Modelleren van inwendige dosis na blootstelling van de huid

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Onderwerpen presentatie

- Relevantie van huidopname, enkele voorbeelden
- Kwantificeren en/of modelleren van huidopname
- Fysiologisch modelleren (PBPK)
- Vergelijking tussen model en experimentele data uit gepubliceerde onderzoeken naar PAK blootstelling

Relevantie van huidopname (1)

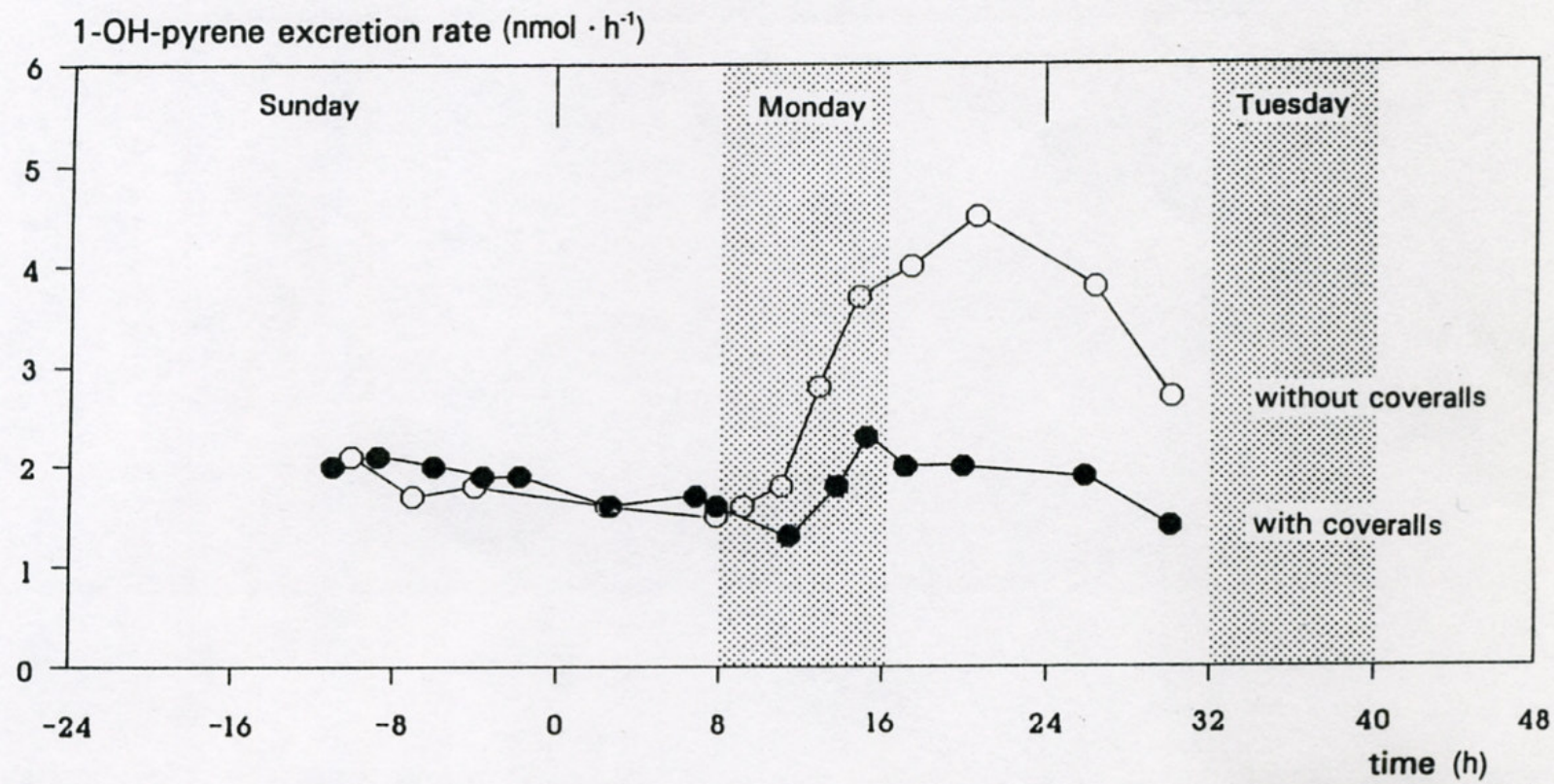

Figure 3. Effect of the coveralls on the urinary 1-OH-pyrene excretion of a creosote-exposed worker (worker 1). The shaded area indicates the hours of exposure (8-h workshift)

Creosoteerders , Van Rooij 1993 Scan J Work Env Health

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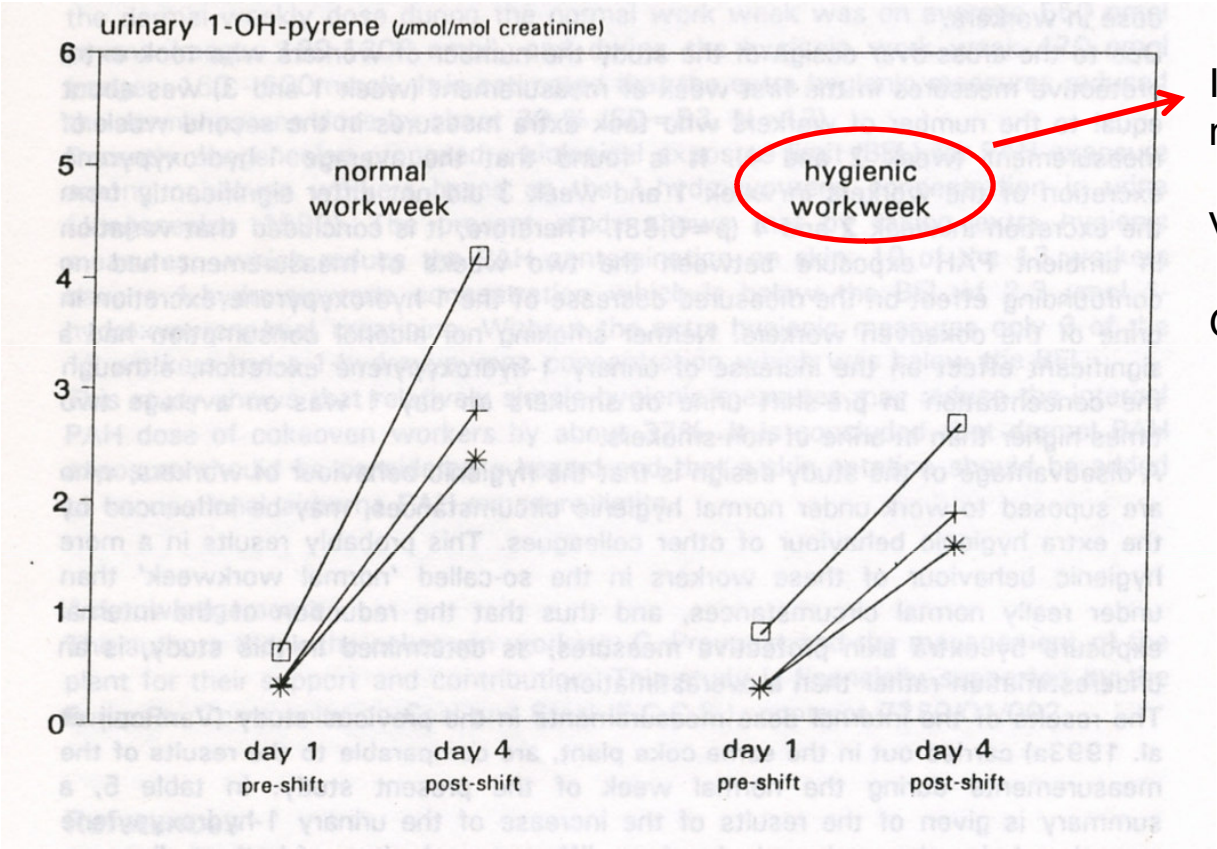
Relevantie van huidopname (2)



Iedere shift schone werkkleding en nieuwe handschoenen

Vaker handen wassen

Gezicht wassen

Cokes-ovens, Van Rooij 1993 British J Indus Med

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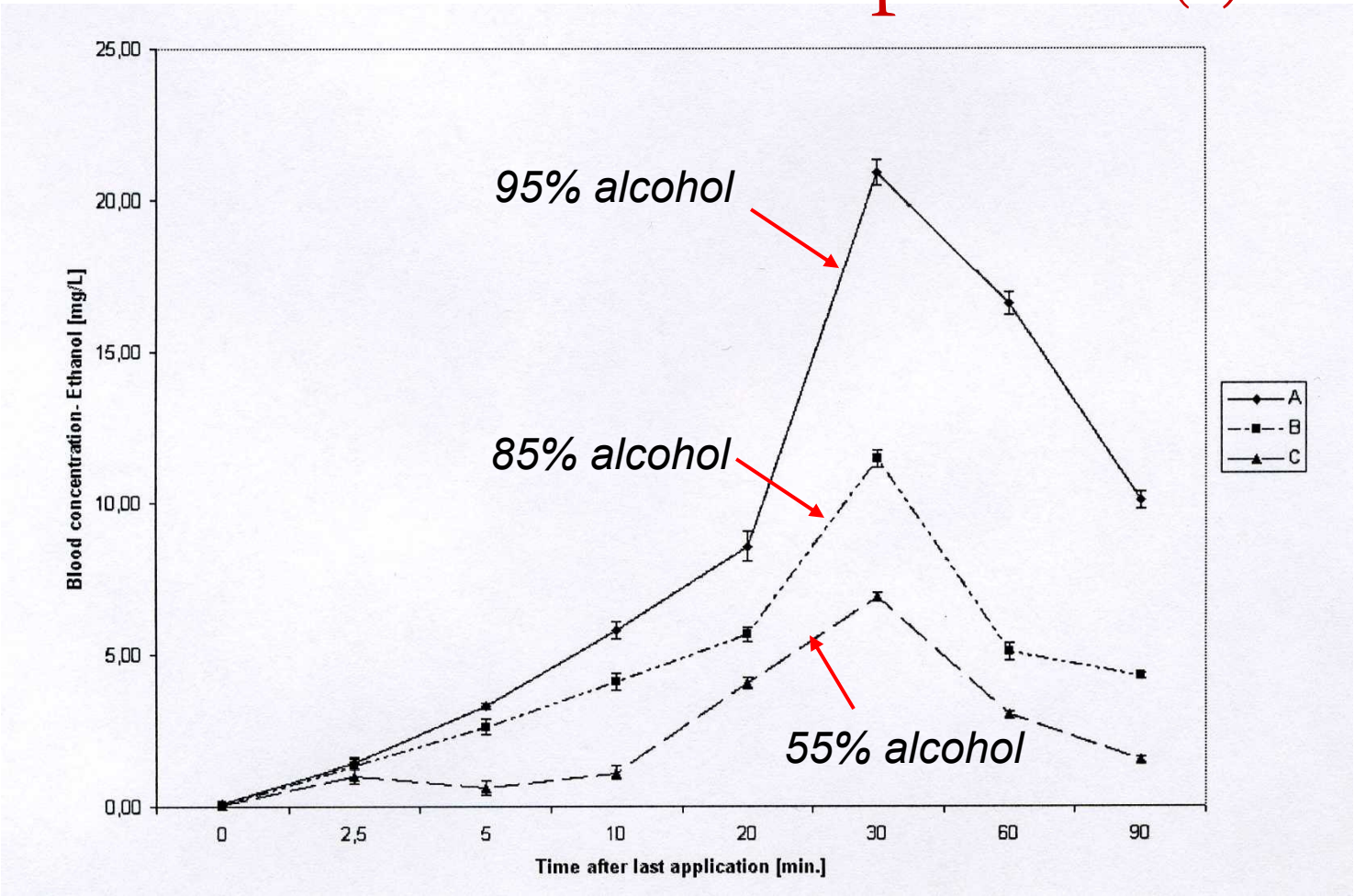
Relevantie van huidopname (3)



Applicatie: 20x 30sec (1 minuut tussenpauze) op beide handen

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Ethanol handspoelmiddelen, Kramer 2008 BMC Inf Dis

Kwantificeren van huidopname

- Toekomst : $DNEL_{dermal}$ in mg/kg.day
- Conventioneel
  - 100% absorptie
  - 10% absorptie bij MW > 500
- Kinetisch model
  - Nabootsing van opname middels diffusie en verdamping

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Skinperm

- Ontwikkeld door Wil ten Berge
- Berekent permeatie coëfficiënt en absorptie van een stof (geen vaste fractie)
- Alleen Log Kow, MW en wateroplosbaarheid nodig
- Gratis beschikbaar (MS Excel)

Substance properties for estimating skin permeation

Debugged version 7.0 of 30 June 2008, info wtberge@planet.nl

Chemical	PROPYLENE GLYCOL
CasNum	57-55-6
Molweight	76,1
VapourPress_Pa_25cg	1,71E+01
WaterSolub_mg/l	1000000
Log(Kow)	-0,92

Up

Down

Concentration in water in mg/liter

Concentration in air in mg/m3

Duration of exposure in minutes

Exposed skin surface in cm2

Go to Record No 15

Calculate Steady State

Dermal deposition in mg/cm2

Calculate aqueous absorption

View Results

Calculate absorption from air

Calculate Evaporation and Absorption

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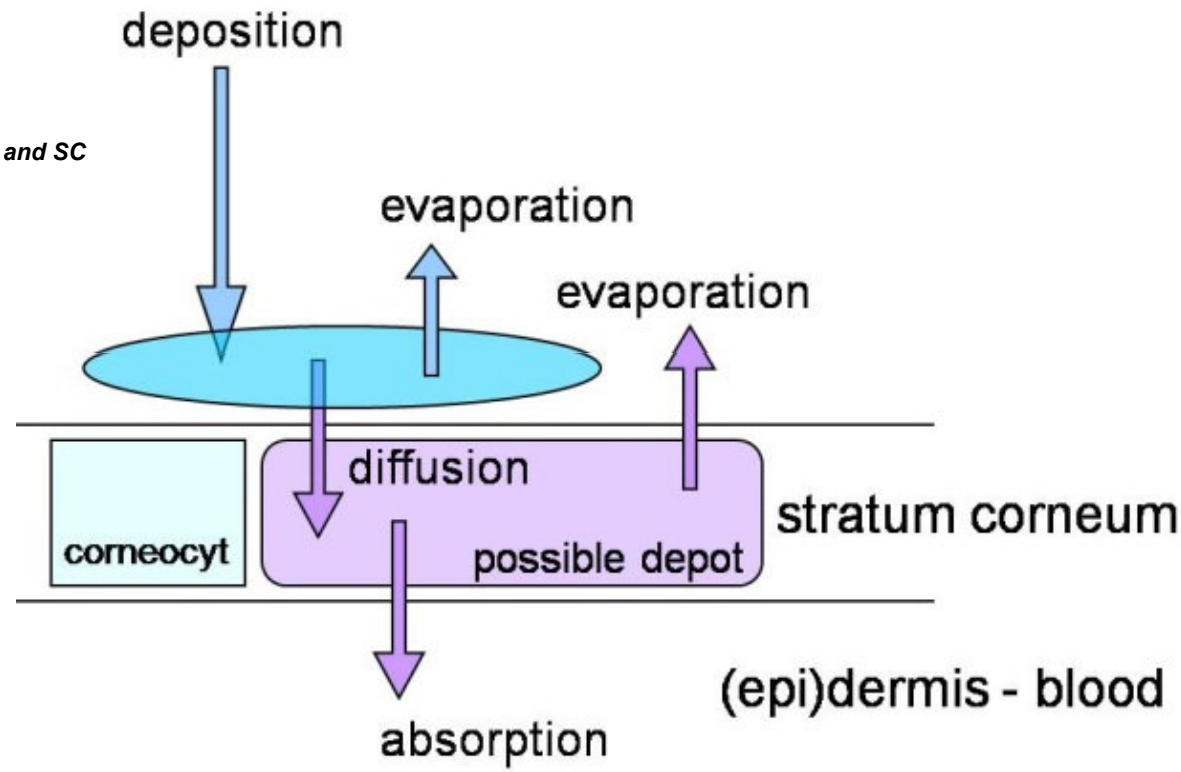
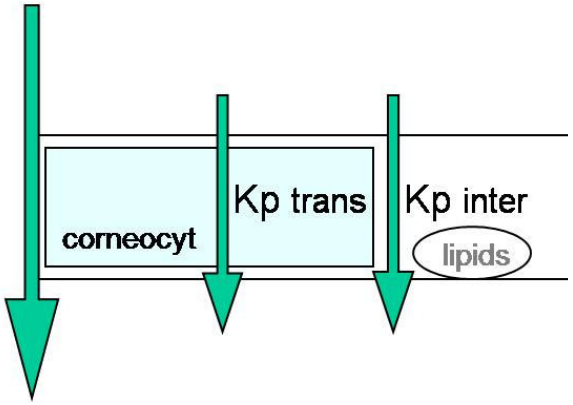
Skinperm (2)

Principle of the membrane model
by Ten Berge

- ***1-layer model (stratum corneum)***
- ***correction for evaporation from applied skin dose and SC***
- ***trans- and intracellular permeation***



Permeatie coefficient



$Kp = Kp_{trans} + Kp_{inter}$

Ten Berge, Chemosphere 2009 / Wilschut en Ten Berge Chemosphere 1995

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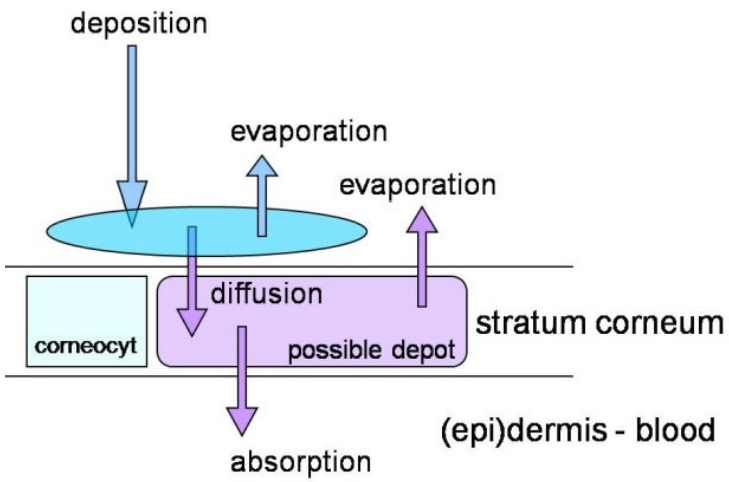
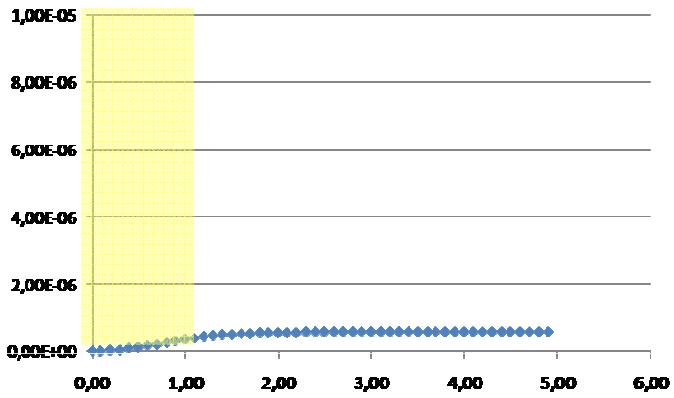
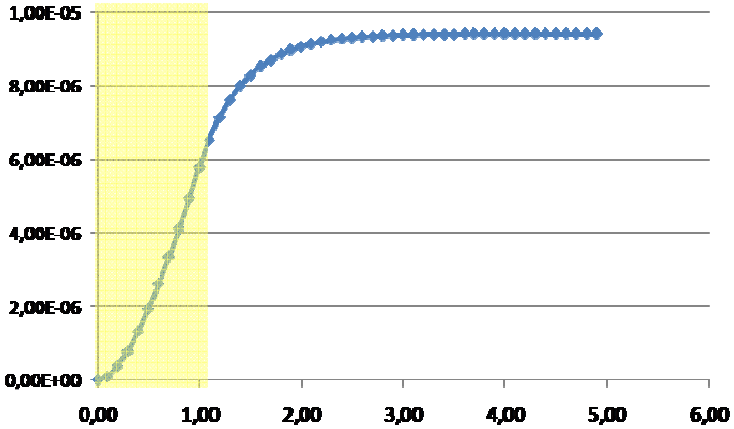
Skinperm (3)



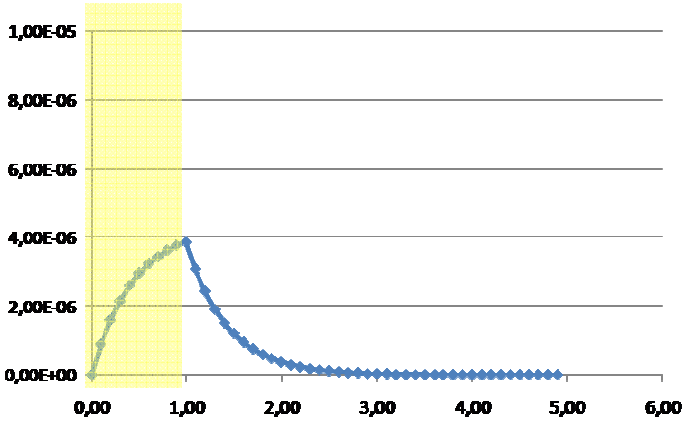
Pyrene evaporated (mg/cm²)



Pyrene absorbed (mg/cm²)



Pyrene in SC (mg/cm²)



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PBPK modelleren

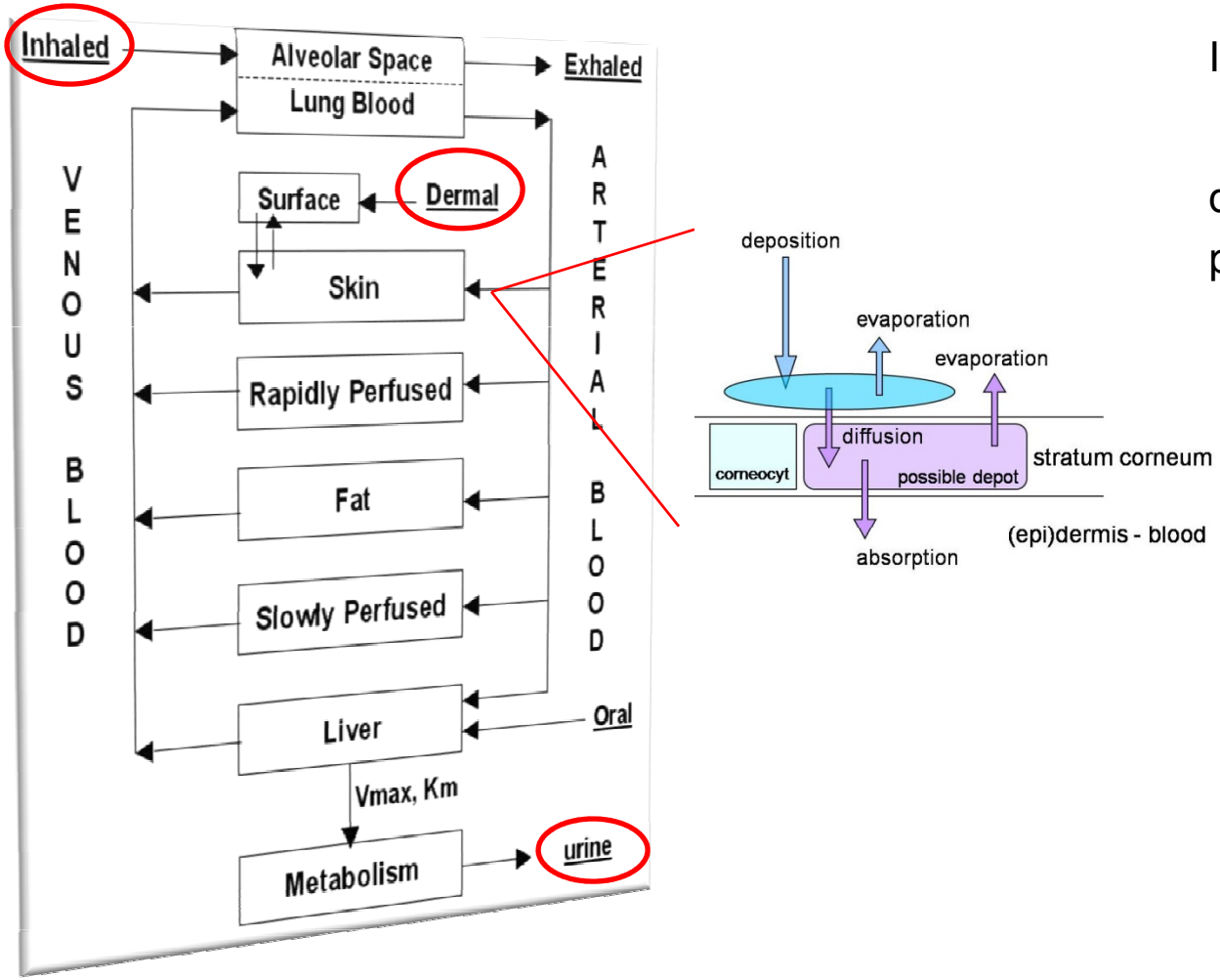
- Physiological Based PharmacoKinetic model
  gebaseerd op fysiologische kenmerken en stofeigenschappen

- Modelleren van ‘flow’ van chemische stof door het lichaam, van opname via omzetting tot uitscheiding

- Van oorsprong voor farmaceutische toepassingen

- Indien bruikbaar voor arbeidsgerelateerde blootstelling vaak zeer specifiek

PBPK model voor pyreen



Experimentele data

Inhalatie van pyreen

dermale blootstelling aan pyreen (pads)

1-hydroxypyreen in urine

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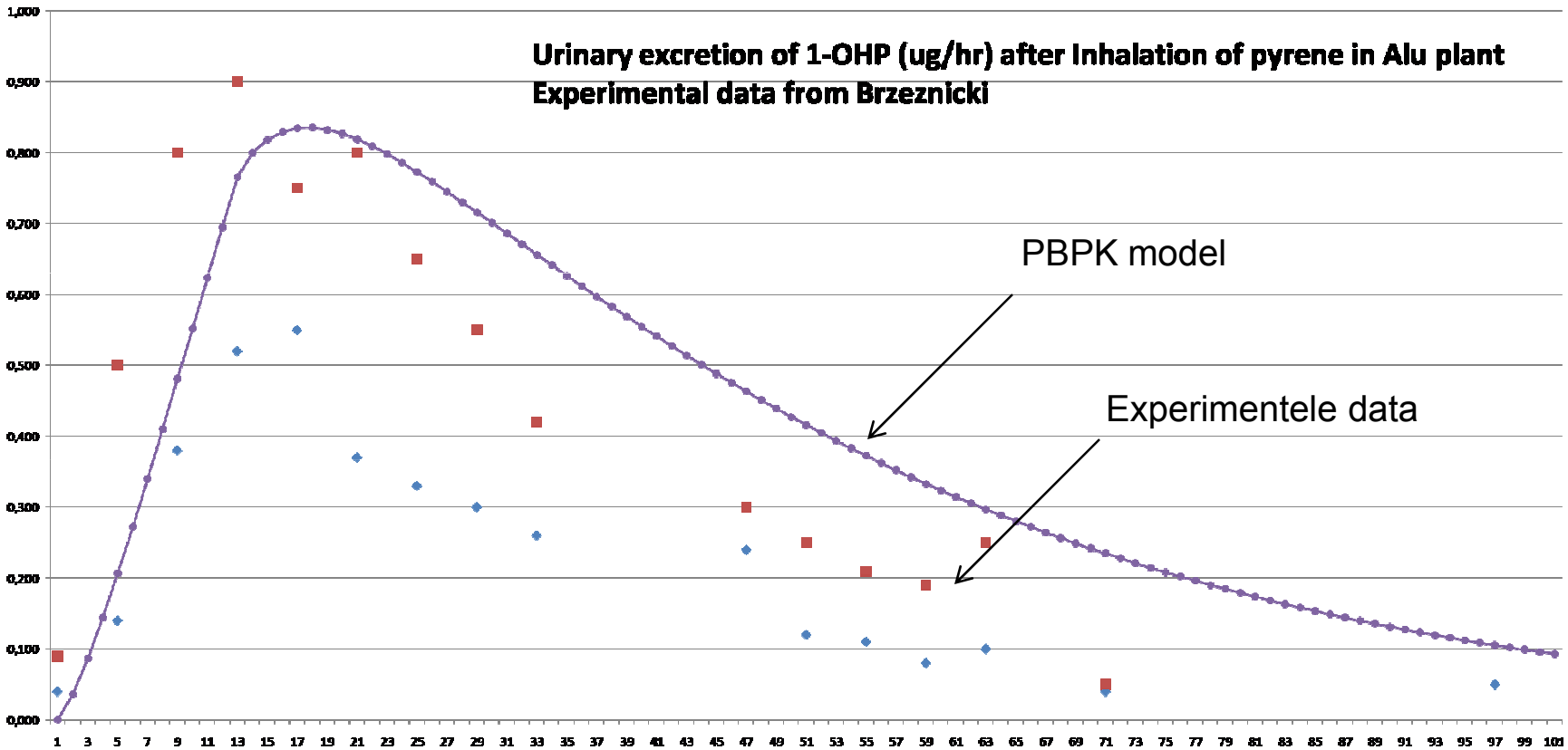
Uitscheiding na inhalatie van pyreen



N=5, Exposure duration: 6 hrs, retention: 60% (35% - 80%), t12 : 9,8 hrs (measured)

Brzeznicki, 1997, Int Archives OEH

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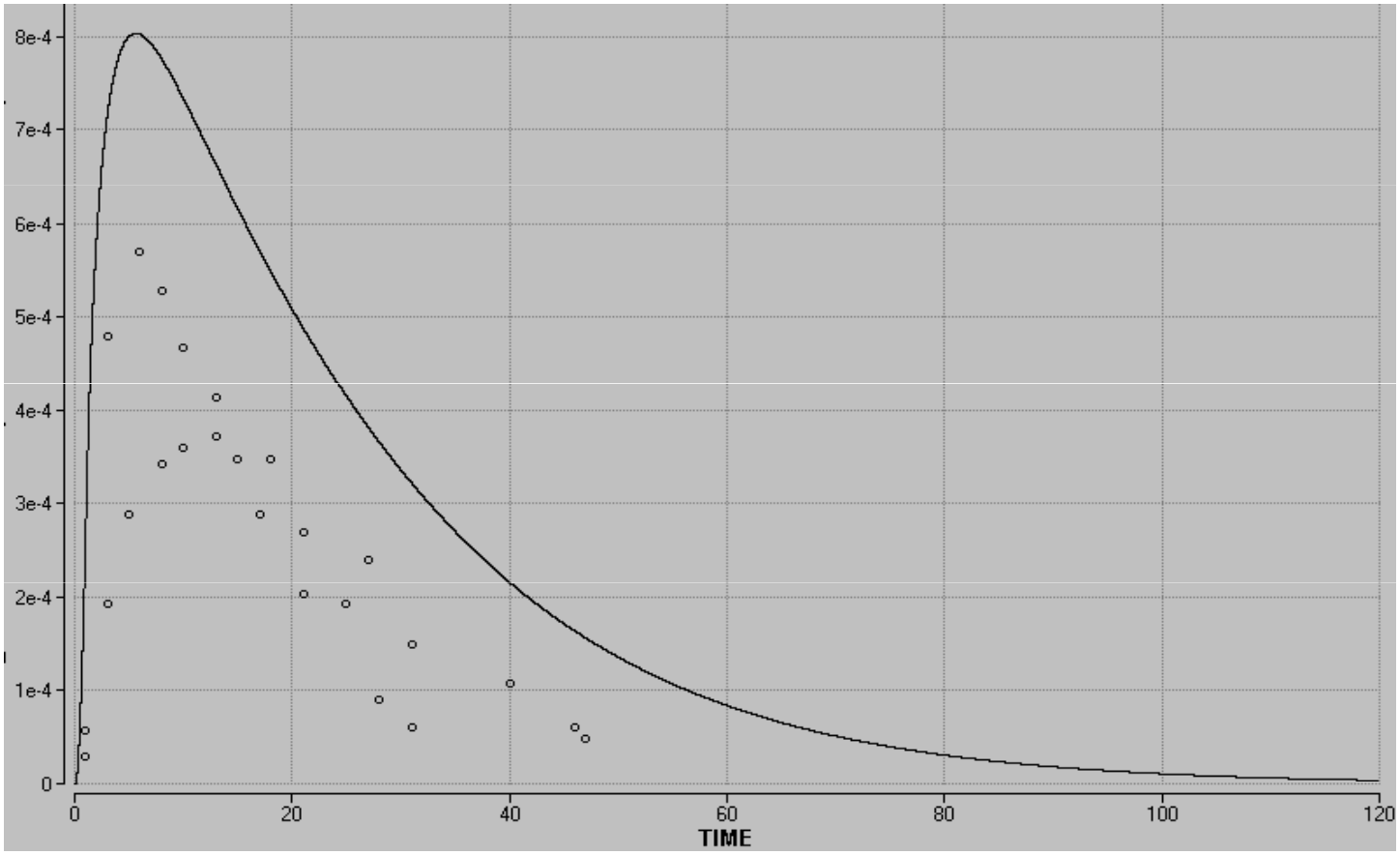
Uitscheiding na dermale opname pyreen



Dermal exposure to pyrene (solved in toluene) for 1 hour, followed by washing of the skin
N=2, t12: 12 hrs (calculated)

Viau, 1995, Science total Env

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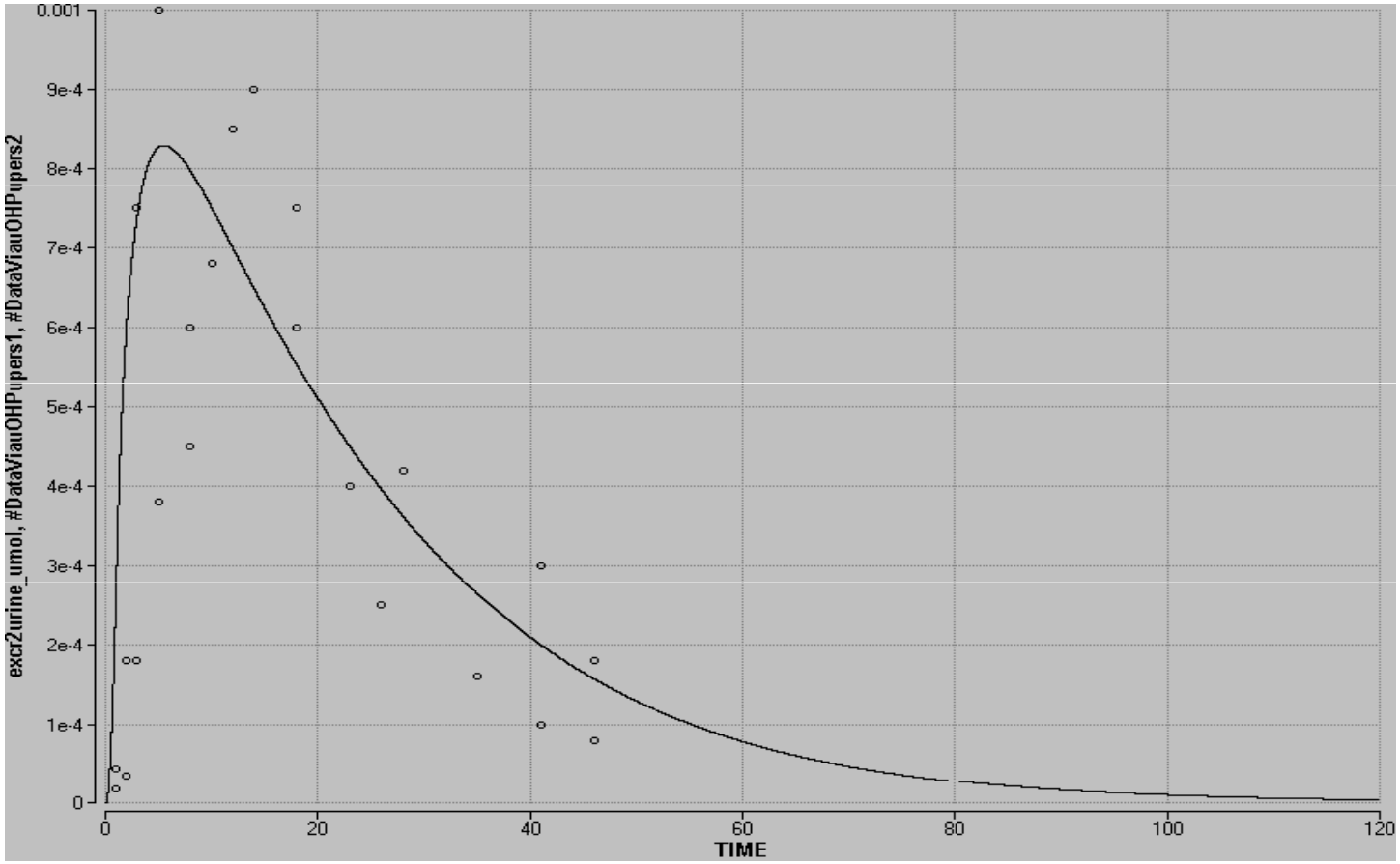
Uitscheiding na dermale opname pyreen



Dermal exposure to creosote oil for 1 hour, followed by washing of the skin, N=2, t12: 15 hrs (calculated)

Viau, 1995, Science total Env

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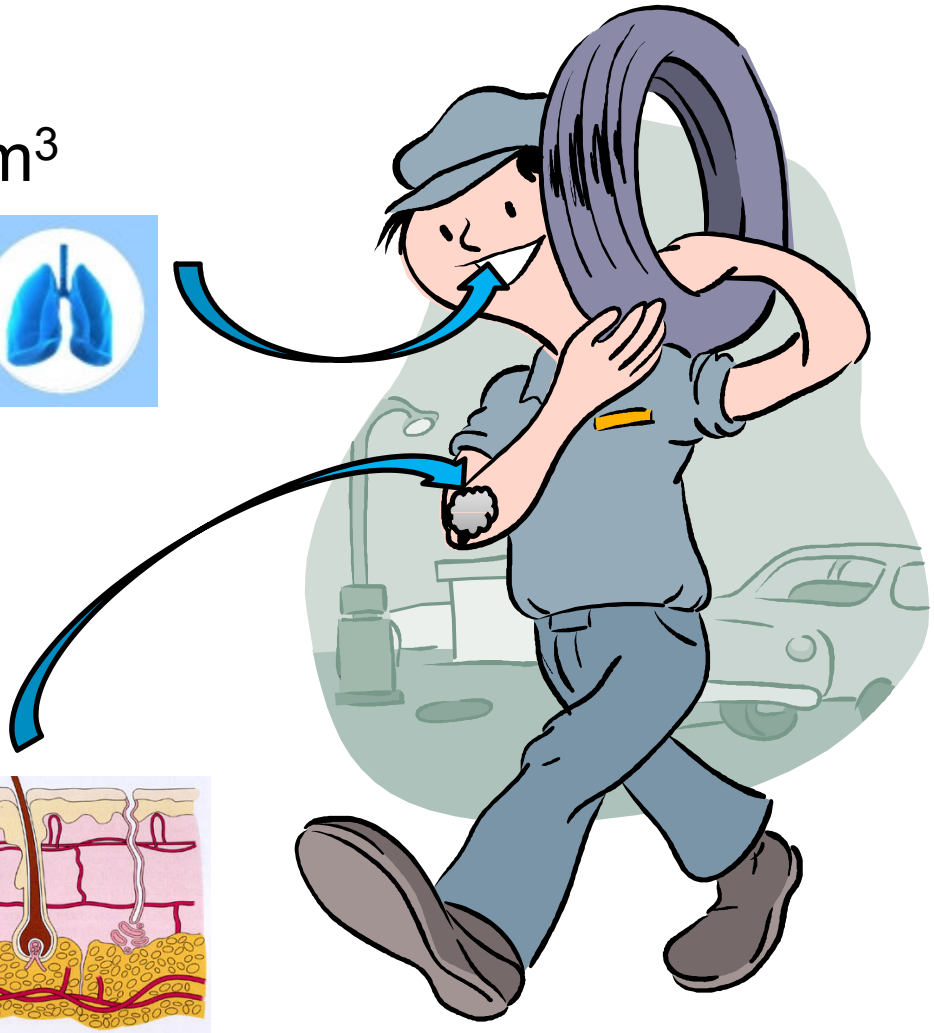
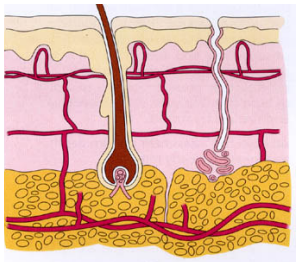
X mg/m^3

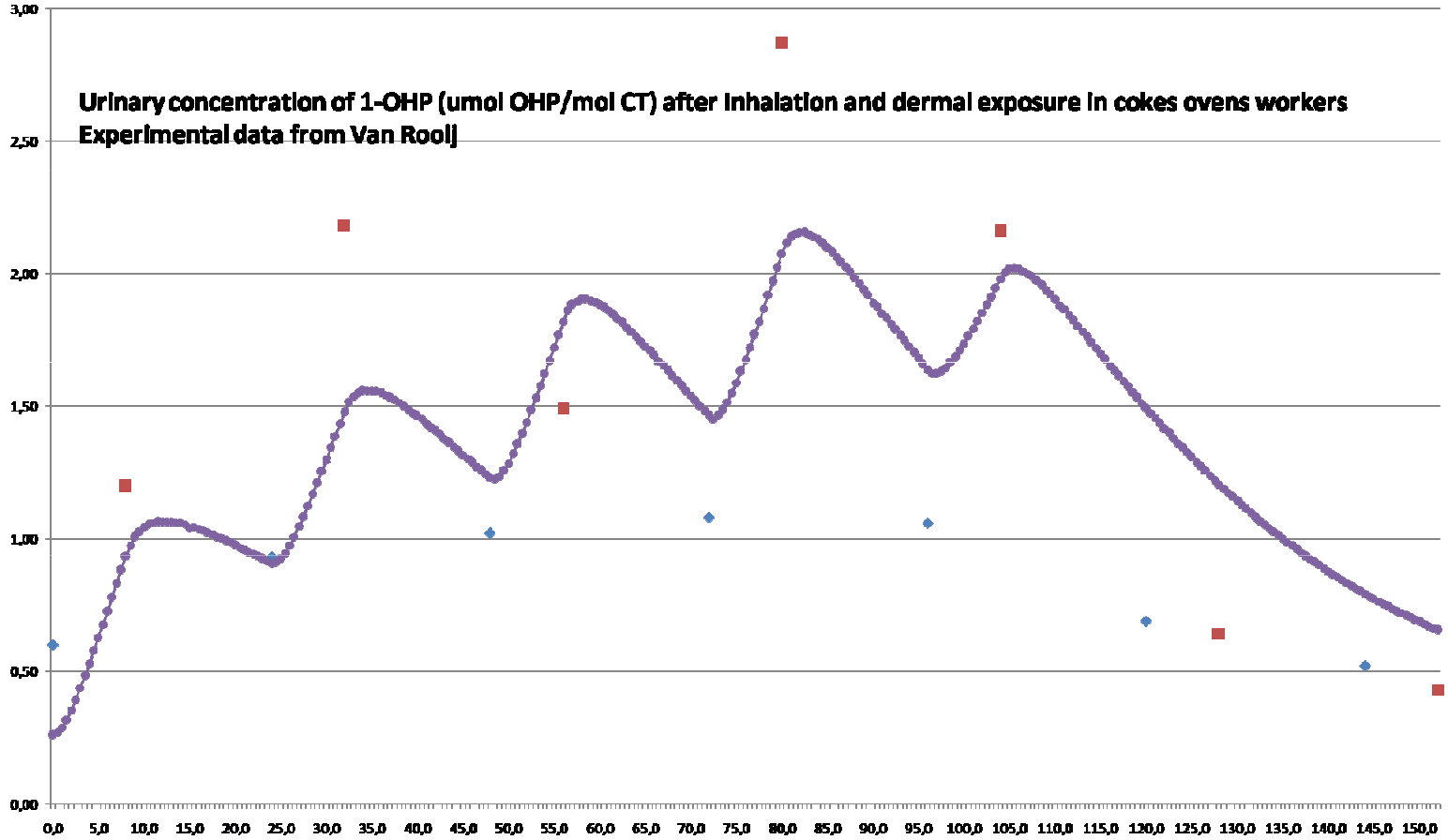




Y mg/cm$^{2\cdot}$ hr

?

Uitscheiding na gecombineerde blootstelling



Inhalation and dermal exposure to pyrene for coke oven workers for 5 consecutive days

N=12, t12: 18 hrs (calculated)

Van Rooij, 1993, British J Indus Med

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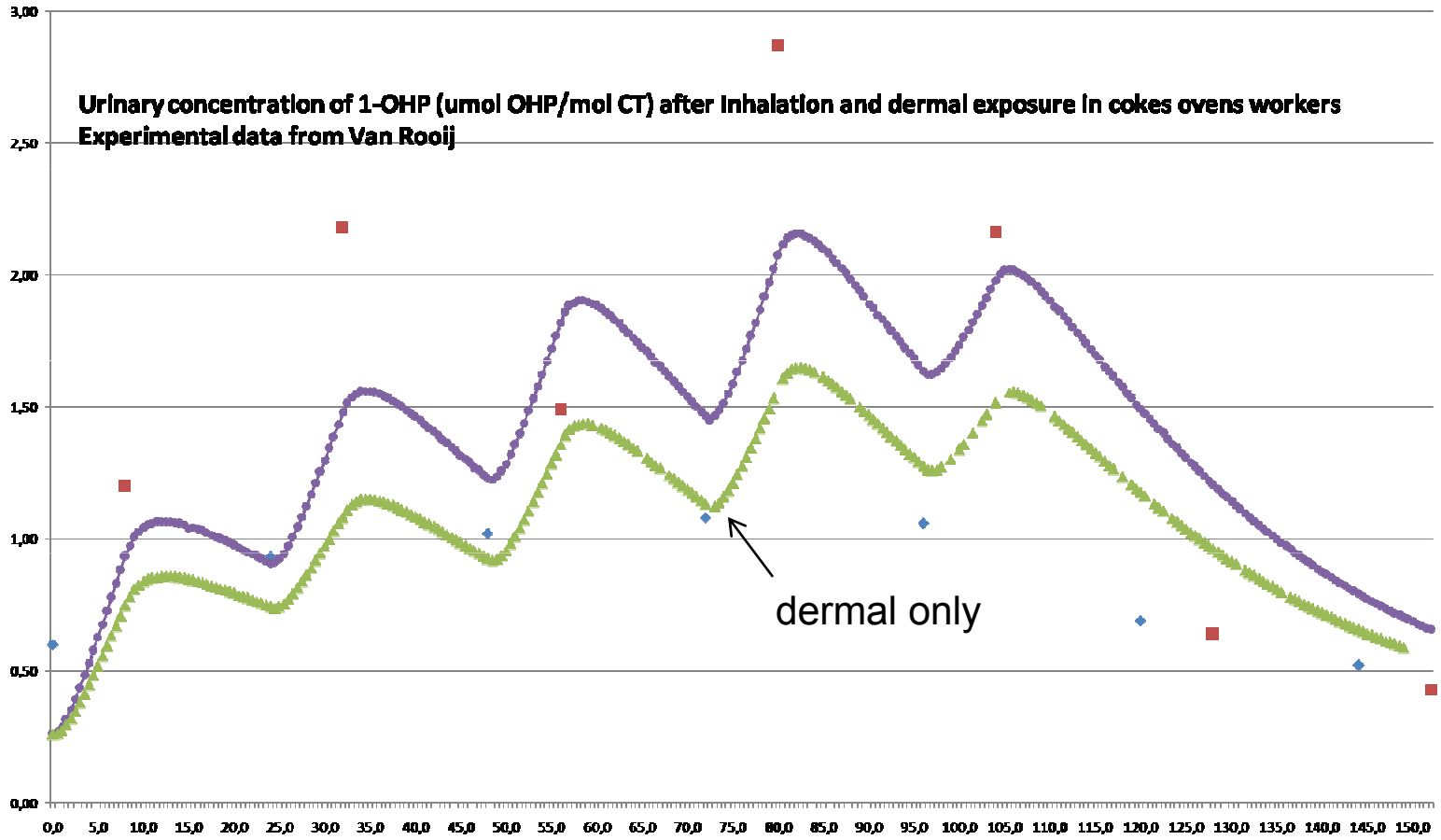
Uitscheiding na gecombineerde blootstelling



Inhalation and dermal exposure to pyrene for coke oven workers for 5 consecutive days
N=12, t12: 18 hrs (calculated)

Van Rooij, 1993, British J Indus Med

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Conclusie

- Door inzet van kinetische (huid) modellen is een hoop inzicht te verkrijgen in o.a.:
  - Multiroute blootstelling
  - Contributie per opnameroute
  - Relatie tussen uitwendige en inwendige (biologische) concentratie

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