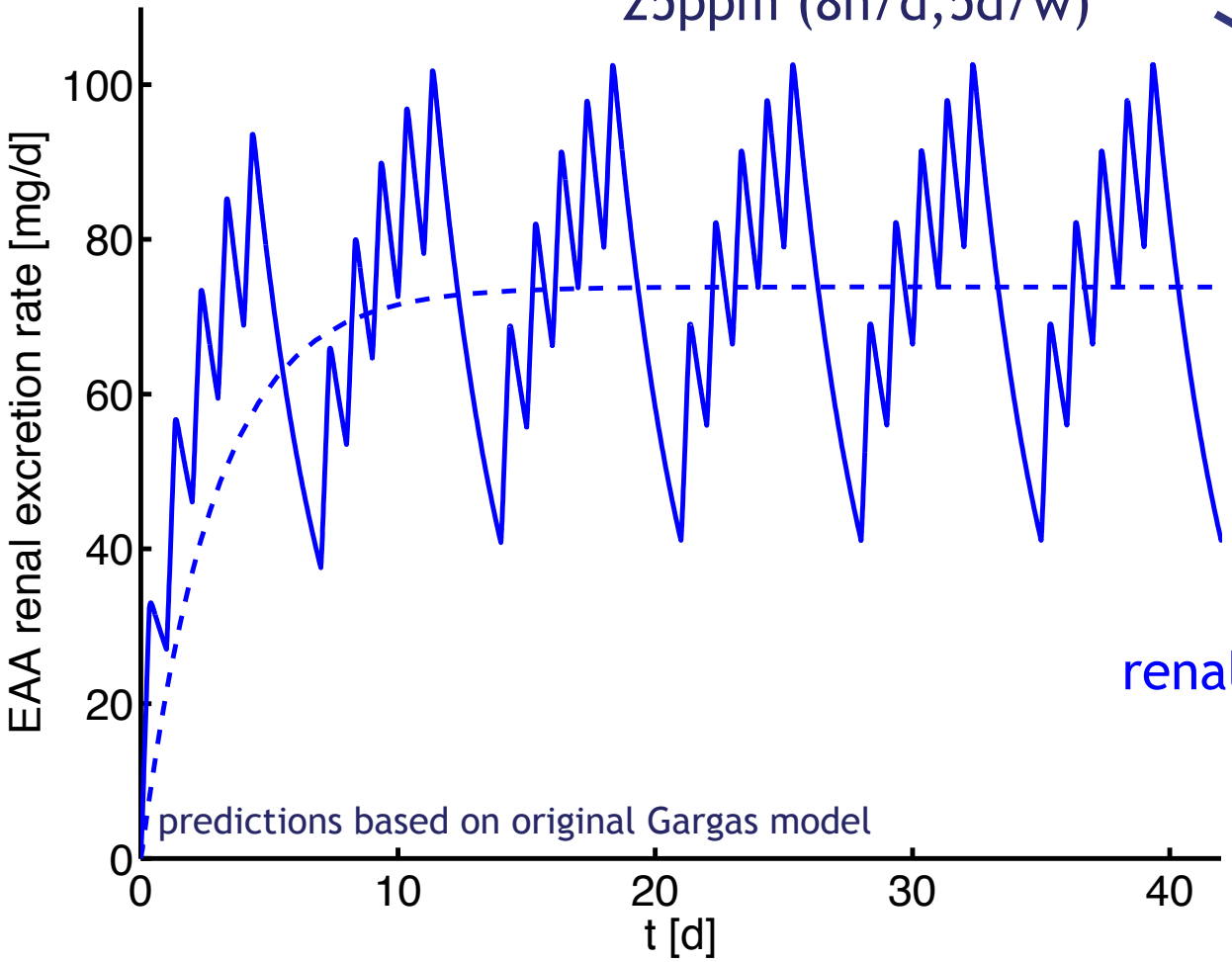
constant 6ppm (24h/d)

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

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)

PBTK-model based prediction

renal excretion: 73mg EAA/day

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 (1st 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 = **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

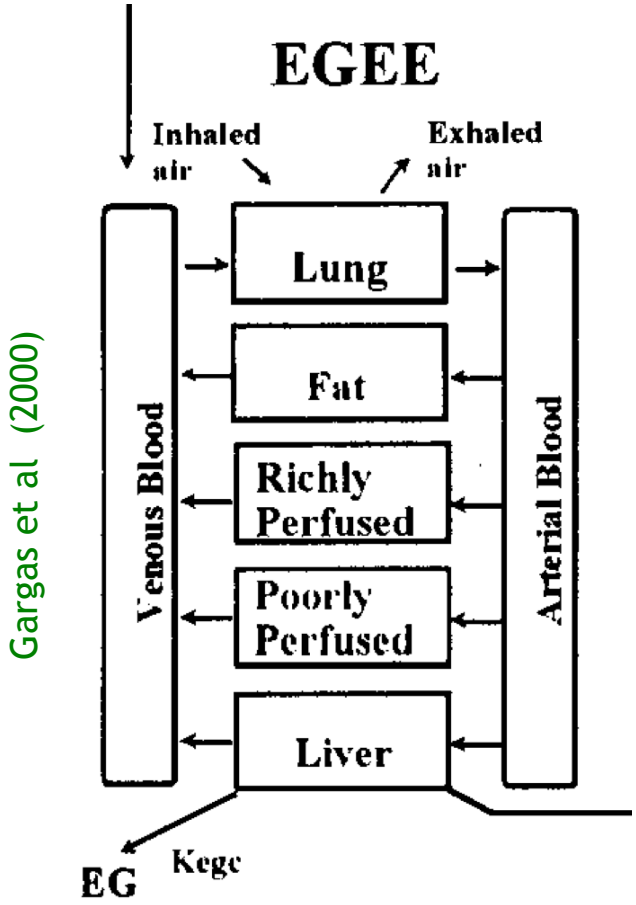
Some points for discussion

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

Generic PBTK model

Gargas et al (2000)

illustration in Gargas et al



parameter values (human)

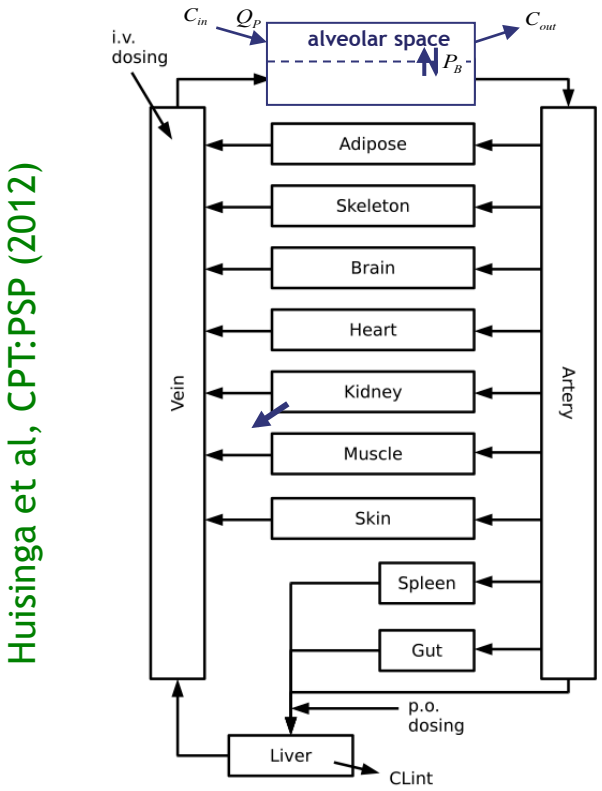
Body weight (start and end of pregnancy)	58, 62 kg	Fixed[b]
Percentage of body weight	Day 0	
Liver	2.4	Measured
Fat	27.6	Measured[c]
Slowly perfused	48.7	Measured
Richly perfused	3.7	Measured[d]
Blood	5.9	Fixed[e]
Flows		
Cardiac output (liters/h/kg$^{0.74}$)	19.2	Fixed
Alveolar ventilation (liters/h/kg$^{0.74}$)	15.3	Fixed

sum = 88.3 %
no difference between sex
ICRP: %Fat 32 (f) vs. 20 (m)

- Make use of established, more physiological representation in PK

Generic PBPK model

generic model structure



Huisinga et al, CPT:PSP (2012)

+

reference values (adult/children, m/f)

Annals of the ICRP

ICRP PUBLICATION 89

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

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]

inter-individual variability

Proposal:

- use this established generic PBPK model
- choose {hea,kid,spl,gut}=richly perfused, {mus,ski,bon} = slowly perfused

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 1. General characteristics and cardio-respiratory parameters at rest of the subjects. The cardio-respiratory data are means ± SD of 20 determinations

Subject	Age (years)	Weight (kg)	Height (cm)	Pulmonary ventilation (l/min)	Oxygen consumption (l/min)	Respiratory frequency (min^{-1})	Heart rate (beats/min)
1	24	72	187.5	8.2 ± 0.9	0.31 ± 0.04	13.7 ± 1.8	73 ± 4
2	31	80	185	8.2 ± 0.4	0.30 ± 0.05	11.0 ± 1.3	59 ± 5
3	27	78	181	7.3 ± 0.5	0.30 ± 0.04	11.4 ± 0.4	56 ± 4
4	26	85.5	182.5	8.4 ± 0.4	0.33 ± 0.04	11.6 ± 1.7	65 ± 5
5	25	85	190	7.0 ± 0.4	0.26 ± 0.05	11.6 ± 2.2	50 ± 4
6	24	78	189	9.8 ± 0.5	0.34 ± 0.06	14.1 ± 0.8	64 ± 4
7	23	63	172	7.5 ± 0.8	0.26 ± 0.04	11.6 ± 1.2	66 ± 4
Mean	26 ± 3	77 ± 8	184 ± 6	8.0 ± 0.6	0.30 ± 0.05	12.1 ± 1.3	62 ± 6

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

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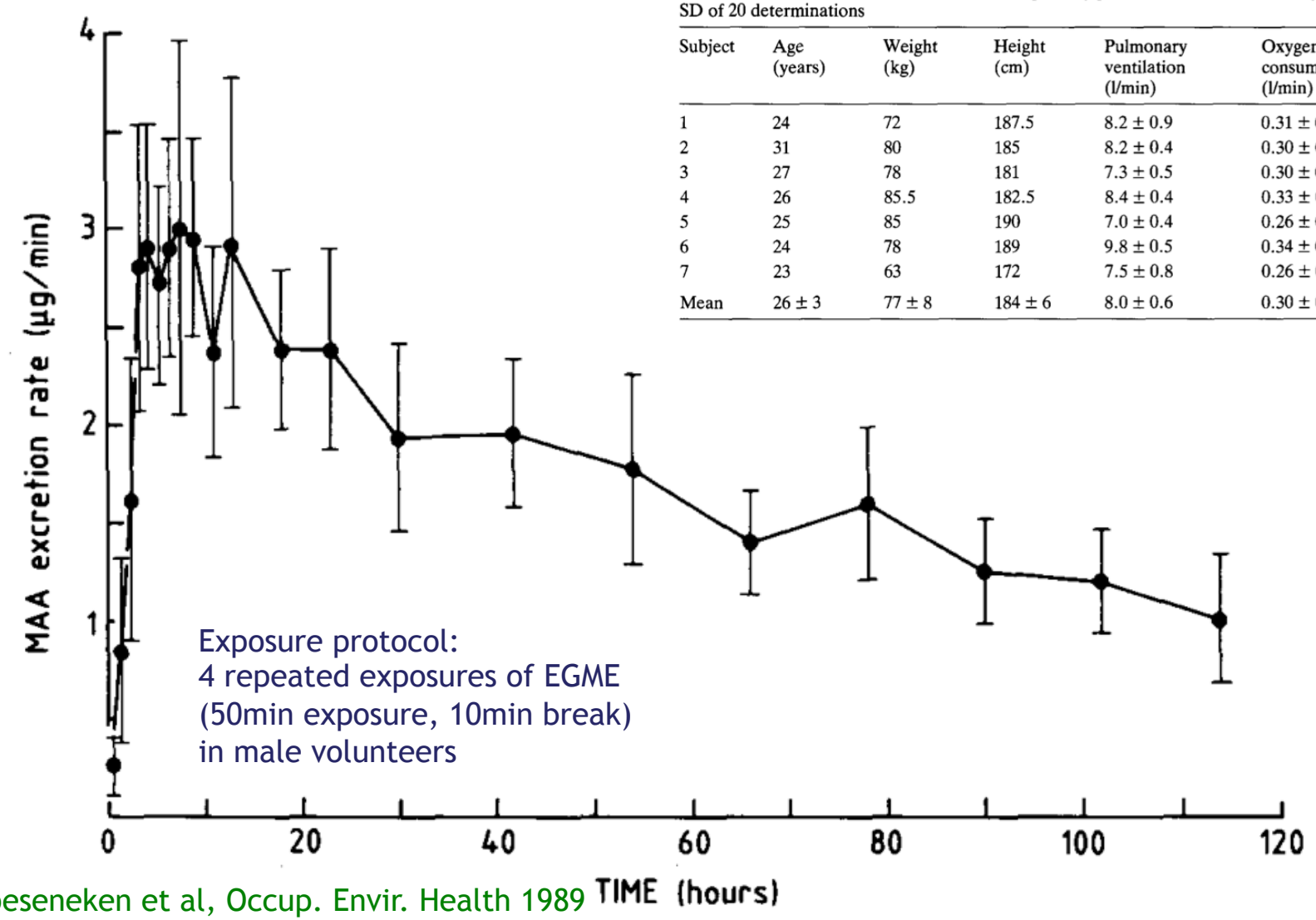

Exposure protocol:
4 repeated exposures of EGME
(50min exposure, 10min break)
in male volunteers

Groeseneken et al, Occup. Envir. Health 1989

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

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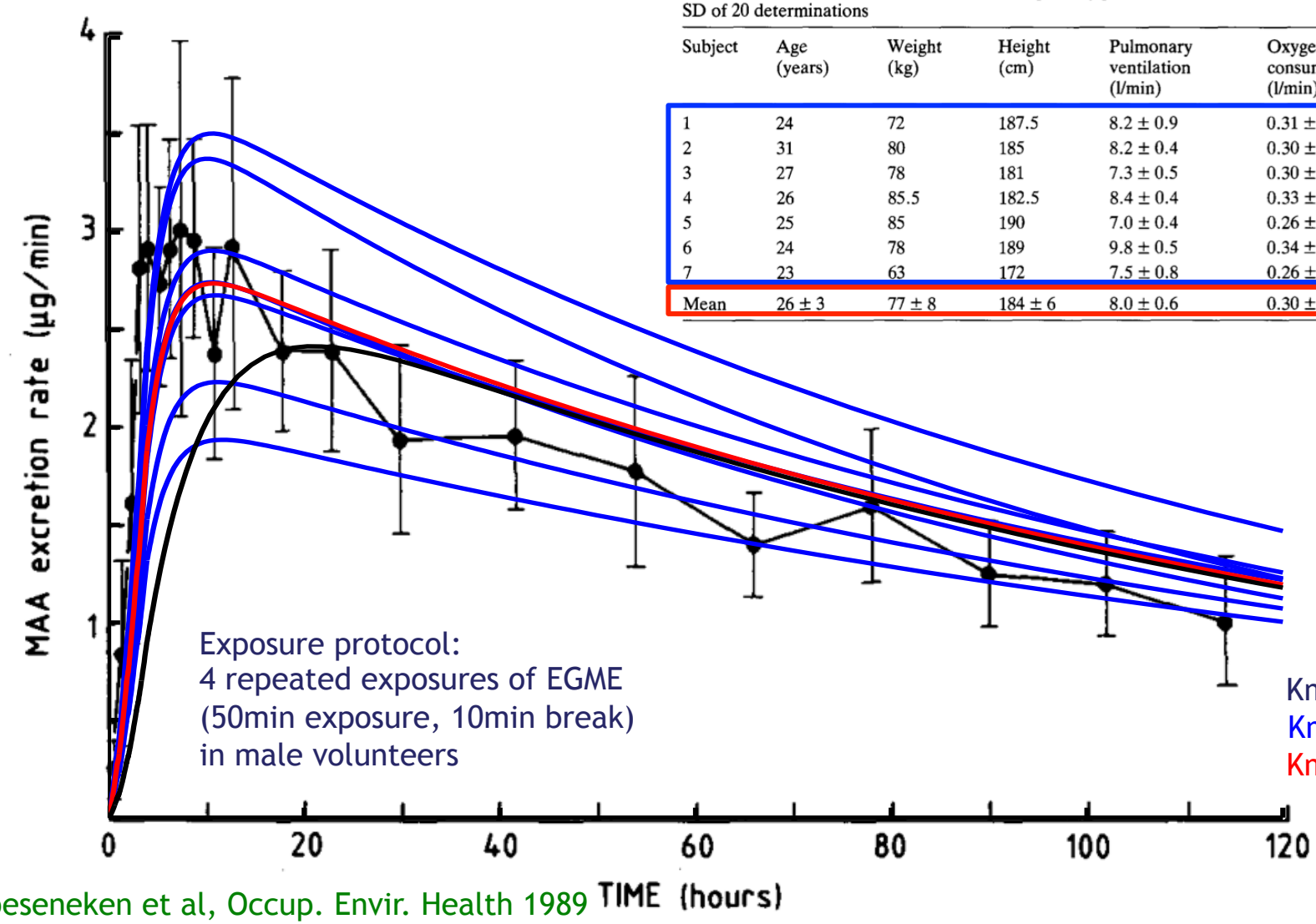
4	26	85.5	182.5	8.4 ± 0.4	0.33 ± 0.04	11.6 ± 1.7	65 ± 5
5	25	85	190	7.0 ± 0.4	0.26 ± 0.05	11.6 ± 2.2	50 ± 4
6	24	78	189	9.8 ± 0.5	0.34 ± 0.06	14.1 ± 0.8	64 ± 4
7	23	63	172	7.5 ± 0.8	0.26 ± 0.04	11.6 ± 1.2	66 ± 4
Mean	26 ± 3	77 ± 8	184 ± 6	8.0 ± 0.6	0.30 ± 0.05	12.1 ± 1.3	62 ± 6



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)

Groeseneken et al, Occup. Envir. Health 1989

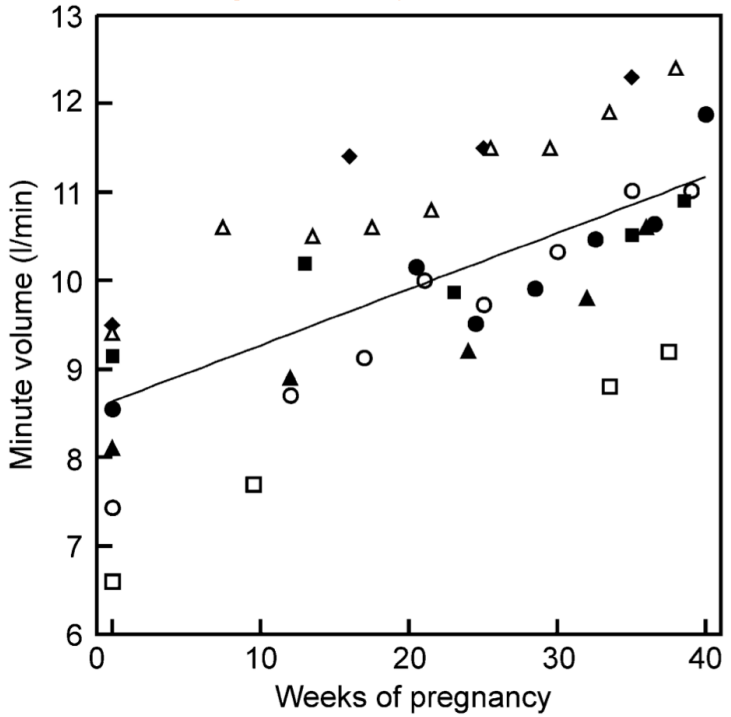
Pregnancy and the definition of HBM values

Pregnancy and the definition of HBM values

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

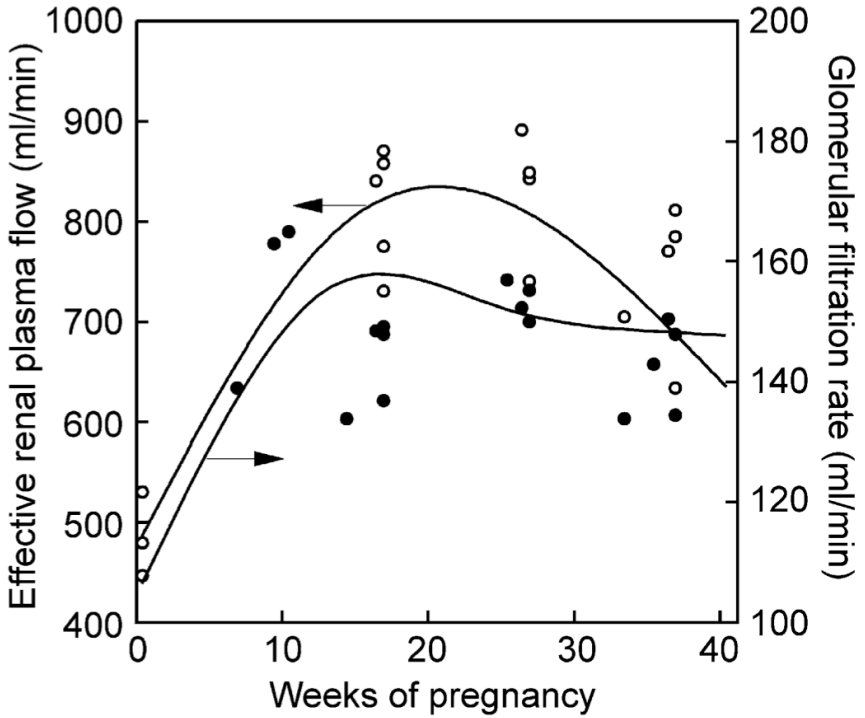
- How to account for physiological changes during pregnancy?

respiratory function



ICRP report No 89 (2002), p. 236

renal function

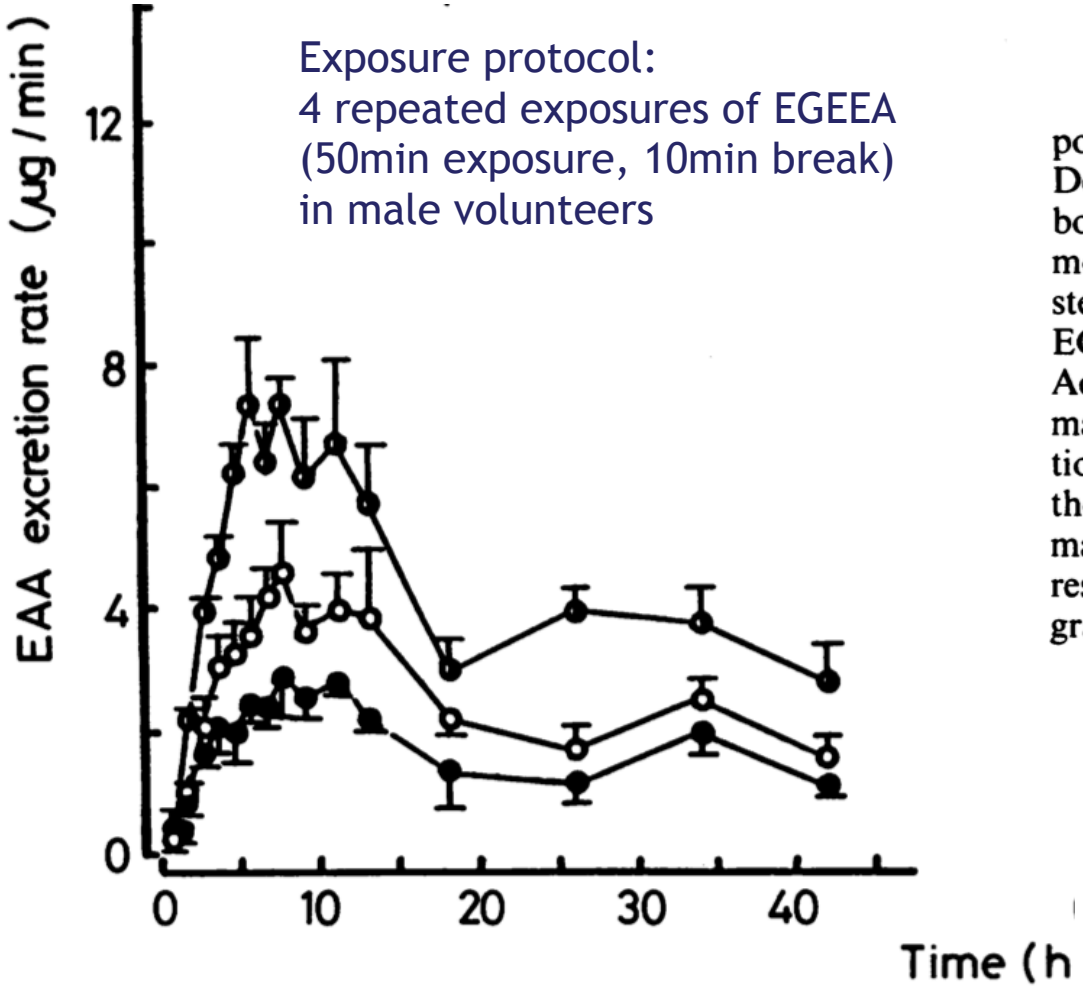


ICRP report No 89 (2002), p. 238

Non-linear relationship between external and internal exposure

Increased conversion of EGEEA → EGEE at higher concentrations

Groeseneken et al, Br J Ind Med 1987;44:488



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

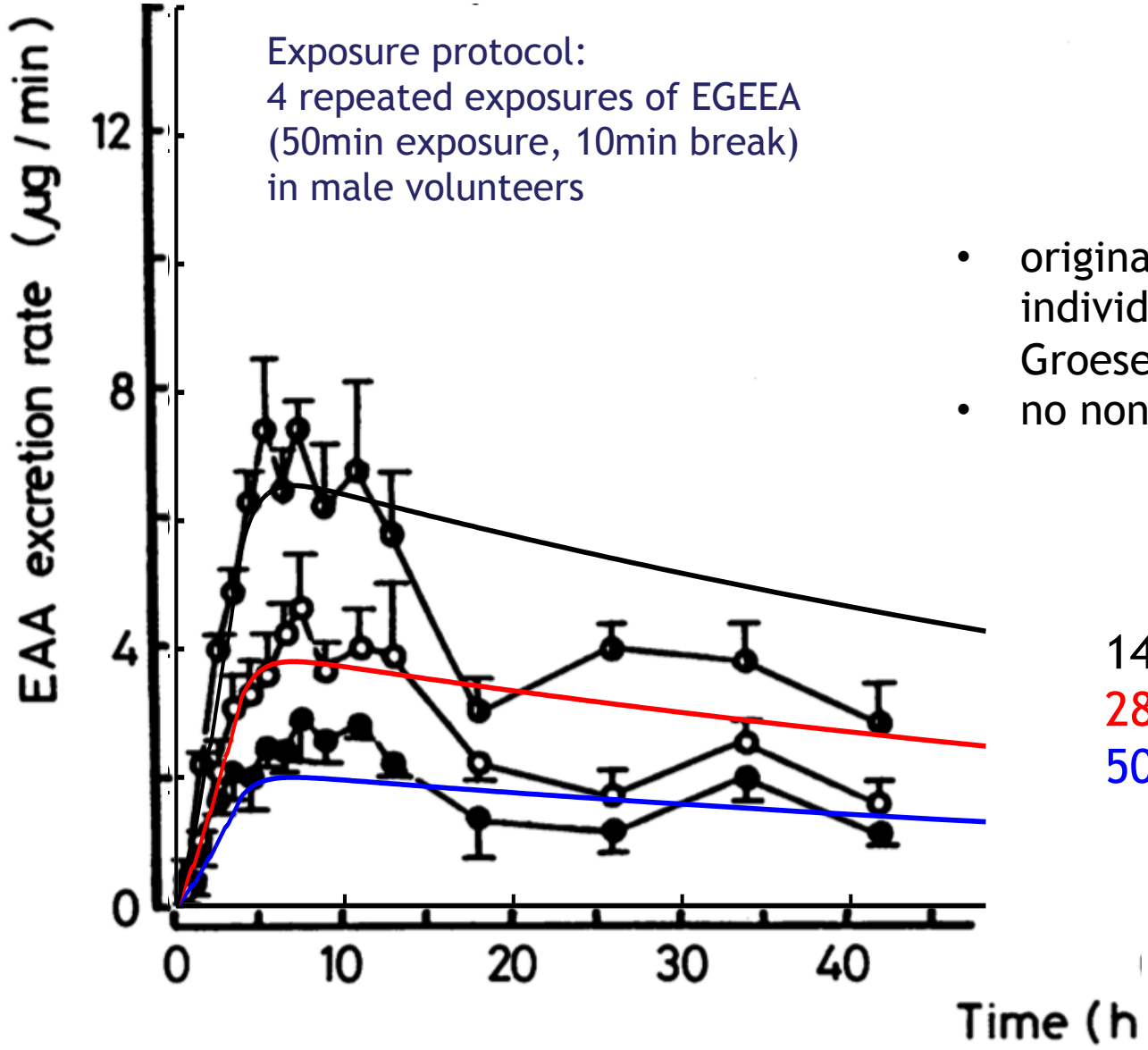
The observation that retention increased when exposure concentration was higher is rather unusual. Depending on the degree of saturation of the metabolic clearance mechanisms, retention is expected at most to remain constant or to decrease. Since the first step in EGEE-Ac metabolism is the conversion to EGEE by (plasma) esterases,[6] 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.

Groeseneken et al, Br J Ind Med 1987;44:309 (p.315)

Fig 1 *Urinary excretion of ethoxyacetic acid during and after a four hour exposure to EGEE-Ac under various conditions: 14 mg/m³ (●), 28 mg/m³ (○), and 50 mg/m³ (◑) at rest or 28 mg/m³ at 30 W (■) and 60 W (□). Data are means ± SEM for five subjects. Statistical data are F ratios from three way ANOVA: c = exposure concentration, w = workload.*

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

Groeseneken et al, Br J Ind Med 1987;44:488



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

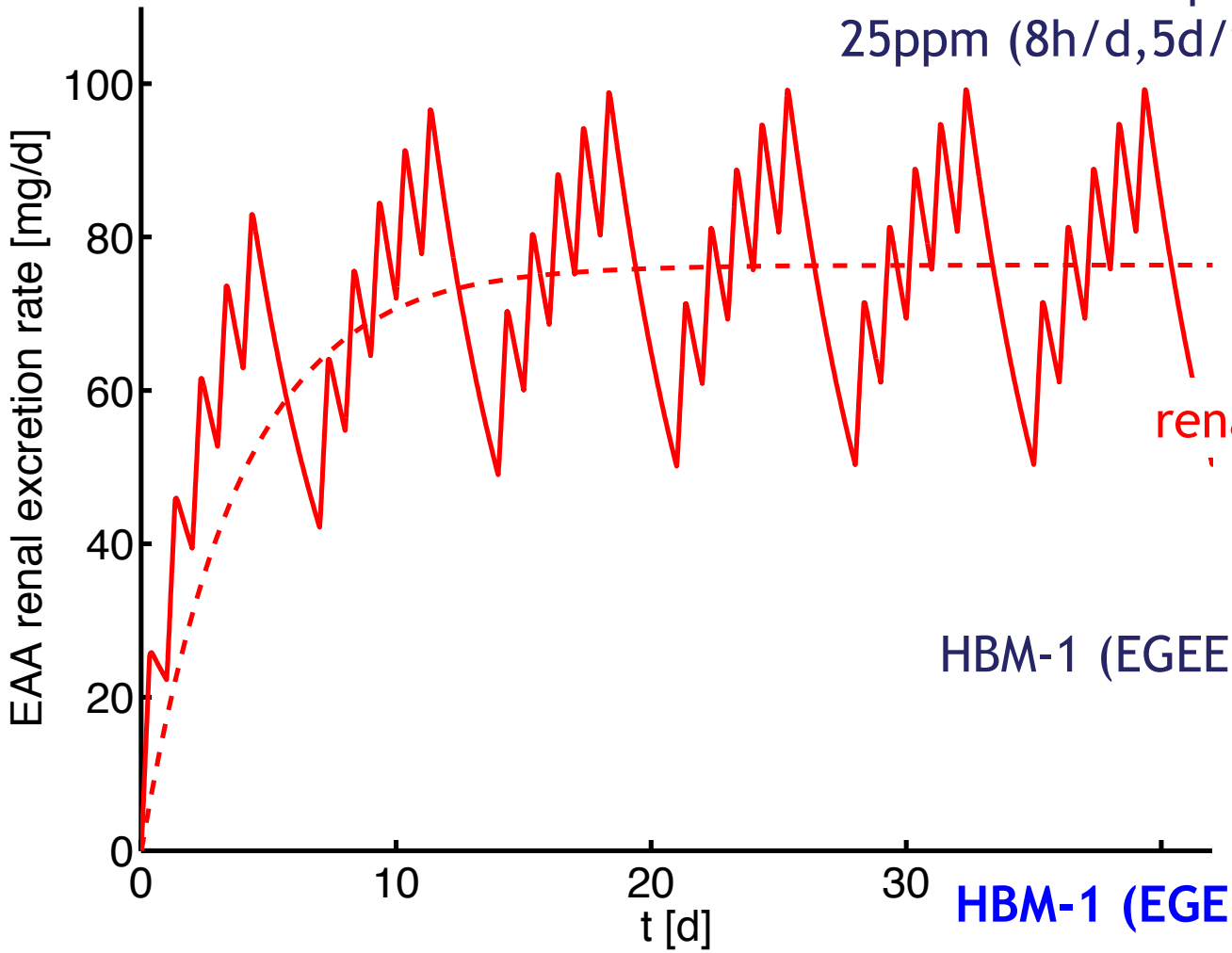
- original Gargas parameters and individual covariates as in Groeseneken
- no nonlinearity metabolism

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)

↓ PBTK

renal excretion: 76 mg EAA/day

↓ UF 14.4

HBM-1 (EGEE) = 5.2 mg EAA/day (in urine)

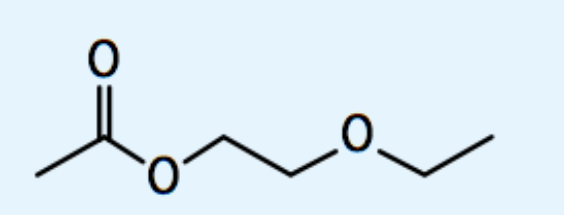
↓ 1.2 L/day urine

HBM-1 (EGEE) = 4.3 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



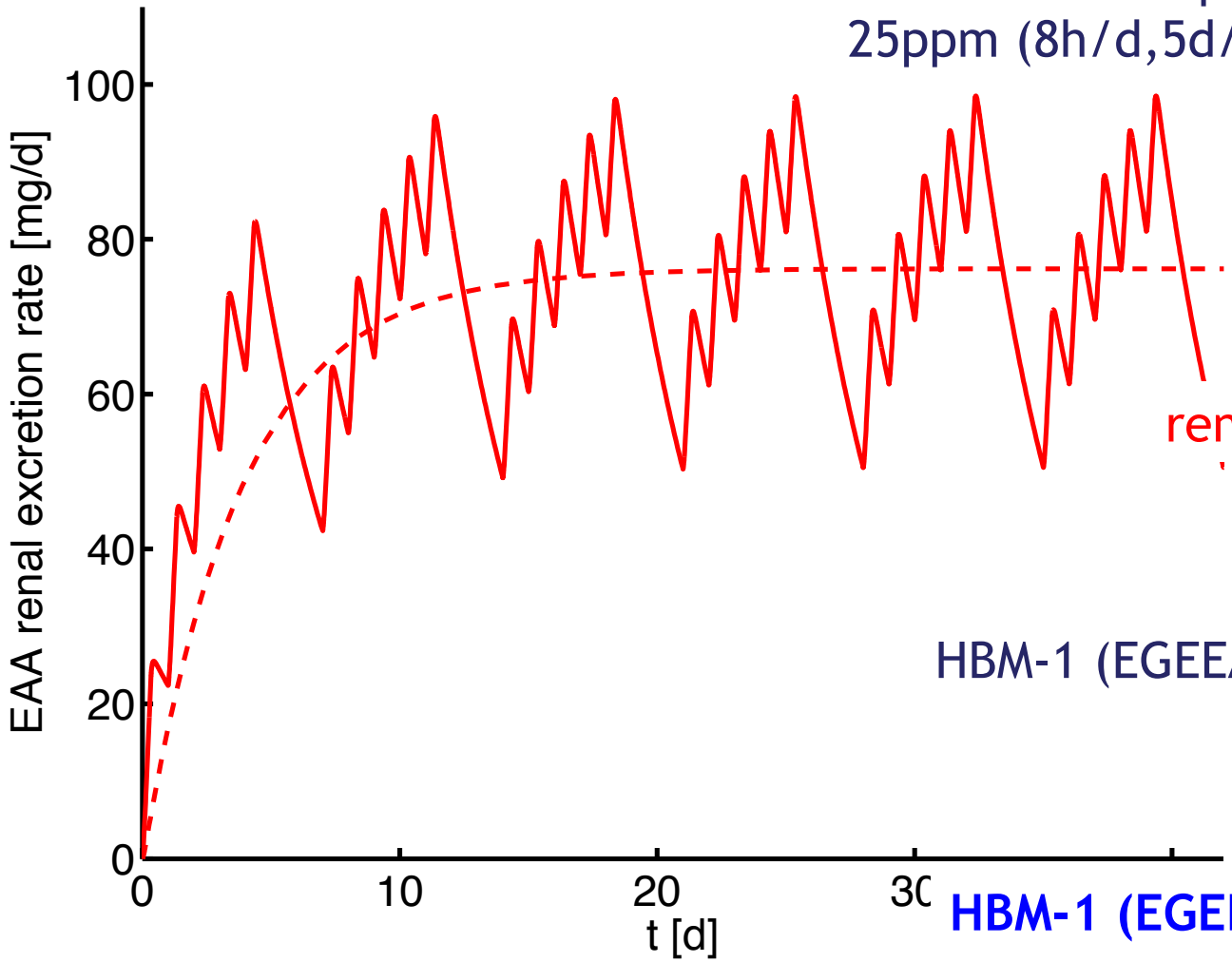
- metabolized to EGEE via plasma esterases

  → 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
  - exposure data: Groeseneken et al, Br J Ind Med 1986;43:615-619
  - extrapolation from rat to human (Gargas et al, Tox Appl Pharmacol 165, 2000)

    NOAL = 25 ppm (blood AUC) or NOAL 40 ppm (Cmax blood)
  - derivation by Sweeney et al Tox Sci 62 (2001)

    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)

↓ PBTK

renal excretion: 76 mg EAA/day

↓ UF 14.4

HBM-1 (EGEEA) = 5.2 mg EAA/day (in urine)

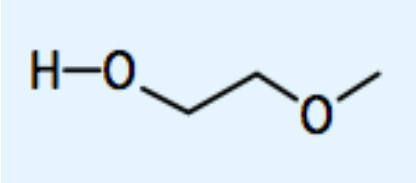
↓ 1.2 L/day urine

HBM-1 (EGEEA) = 4.3 mg EAA/L (in urine)

→ cumulative HBM-1 for exposure EGEEA+EGEE = 4.3 mg EAA/L (in urine)

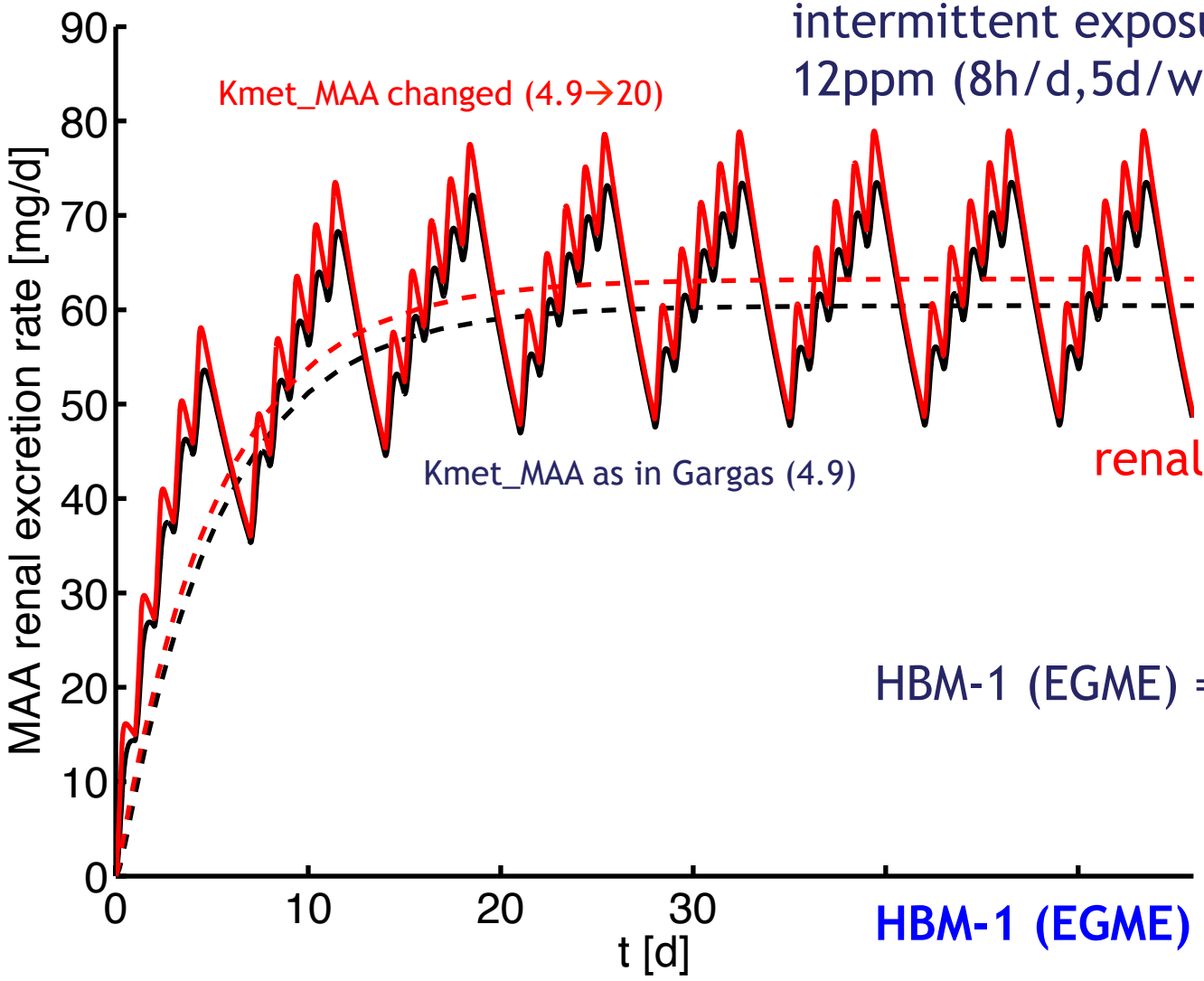
Ethylene glycol monomethyl ether (EGME)

- 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
  - exposure data: Groeseneken et al, Occup. Envir. Health 1989
  - extrapolation from rat to human (Sweeney et al Tox Sci 62 (2001), based on Gargas et al, Tox Appl Pharmacol 165, 2000)
    NAEL = 12 ppm
  - OEL = 0.9 ppm

Generic PBTK prediction for EGME: female (60kg, Qalv=5.5 L/min)



intermittent exposure
12ppm (8h/d,5d/w)

constant 2.9 ppm (24h/d)

↓ PBTK

renal excretion: 63 mg MAA/day

↓ UF 13.6

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

↓ 1.2 L/day 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)

Tab. 5 Abgeleitete Luft-Richtwerte und die verwendeten Assessmentfaktoren (AF)

Ableitung Richtwert	US-EPA [53] RfC	OEHHA [54] REL-chron	Sweeney et al. [28] OEL	Ad-hoc-AG [3] RW II und RW I
Kritische Studie	Miller [33]	Miller [33]	Hanley [35]	Miller [34]
Studientyp	Inhalation s.c.	Inhalation s.c.	Inhalation (Gestation)	Inhalation s.c
Spezies	Kaninchen	Kaninchen	Ratte	Kaninchen
Dosis EGME	0, 30, 100, 300 ppm	0, 30, 100, 300 ppm	0, 3, 10, 50 ppm	0, 30, 100, 300 ppm
Dosierung	6 h/d, 5 d/w, 13 Wochen	6 h/d, 5 d/w, 13 Wochen	Für 6 h/d an den Tagen 6–15 der Gestation	6 h/d, 5 d/w, 13 Wochen
POD	NOAEL 30 ppm Hodentoxizität	NOAEL 30 ppm Hodentoxizität	NOAEL 10 ppm Reproduktionstoxizität, Fetus	LOAEL 30 ppm =95 mg/m^3 Hodentoxizität
Extrapolationen (Assessmentfaktoren, AF)				
Datenqualität + Studiendauer	10	10		2
Expositionszeit	5,6 [24/6×7/5] (5,4 ppm ~17 mg/m^3)	5,6 [24/6×7/5] (5,4 ppm ~17 mg/m^3)	PBPK von MAA 12 ppm [8 h/d, 5 d/w über 8 Wochen]	5,6 [24/6×7/5]
Interspezies	10	3	2,5	2,5
Intraspezies	10	10	3,2 (Dynamik)	10
			1,8 (Kinetik)	2 (Kinderfaktor)
Gesamtfaktor	1000	300	14	580
Ergebnis (mg EGME/m^3)	0,02 mg/m^3	0,06 mg/m^3	3 mg/m^3 (0,9 ppm)	0,2 mg/m^3 (RW II) (gerundet) (95/560=0,17)/10 → 0,02 mg/m^3 (RW I)

HBM Kommission, **Stoffmonographie für Glykolether, die zu Methoxyessigsäure ver- stoffwechselt werden - Referenz- und Human-Biomonitoring (HBM)-Werte für Methoxy- essigsäure im Urin, Bundesgesundheitsblatt 2014**

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 22nd, 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.