Estimation of Bioavailability of Environmental Estrogens in Population Models

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Contents

Introduction

Endocrine Active Compounds

Alter signaling processes of the endocrine system by hormone mimetic effects

Environmental Estrogens/ Xenoestrogens

– Synthetic compounds

(DDT, bisphenol A, alkylphenols, e.g. p-tert-octylphenol)

– Phytoestrogens

(isoflavones, e.g. daidzein)

Risk Assessment

- Exposure to synthetic and natural estrogens
- Estrogenic and anti-estrogenic effects of the same compound
- Endocrine effects are not necessarily adverse effects
- Background level of endogenous estrogens

Biological Endpoints Proposed to be associated with Endocrine Active Compounds

- Cancers (ovarian, breast, testicular)
- Transplacental carcinogenesis
- Decreased sperm count and motility
- Malformations of female reproductive tract and male urogenital tract
- Increased ectopic pregnancies
- Decreased reproductive success
- Decreased weights of uterus or testes
- Altered estrous or mentrual cycling
- Steroid receptor binding or inhibition
- Altered hormone levels
- Altered cell proliferation and cell differentiation
- Altered behaviour
- Hyperactivity
- Degraded immune function
- Imposex/ hermaphroditism

Investigated Compounds

Daidzein

Phytoestrogen

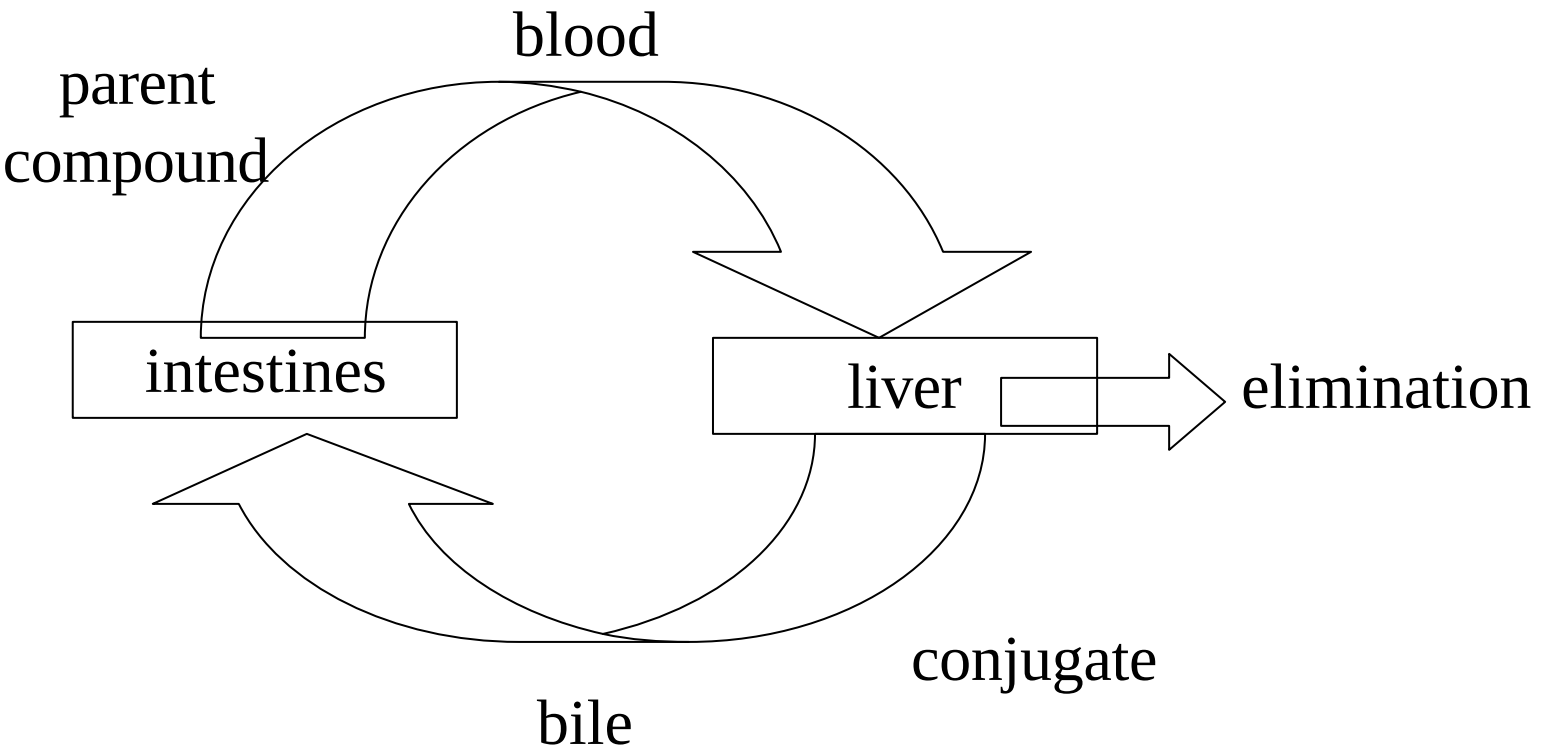
Bisphenol A

Industrial chemical

p-tert-Octylphenol

Industrial chemical

Enterohepatic Circulation



Data

Institute of Occupational Physiology at the University of Dortmund (*IfADo*):

- Animal experiments with female DA/Han rats
- 3-7 blood samples per animal
- Daidzein, bisphenol A, *p*-*tert*-octylphenol
- Application: intravenously (low dose)
  orally (low dose, high dose)

Models

Oral Bioavailability

$$F_{oral} = \frac{AUC_{oral} \cdot dose_{intravenous}}{AUC_{intravenous} \cdot dose_{oral}}$$

F_{oral} : oral bioavailability

AUC: area under the concentration-time curve

Oral: after oral application

Intravenous (short: i.v.): after intravenous application

Models

Three-exponential function

(intravenous application)

$$C_p = A \cdot e^{-\alpha t} + B \cdot e^{-\beta t} + C \cdot e^{-\gamma t}$$

Population Model

$$\ln(AUC),\ s^2 \mid \qquad \ln(AUC_i) \sim N(\ln(AUC),\ s^2 g(\ln(AUC_i)))$$

$$i = 1, \ldots, N$$

$$\ln(AUC_{a\ priori}),\ t^2 \mid \quad \ln(AUC) \sim N(\ln(AUC_{a\ priori}),\ t^2)$$

$$r,\ l \mid \qquad 1/\ s^2 \sim Ga(r,\ l)$$

$AUC_{a\ priori}$ prior information, $g(x) = x^2$

$E(1/\ s^2) = r/\ l \approx 1/\ t^2$

$$\hat{\tau}^2 = \sum_{i=1}^{N} \left(\ln(AUC_i) - \ln(AUC_{a\ priori})\right)^2 \Big/ N - 1$$

Bayes Estimate

In case of fixed s^2 the posterior distribution of $\ln(AUC)$ is given by

$\ln(AUC) \sim N(Bb, B)$, where

$$B^{-1} = \sum_{i=1}^{N} \left(\sigma^2 g(\ln(AUC_i))\right)^{-1} + \left(\tau^2\right)^{-1} \text{ and}$$

$$b = \sum_{i=1}^{N} \left(\sigma^2 g(\ln(AUC_i))\right)^{-1} \ln(AUC_i) + \left(\tau^2\right)^{-1} \ln(AUC_{apriori})$$

EM Algorithm

E-step:

$$\ln(AUC)^{(l)} = \left[\sum_{i=1}^{N}\left(\sigma^{2(l-1)} g(\ln(AUC_i))\right)^{-1} + \left(\hat{\tau}^2\right)^{-1}\right] \cdot \left[\sum_{i=1}^{N}\left(\sigma^{2(l-1)} g(\ln(AUC_i))\right)^{-1} \cdot \ln(AUC_i) + \left(\hat{\tau}^2\right)^{-1} \cdot \ln(AUC_{apriori})\right]$$

EM Algorithm

M-step:

$$\sigma^{2(l)} = \frac{\sum_{i=1}^{N} \left(\ln(AUC_i) - \ln(AUC^{(l)})\right)^2 / g\left(\ln(AUC_i)\right) + 2\lambda}{N + 2\cdot(r-1) - 1}$$

Starting value:

$$\sigma^{2(0)} = \frac{\sum_{i=1}^{N} \left(\ln(AUC_i) - \ln(AUC_\bullet)\right)^2 + 2\cdot\lambda}{\left(N + 2\cdot(r-1) - 2\right)} \text{ with}$$

$$\ln(AUC_\bullet) = \sum_{i=1}^{N} \ln(AUC_i) \Big/ N$$

Results

- Difficulties with estimation of AUC_i
- Fast convergence of the EM algorithm:

  1-3 iterations
- Impact of the choice of $g(.)$

Daidzein

Estimates of oral bioavailability

$F_{10\ apriori}$=	9.7 %	$g(x)$ =		
$F_{100\ apriori}$=	2.2 %	1	x	x^2
Dose in mg/kg	$s^{-2} \sim$	$F\text{-}AUC_{i.v.\ apriori}$ $F_{pop.\ mean}$	$F\text{-}AUC_{i.v.\ apriori}$ $F_{i.v.\ pop.\ mean}$	$F\text{-}AUC_{i.v.\ apriori}$ $F_{i.v.\ pop.\ mean}$
10 (i.v.)	*Ga*(8;2)			
10 (oral)	*Ga*(2;1,815)	8.69 % 8.38 %	8.37 % 8.28 %	9.07 % 9.06 %
100 (oral)	*Ga*(,2;3,19)	1.22 % 1.18 %	1.26 % 1.25 %	1.79 % 1.79 %

Daidzein

Estimates of *AUC*, *B*, and s^2 for group B (10 mg/kg oral)

$AUC_{apriori}$=	48623	$g(x)$ =	
Estimate of	1	x	x^2
AUC	43565	41954	45442
B	36.24	5.08	1.50
σ^2	0.34	0.29	0.28

Bisphenol A

$F_{10\ apriori}$= 16.4 % $F_{100\ apriori}$= 5.6 %		$g(x)=x^2$	
Dose in mg/kg	s^{-2} ~	$F\text{-}AUC_{i.v.\ apriori}$	$F_{population\ mean}$
10 (i.v.)	*Ga*(1;2)		
10 (oral)	*Ga*(1;7)	15.41 %	20.27 %
100 (oral)	*Ga*(1;4)	3.81 %	5.01 %

p-tert-Octylphenol

$F_{50\ apriori}$= 12.3 % $F_{200\ apriori}$= 8.4 %		$g(x)=x^2$	
Dose in mg/kg	s^{-2} ~	$F\text{-}AUC_{i.v.\ apriori}$	$F_{population\ mean}$
5 (i.v.)	*Ga*(2;2)		
50 (oral)	*Ga*(3;2)	11.75 %	12.41 %
200 (oral)	*Ga*(3;2)	8.13 %	8.58 %

Discussion

- Estimation of AUC_i:
  - Spline functions
  - Linear approximation
  - $y(t) = y_N \cdot \exp\{\dot{y}_N \cdot (t - t_N) / y_N\}$
- EM algorithm: 1-3 iterations
  - 4-stage model, 4×4 matrices: 7-15 minutes
- Impact of prior density
- Comparison with pregnant rats for daidzein