NEUROSOME

Exploring The Neurological Exposome

Computational methods in toxicology

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http://www.enve-lab.eu

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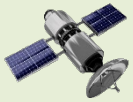
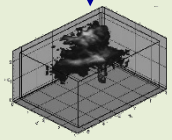
Connectivity-based workflow for exposome studies

Environmental sensors

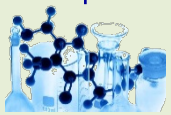
Remote sensing



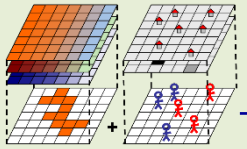
Exposure modelling

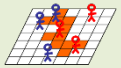


Environmental modeling / data management



Environmental analysis

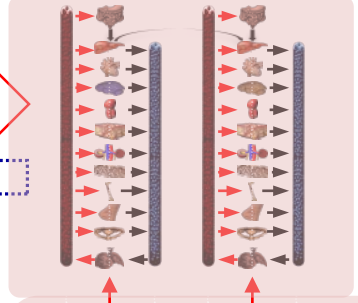




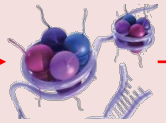
Agent based modelling

Ubiquitous personal sensors

Environmental data

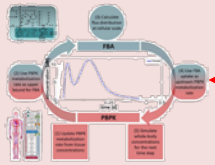


Human biosampling

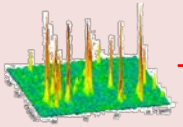


Epigenetics

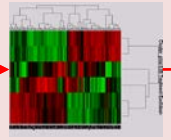
Genomics



Fluxomics (dynamic flux balance analysis)



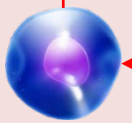
Metabolomics



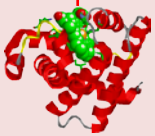
Transcriptomics

Biological data

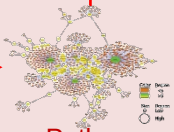
Bioinformatics / systems biology



Cellular/tissue effects

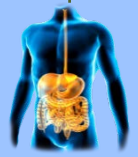


Molecular initiating events

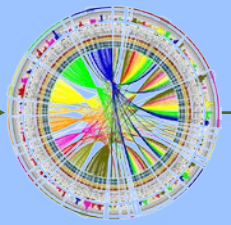


Pathway analysis

Clinical data



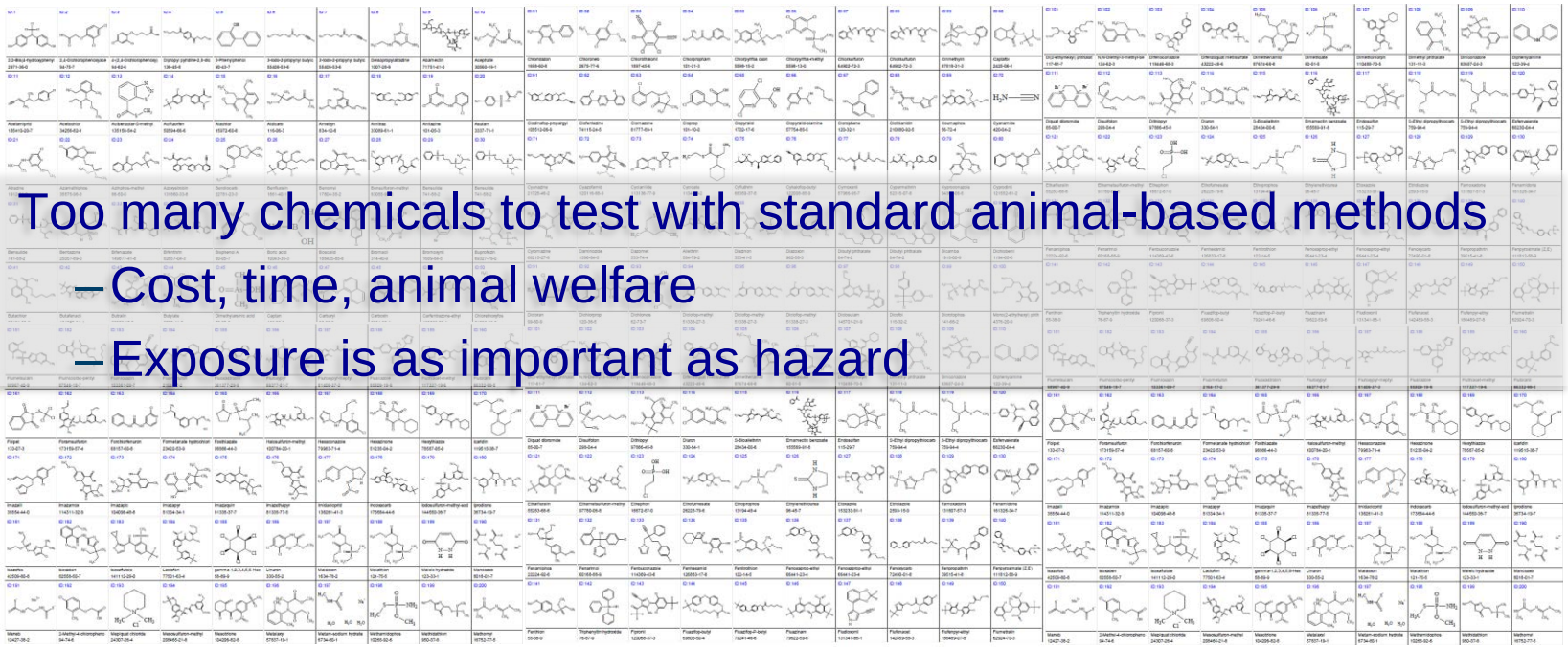
Systems Effects / Individual exposome



EWAS

Community Effects / Cohorts

"*anything that we can do with a computer in toxicology*"



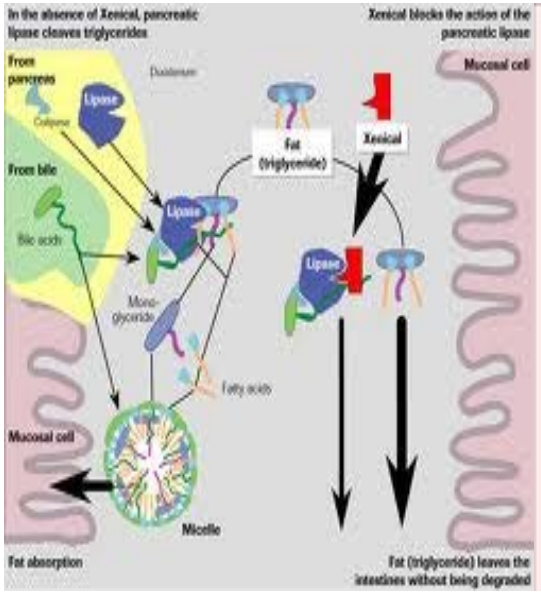
- Too many chemicals to test with standard animal-based methods
  - Cost, time, animal welfare
  - Exposure is as important as hazard

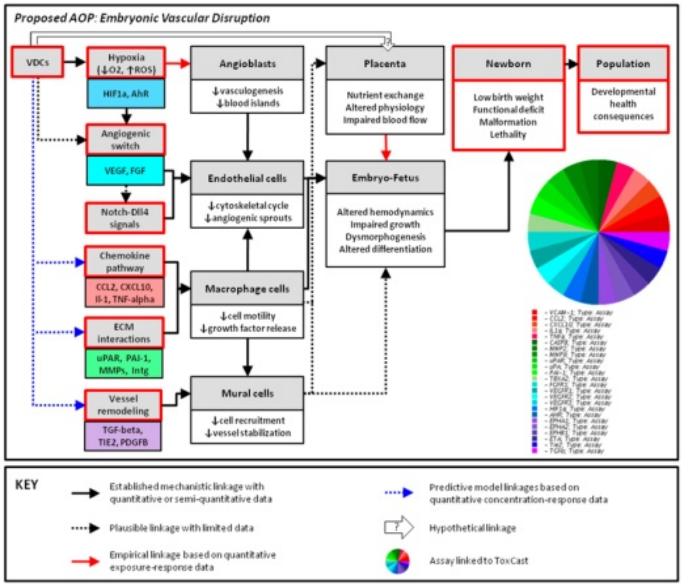
"*integration of modern computing and information technology with molecular biology to improve agency prioritization of data requirements and risk assessment of chemicals*"

Risk assessment of chemicals

Need for better mechanistic data

- Determine human relevance
- What is the relevant Mode of Action (MOA) or Adverse Outcome Pathway (AOP)?

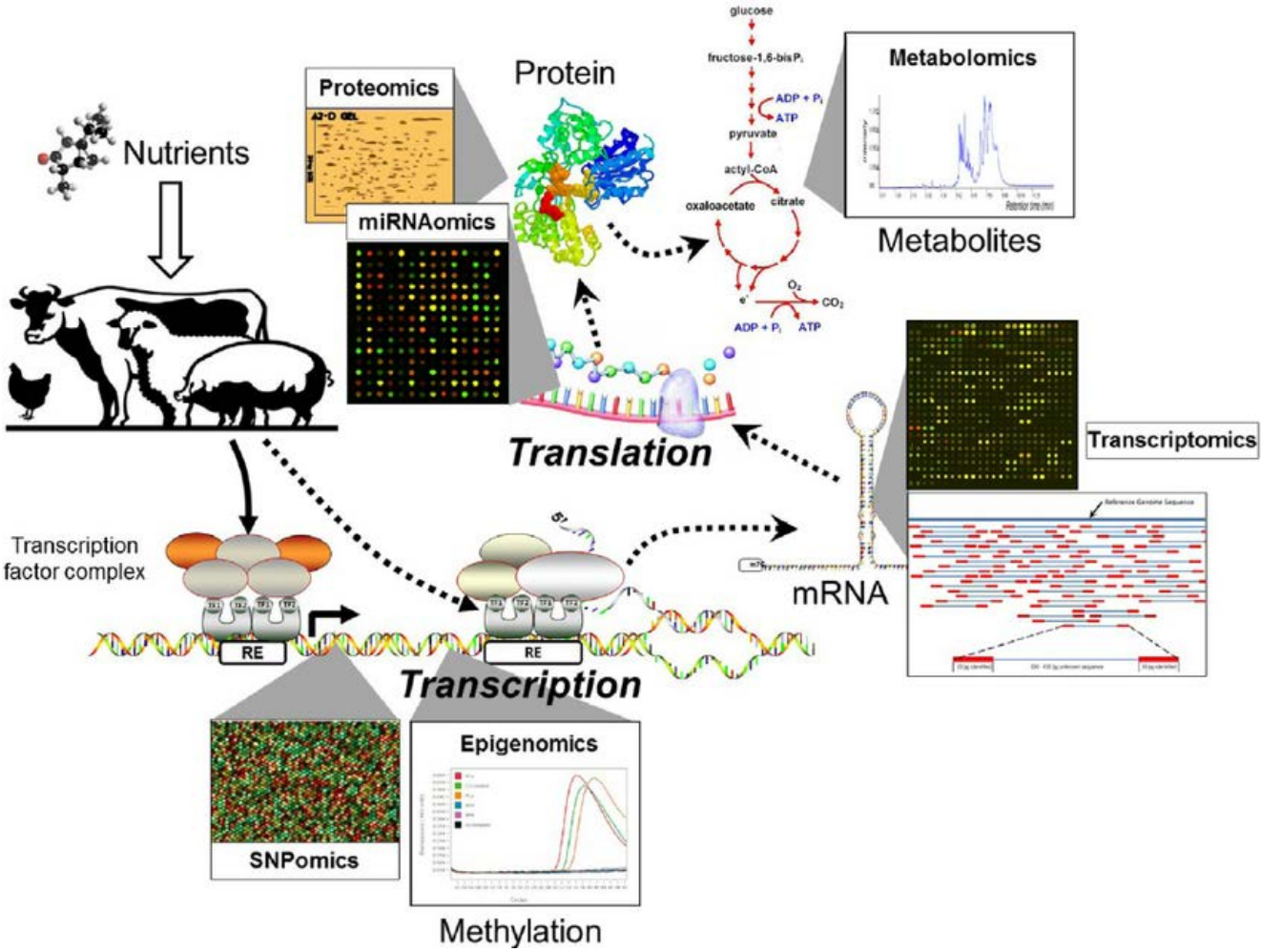




Bioinformatics for multi-omics

- Introduction to “omics”

- Metabolomics
- Metabonomics
- Transcriptomics
- Genomics
- Proteomics
- Bionomics
- Toxicogenomics
- And many more



But what is “omics”?

- A useful concept in biology which informally annotates a field of study ending in ‘-omics’. Omics aims at the collective characterization and quantification of pools of biological molecules that translate into the structure, dynamics and function, of an organism

- "Omics is a general term for a broad discipline of science and engineering for analyzing the interactions of biological information objects in various ‘omes’. […] The main focus is on: 1) mapping information objects such as genes, proteins, and ligands; 2) finding interaction relationships among the objects; 3) engineering the networks and objects to understand and manipulate the regulatory mechanisms; and 4) integrating various omes and omics subfields."

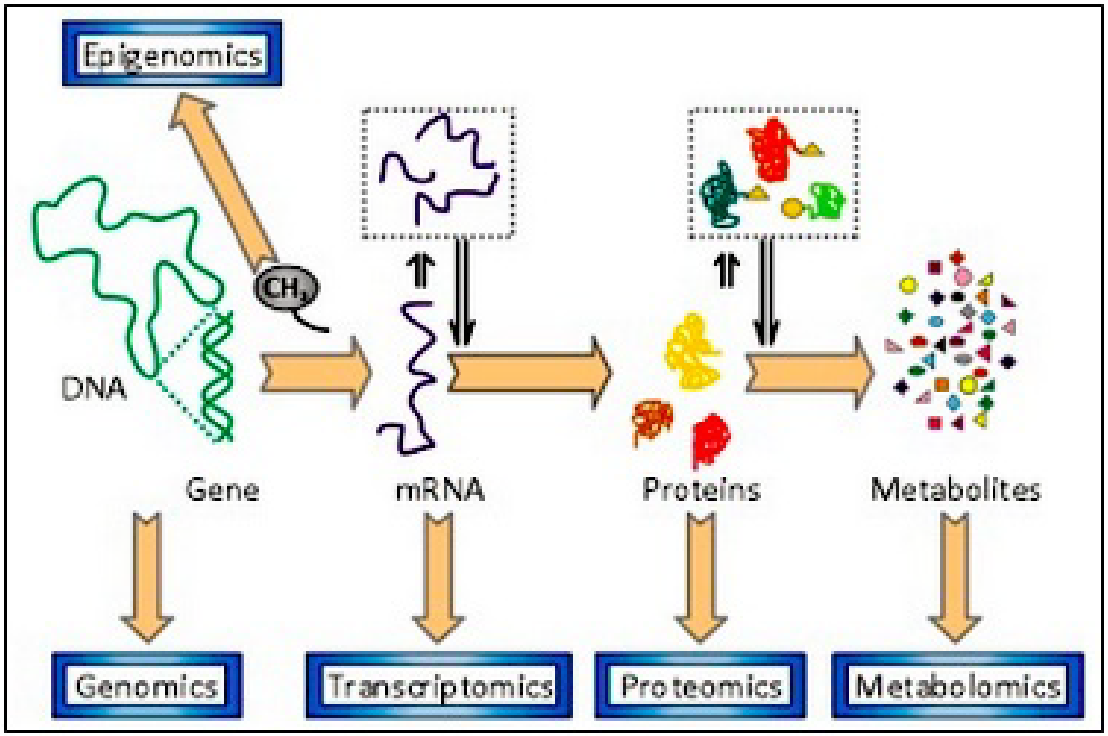


Image Source: Goodacre, J. Exp. Bot 2005.

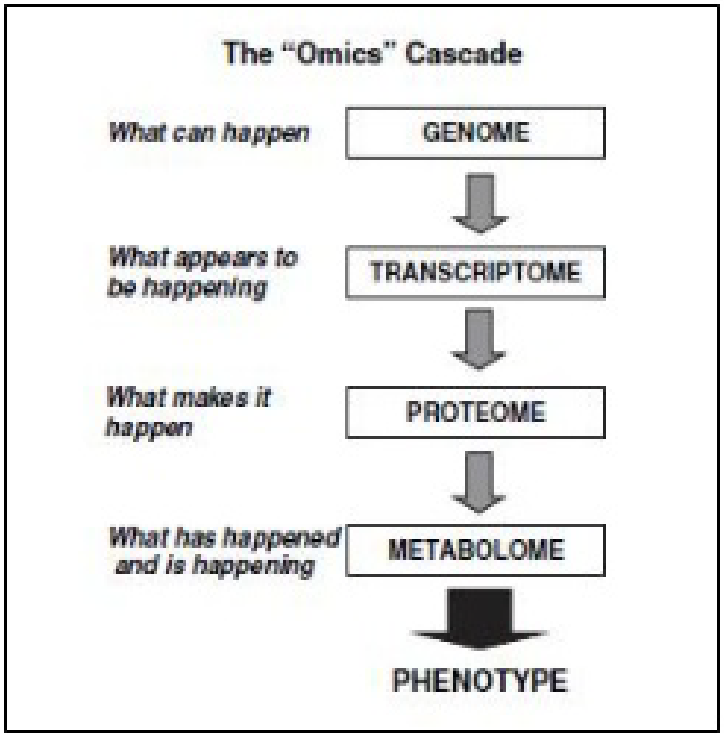
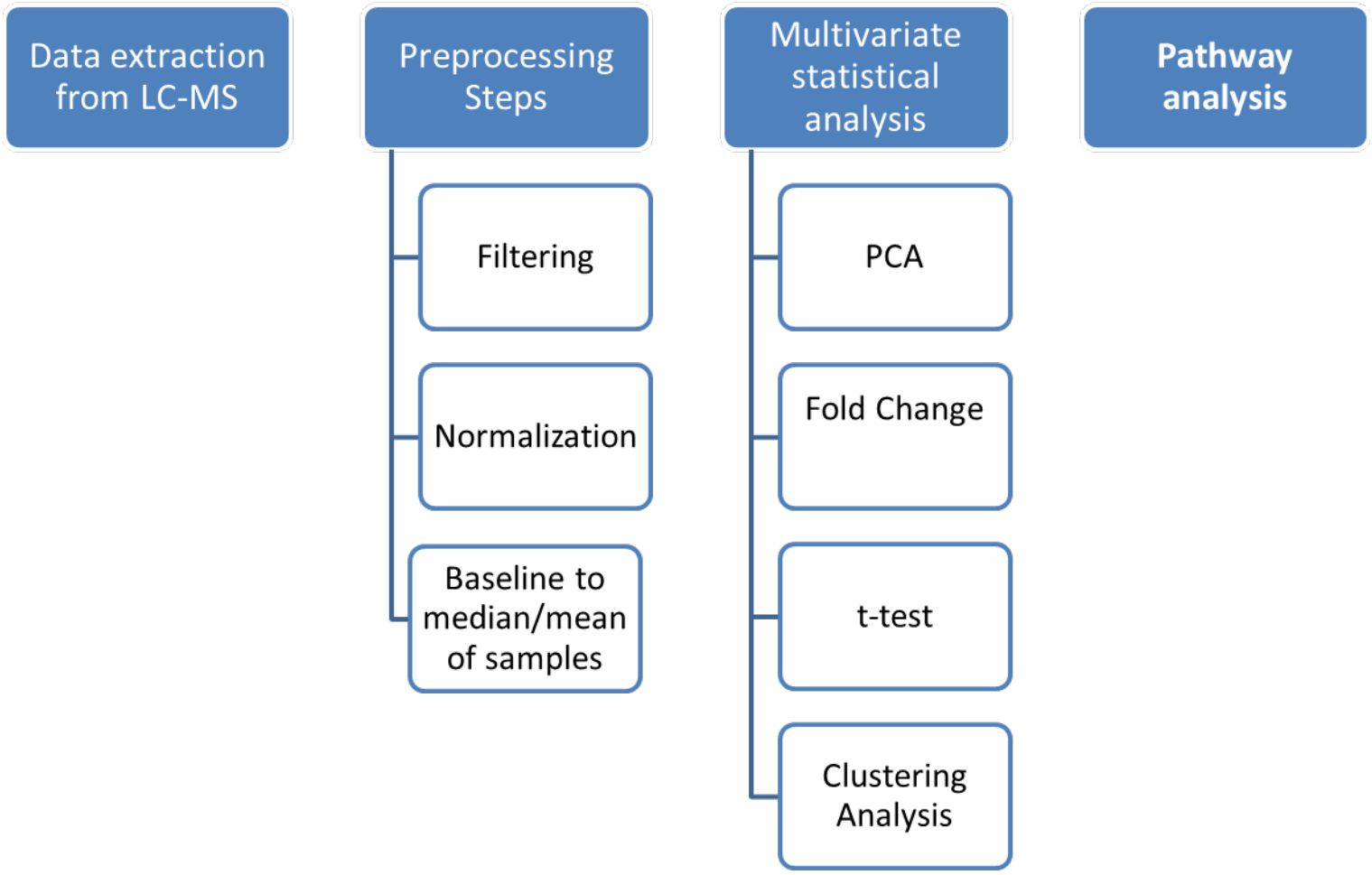


Image Source: http://fluorous.com/images/omics.JPG

Pathway Analysis Workflow



Pathway Analysis-SEA

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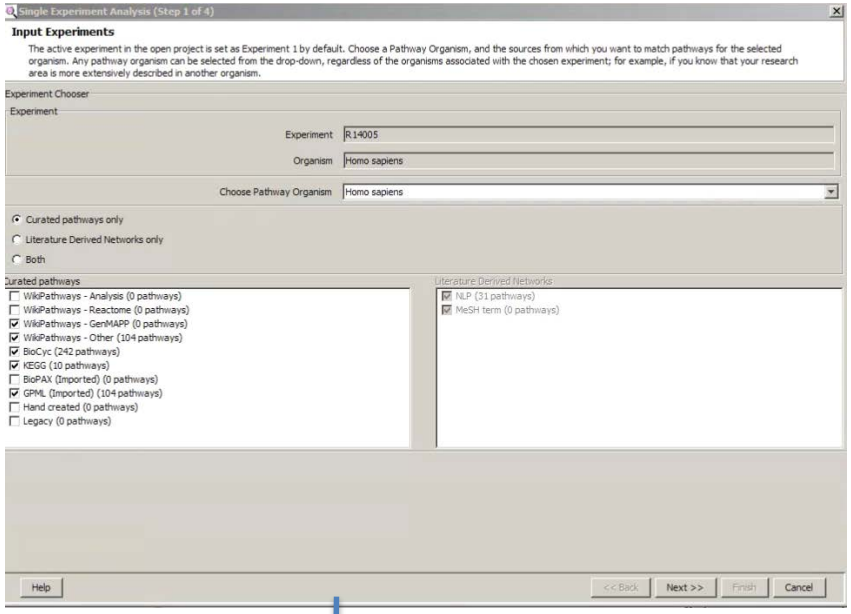
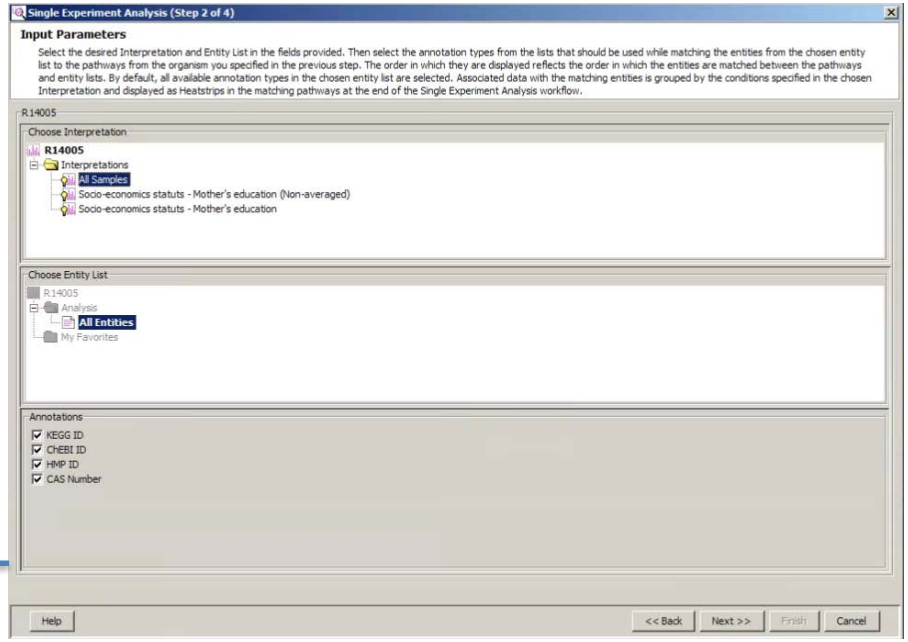


To start a SEA follow the pathway: Workflow→Pathway Analysis→Single Experiment Analysis

Choose pathway databases

Choose annotations



Pathway Analysis-SEA Results

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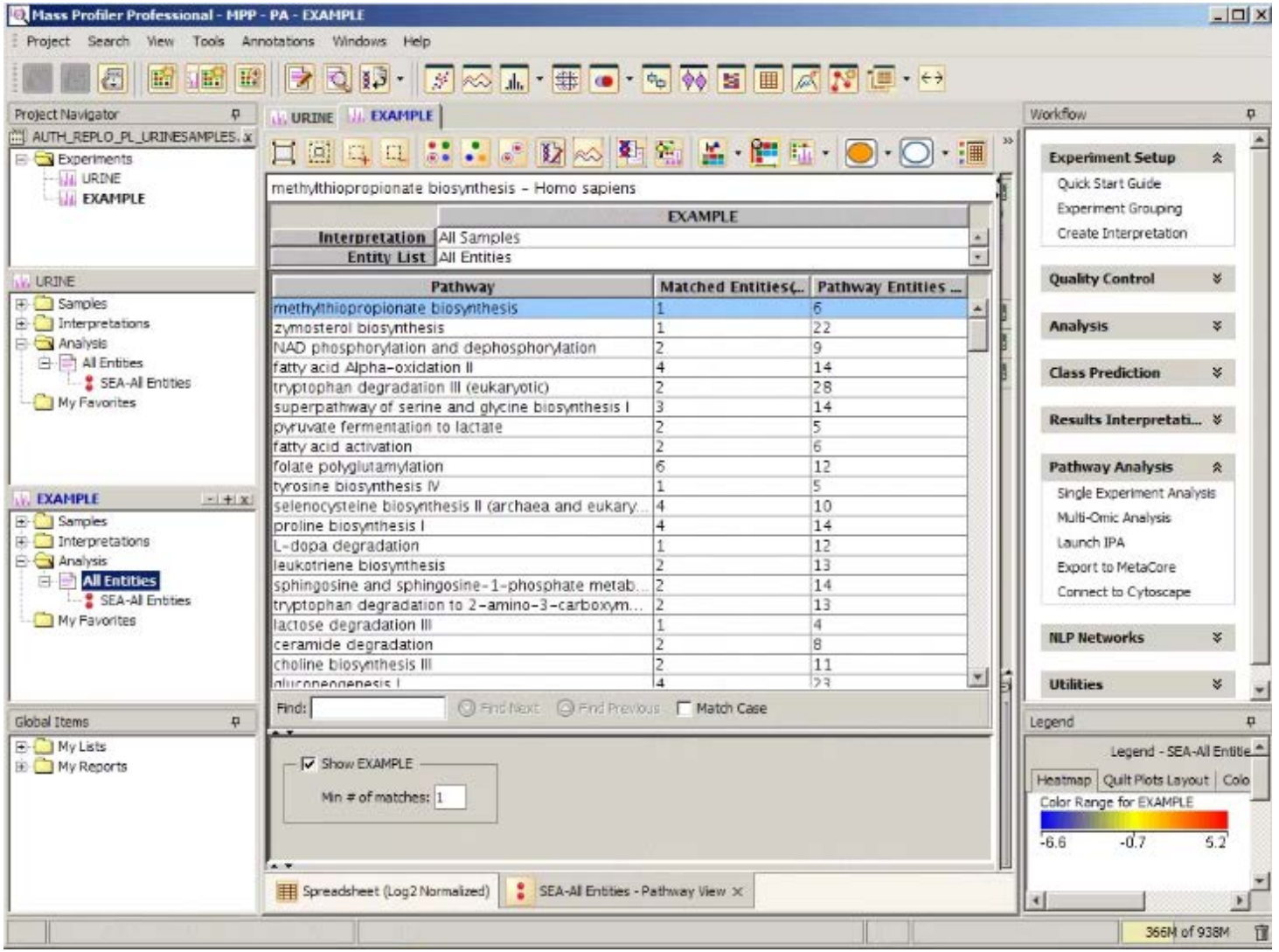
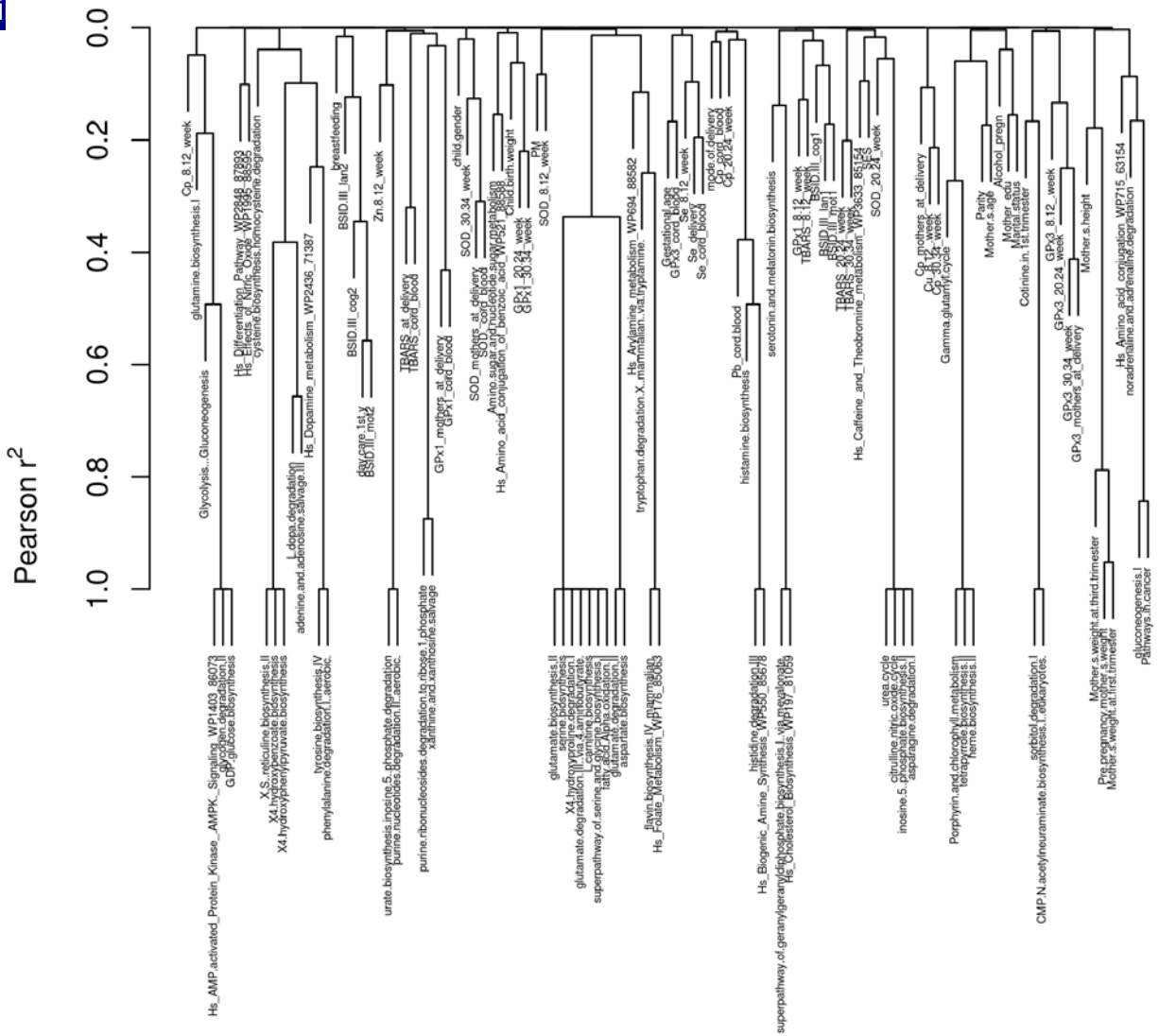


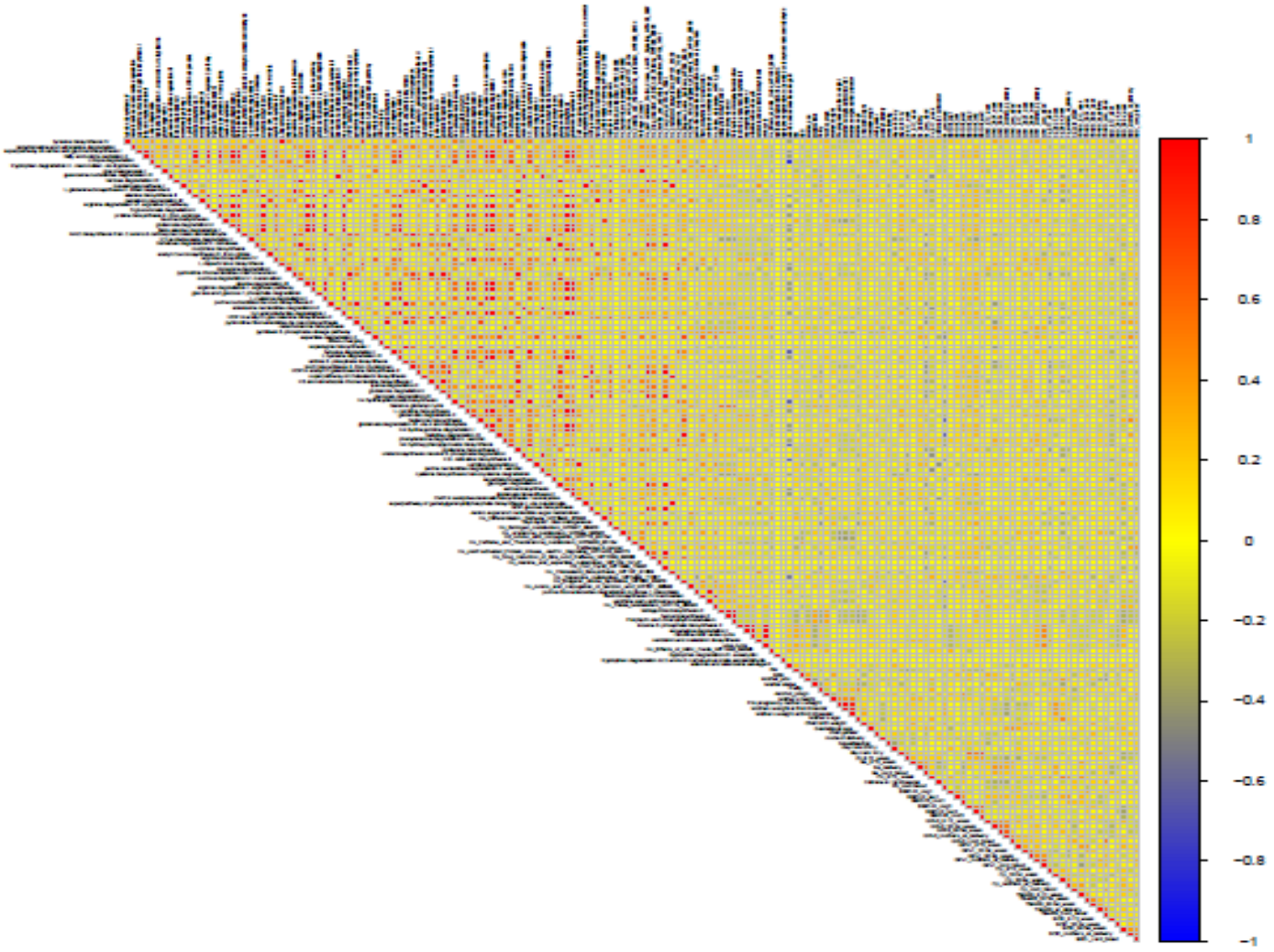
Case Study Repro_PL

- **Urine** and **cord blood** samples of pregnant women exposed to environmental contaminants (phthalates, Pb, Hg)
  - Urinary concentrations of phthalates
  - Cord blood Pb
  - Hair Hg
- EWAS analysis
- LC MS/MS (Thermo Orbitrap) for metabolites identification
- NMR (Agilent 600MHz)
- Agilent Genespring / Mass Profiler Pro for pathway identification

Urine samples

Hierarchical clustering using the Pearson correlation




1
0.8
0.6
0.4
0.2
0
−0.2
−0.4
−0.6
−0.8
−1

Correlation Globe

External exposure and metabolic pathway perturbation

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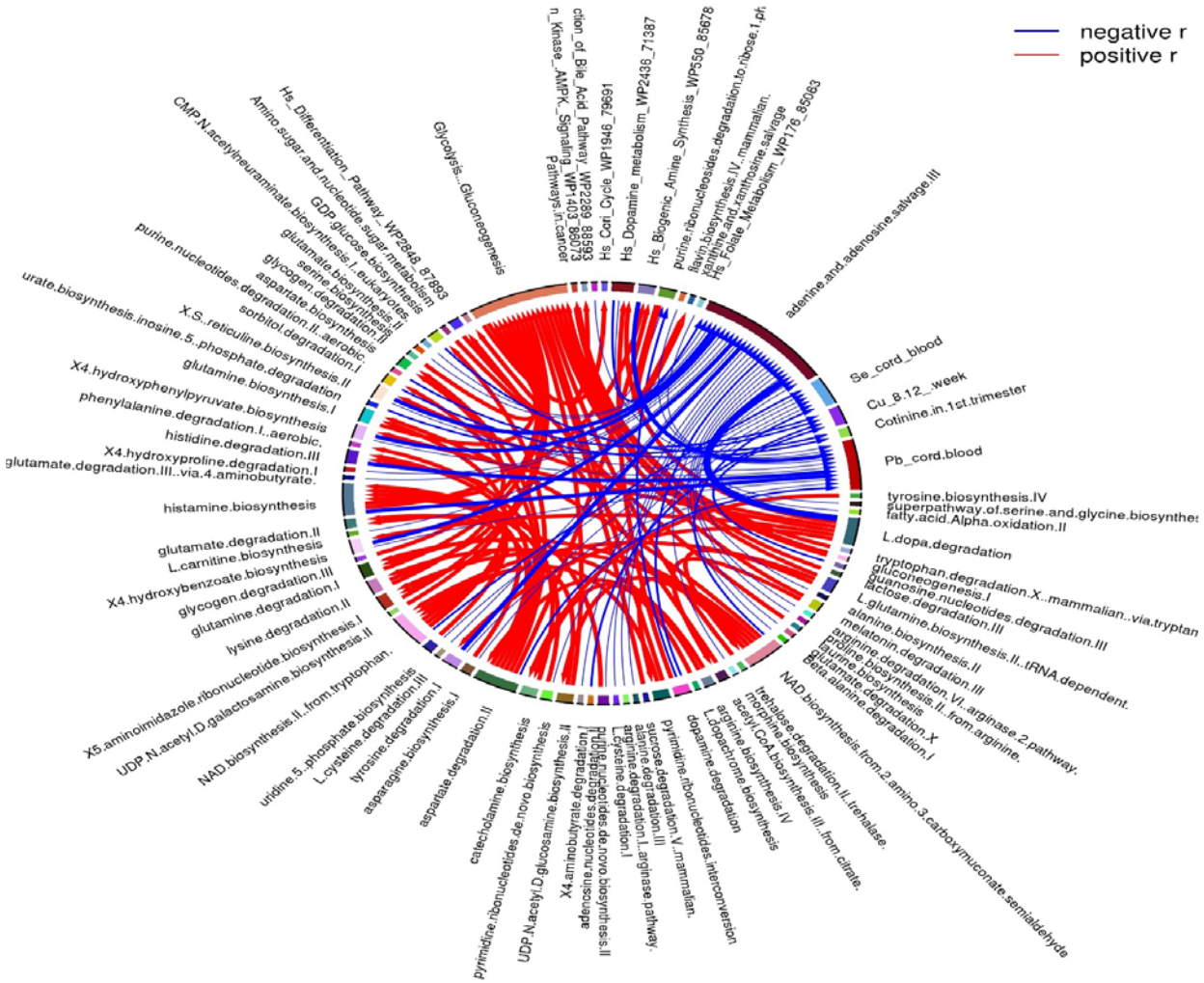

Correlation Globe

health outcomes and metabolic pathway perturbations

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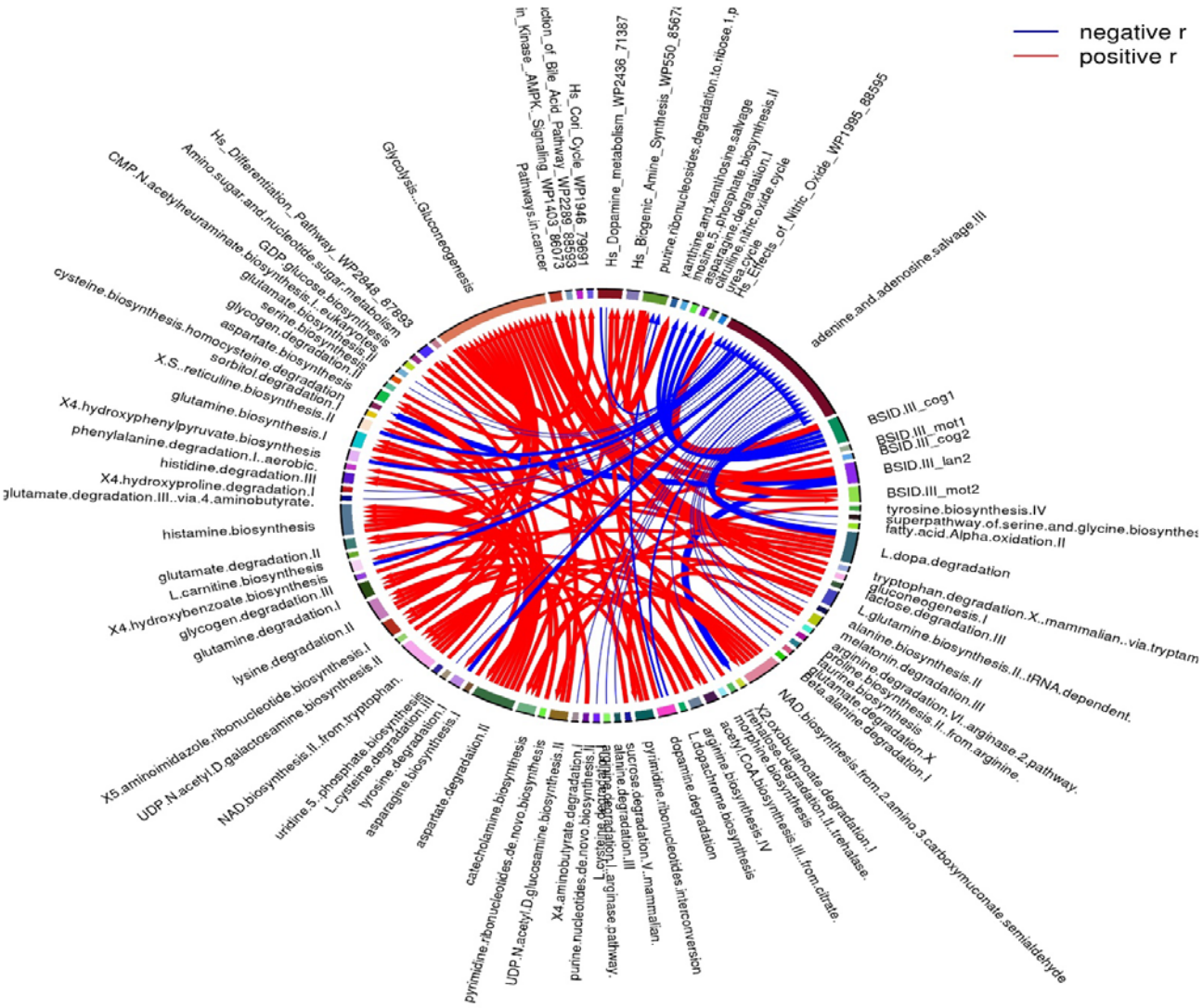

Volcano Plot

Cognitive development

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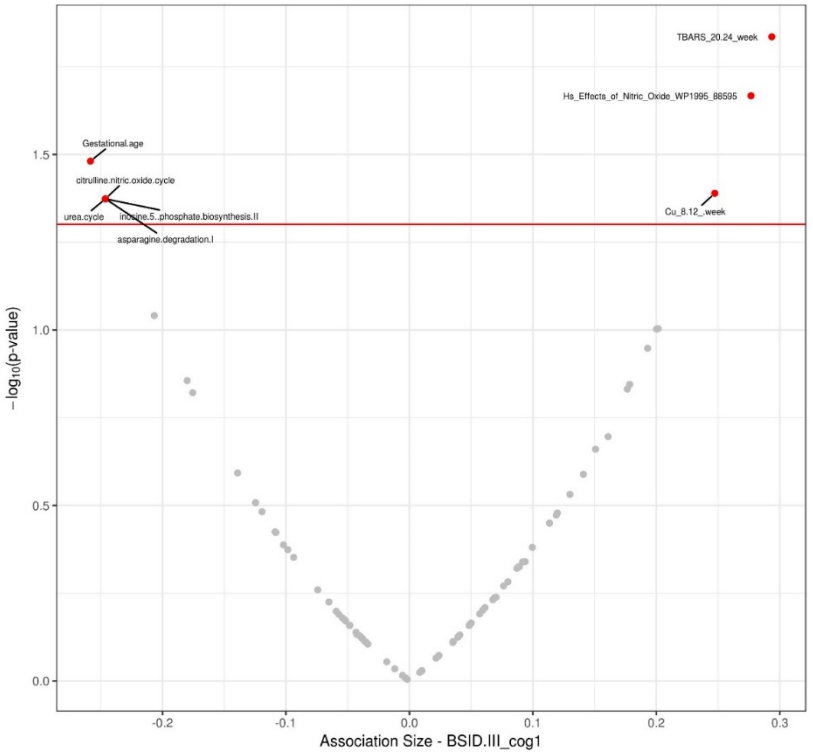

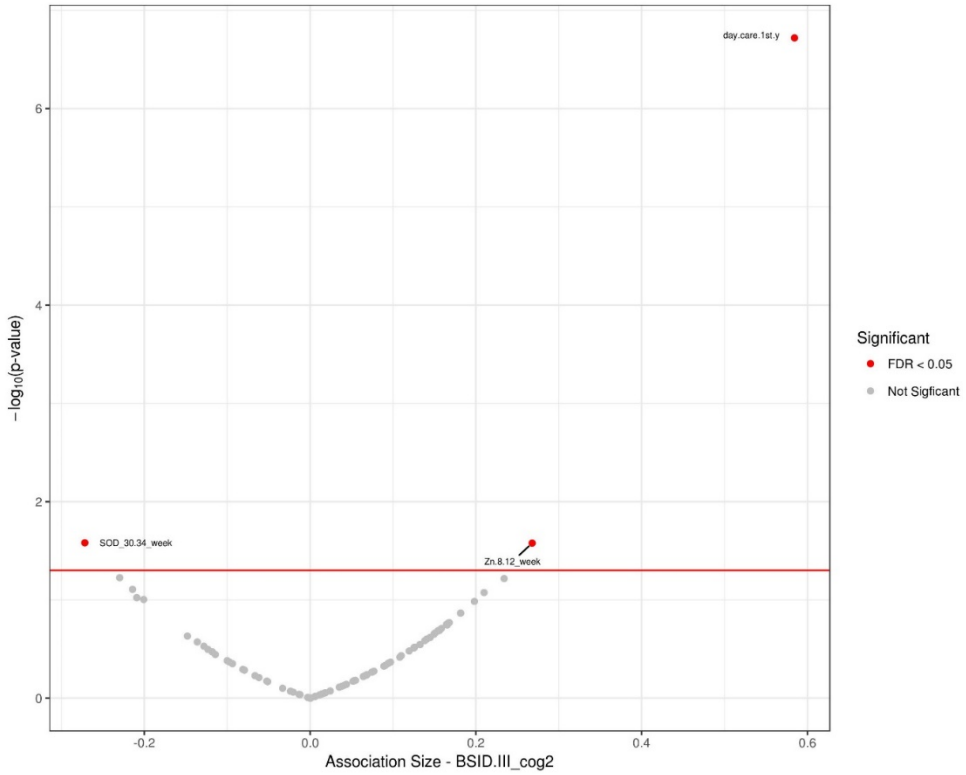

1st year

year

2nd

Volcano Plot

Cognitive development

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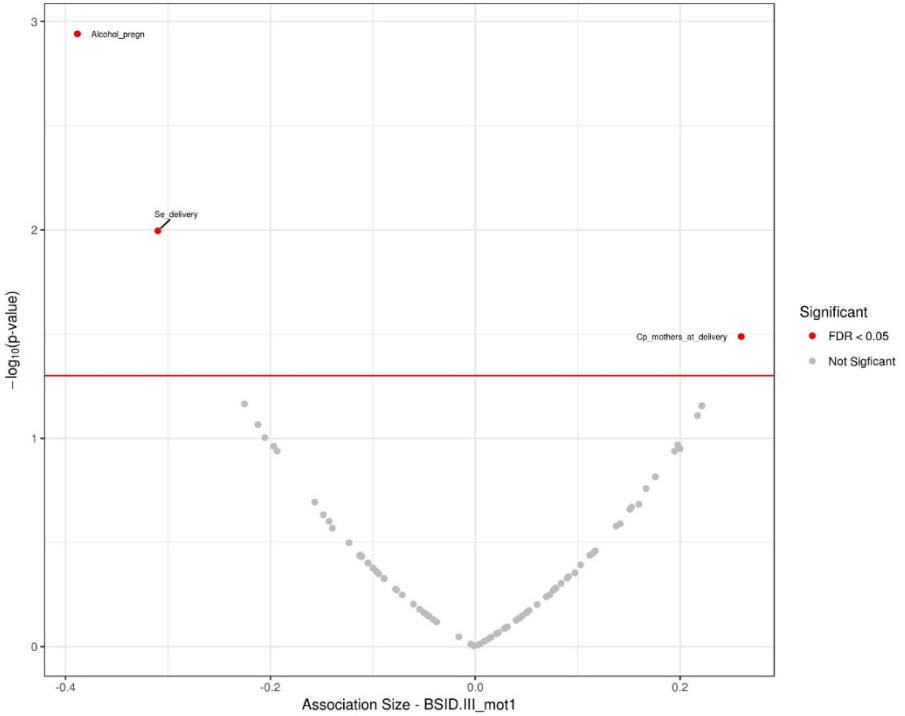
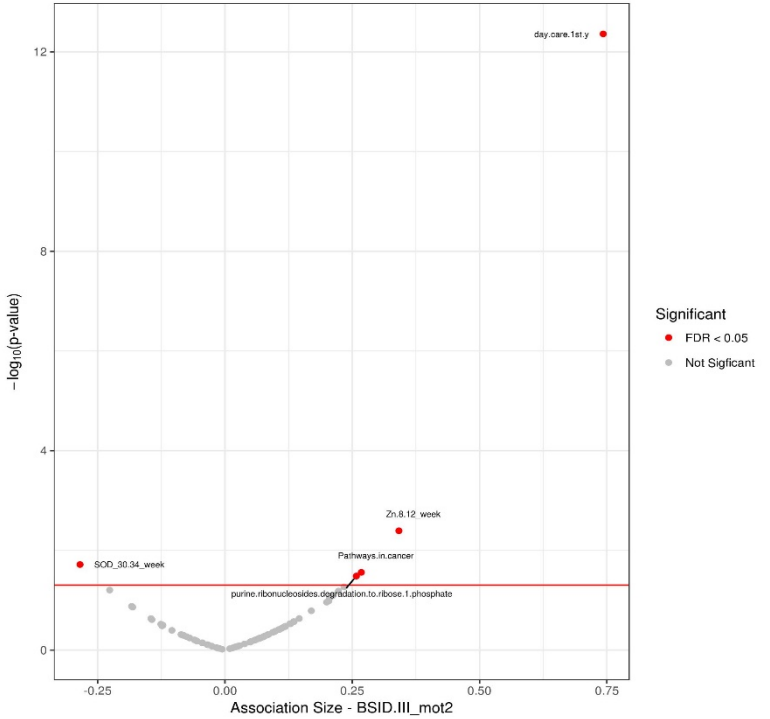
	BSID.III_cog1
Effects of Nitric Oxide	+
Thiobarbituric acid reactive substances (TBARS_20.24_week)	+
Cu 8-12 week	+
Attendance to day care school during the 2st year after birth	+
Gestational age	-
Inosine 5 phosphate biosynthesis II	-
Asparagine degradation I	-
Citrulline nitric oxide cycle	-
Urea cycle	-

	BSID.III_cog2
Zn 8-12 week	+
Superoxide Dismutase-SOD 30-34 week	-

	BSID.III_lan1
Glutathione Peroxide-GPx3 8-12_ week	+
Glutathione Peroxide-GPx3 20-24 week	+
Glutathione Peroxide-GPx3 30-34 week	+
Glutathione Peroxide-GPx3 mothers at delivery	+
SOD 30-34 week	+
Thiobarbituric acid reactive substances (TBARS_8.12_week)	+
GPx1 cord blood	-

	BSID.III_lan2
Oxobutanoate degradation I	+
Cysteine biosynthesis/homocysteine degradation	+
Glycolysis/Gluconeogenesis	+
Drug Induction of Bile Acid Pathway	+
Attendance to day care school during the 1st year after birth	+
Zn 8-12 week	+
Superoxide Dismutase-SOD 30-34 week	-





1st year

year

2nd

	BSID.III_mot1
Lysine degradation II	+
Se delivery	-

	BSID.III_mot2
purine ribonucleosides degradation to ribose 1 phosphate	+
Attendance to day care school during the 1st year after birth	+
Zn 8-12 week	+
Superoxide Dismutase-SOD 30-34 week	-

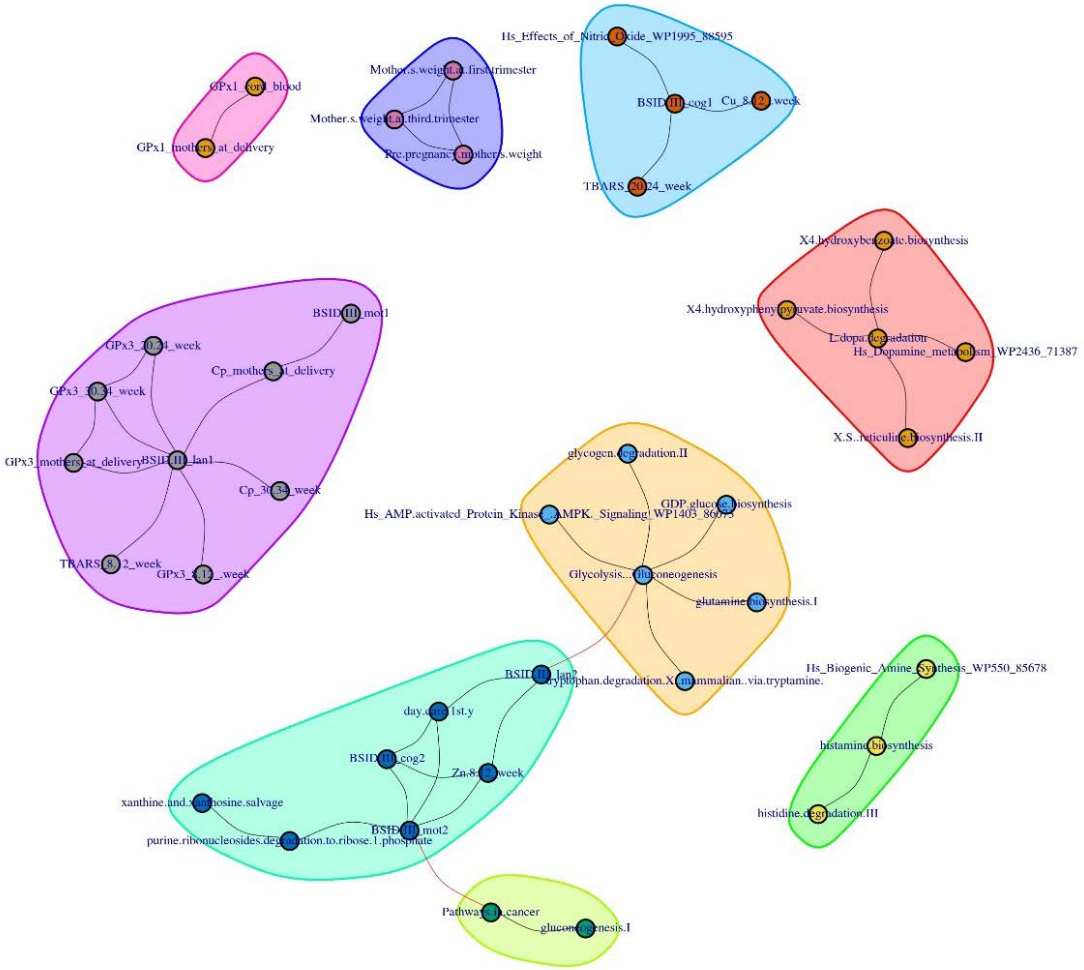


Fig. Undirected community network. Cluster on the correlation results of EWAS analysis.

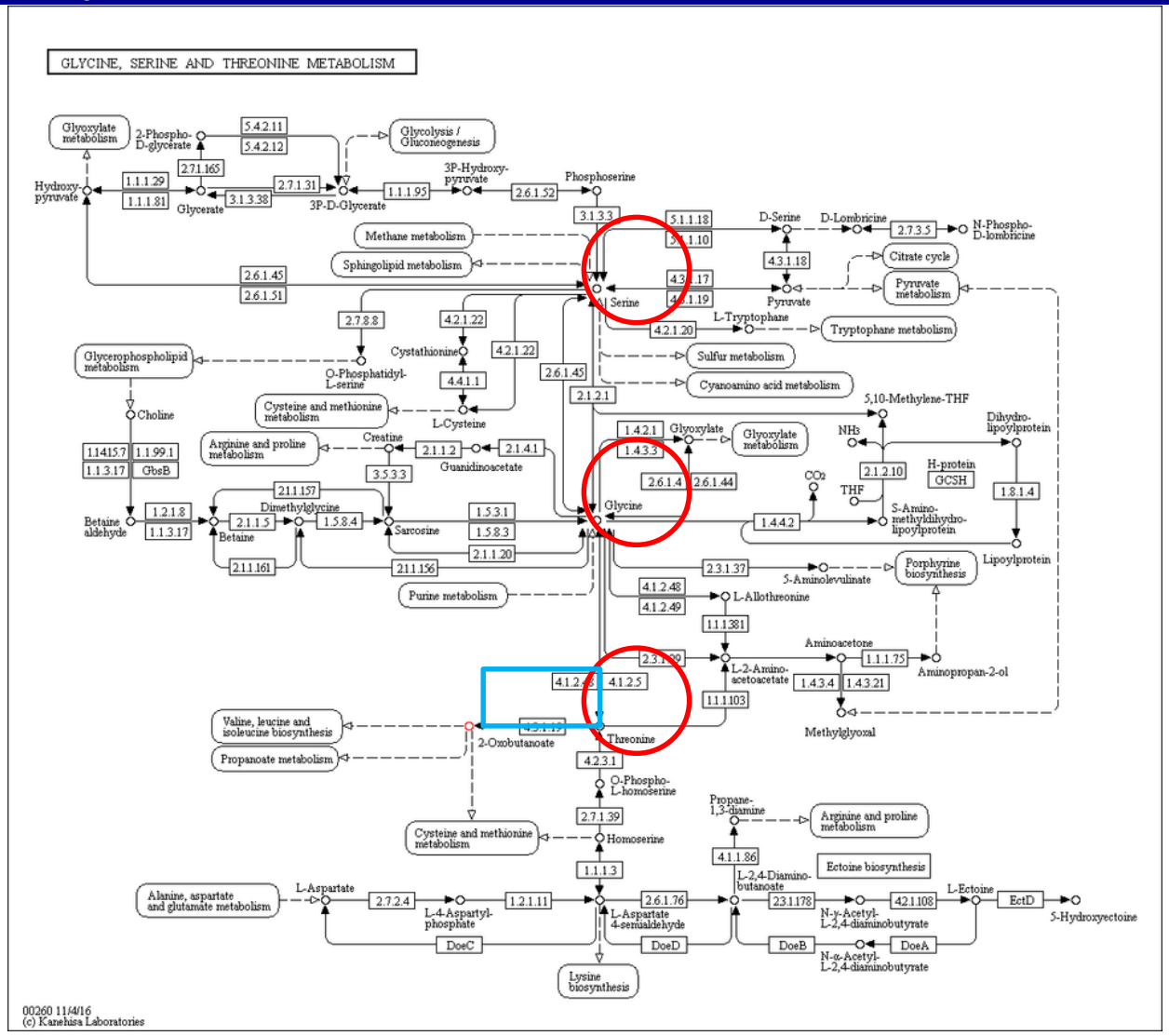
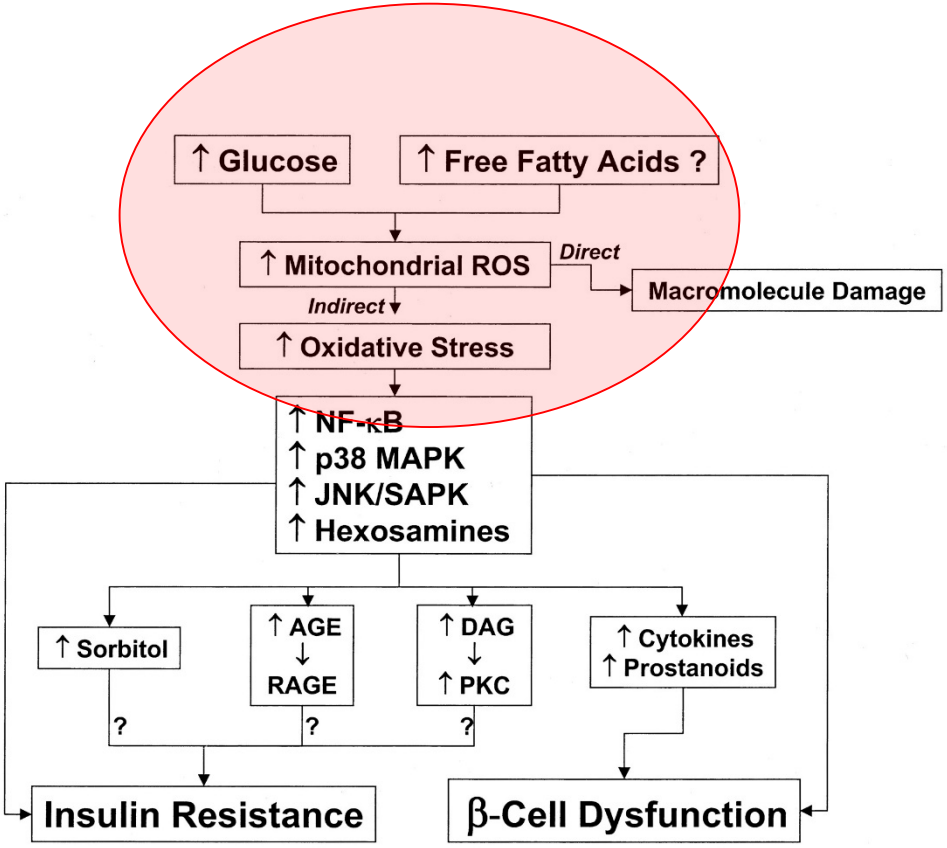
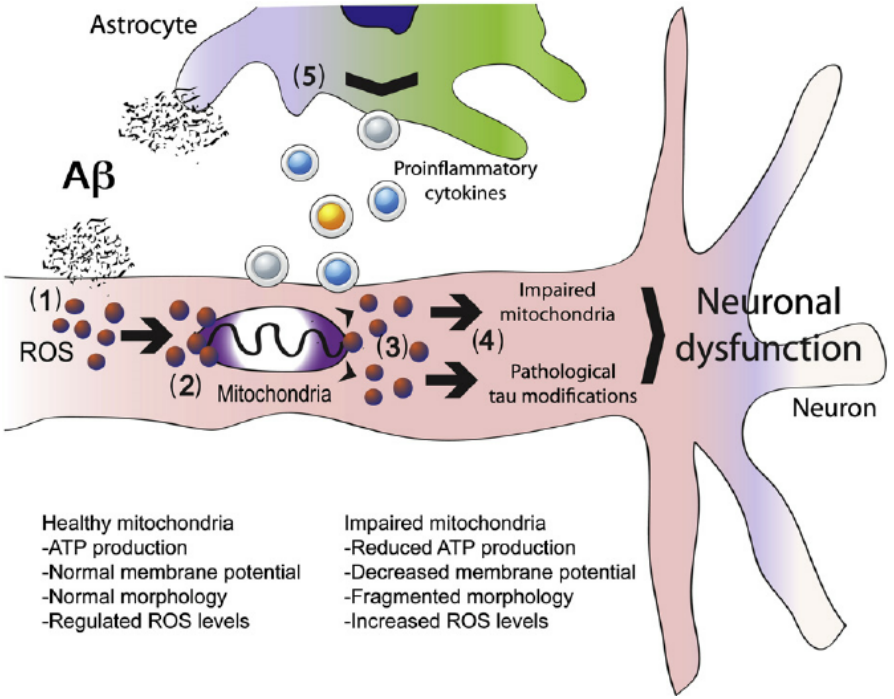


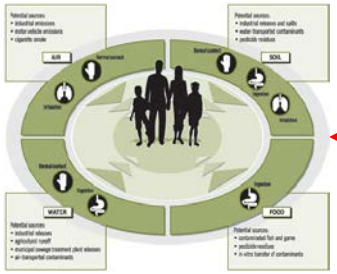
Figure 46 Serine, Theorine and Glycine metabolism (KEGG)


↑ Glucose
↑ Free Fatty Acids ?
↑ Mitochondrial ROS
Direct
Macromolecule Damage
Indirect
↑ Oxidative Stress
↑ NF-κB
↑ p38 MAPK
↑ JNK/SAPK
↑ Hexosamines
↑ Sorbitol
↑ AGE
↓
RAGE
↑ DAG
↓
↑ PKC
↑ Cytokines
↑ Prostanoids
?
?
?
Insulin Resistance
β-Cell Dysfunction

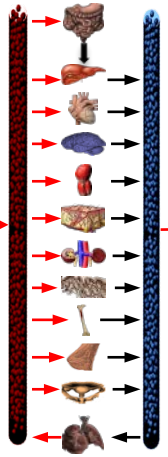

Astrocyte
(5)
Aβ
Proinflammatory cytokines
(1)
ROS
(2)
Mitochondria
(3)
(4)
Impaired mitochondria
Pathological tau modifications
Neuronal dysfunction
Neuron
Healthy mitochondria
-ATP production
-Normal membrane potential
-Normal morphology
-Regulated ROS levels
Impaired mitochondria
-Reduced ATP production
-Decreased membrane potential
-Fragmented morphology
-Increased ROS levels

Biokinetics

Environmental stressors

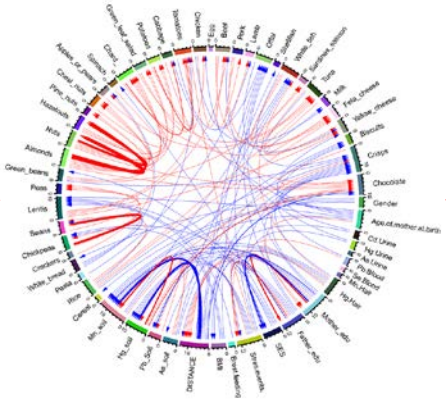


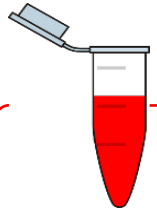
Human exposure



PBBK modelling

Community Effects / Cohorts



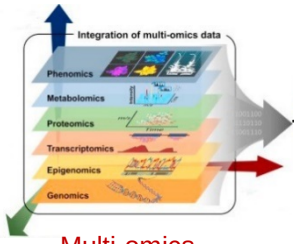


Human biosampling

Dose

In vitro

Bioinformatics / Systems biology / AOPs



Multi-omics

Development of generic multi-route lifetime PBPK model

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PBPK models serve three main purposes:

- internal dose assessment (I)

- to provide the framework for exposure reconstruction (III)

- to derive Biomonitoring Equivalents (BEs) for risk characterization (III)

PBPK models are modeling tools that describe the mechanisms of absorption, distribution, metabolism and elimination (ADME) of chemicals in the body resulting from acute and/or chronic exposure regimes. Within the boundary of the identified compartment (e.g., an organ or tissue or a group of organs or tissues), whatever inflows must be accounted for via whatever outflows or whatever is transformed into something else.

This mass balance is expressed as a mathematical equation with appropriate parameters carrying biological significance. A generic equation, for any tissue or organ, is:

$$V_i \frac{dC_{ij}}{dt} = Q_i (CA_j - CV_{ij}) - Metab_{ij} - E\lim_{ij} + Absorp_{ij} - \Pr Binding_{ij}$$

Development of generic multi-route lifetime PBPK model

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$$V_i \frac{dC_{ij}}{dt} = Q_i(CA_j - CV_{ij}) - Metab_{ij} - E\lim_{ij} + Absorp_{ij} - \Pr Binding_{ij}$$

Where:

V_i represents the volume of tissue group ***i***,

Q_i is the blood flow rate to tissue group ***i***,

CA_j is the concentration of chemical ***j*** in arterial blood, and

C_{ij} and CV_{ij} are the concentrations of chemical ***j*** in tissue group ***i*** and in the effluent venous blood from tissue ***i***, respectively.

$Metab_{ij}$ is the rate of metabolism for chemical ***j*** in tissue group ***i***; liver, being the principal organ for metabolism would have significant metabolism and, with some exception, usually $Metab_{ij}$ is equal to zero in other tissue groups.

$Elim_{ij}$ represents the rate of elimination from tissue group ***i*** (e.g., biliary excretion from the liver),

$Absorp_{ij}$ represents uptake of the chemical from dosing (e.g., oral dosing)

$PrBinding_{ij}$ represents protein binding of the chemical in the tissue. All these terms are zero unless there is definitive knowledge that the particular organ and tissue of interest has such processes.

Development of generic multi-route lifetime PBPK model

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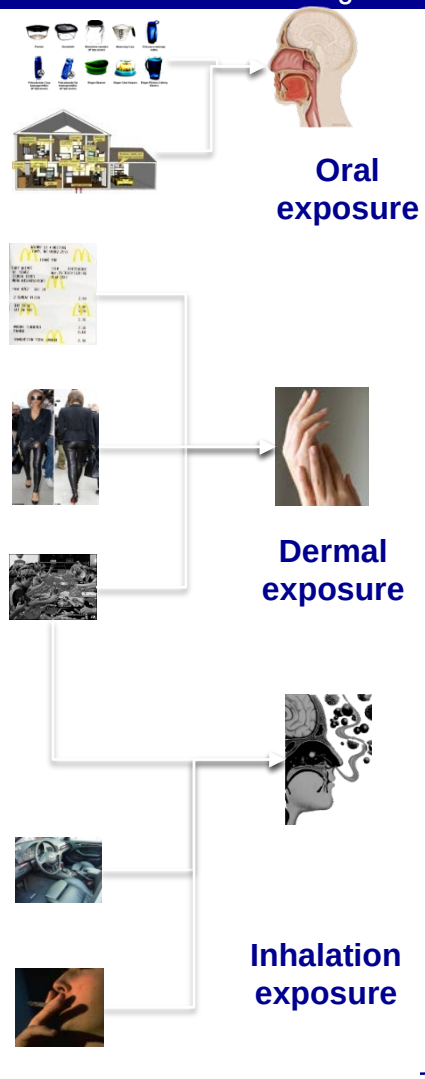

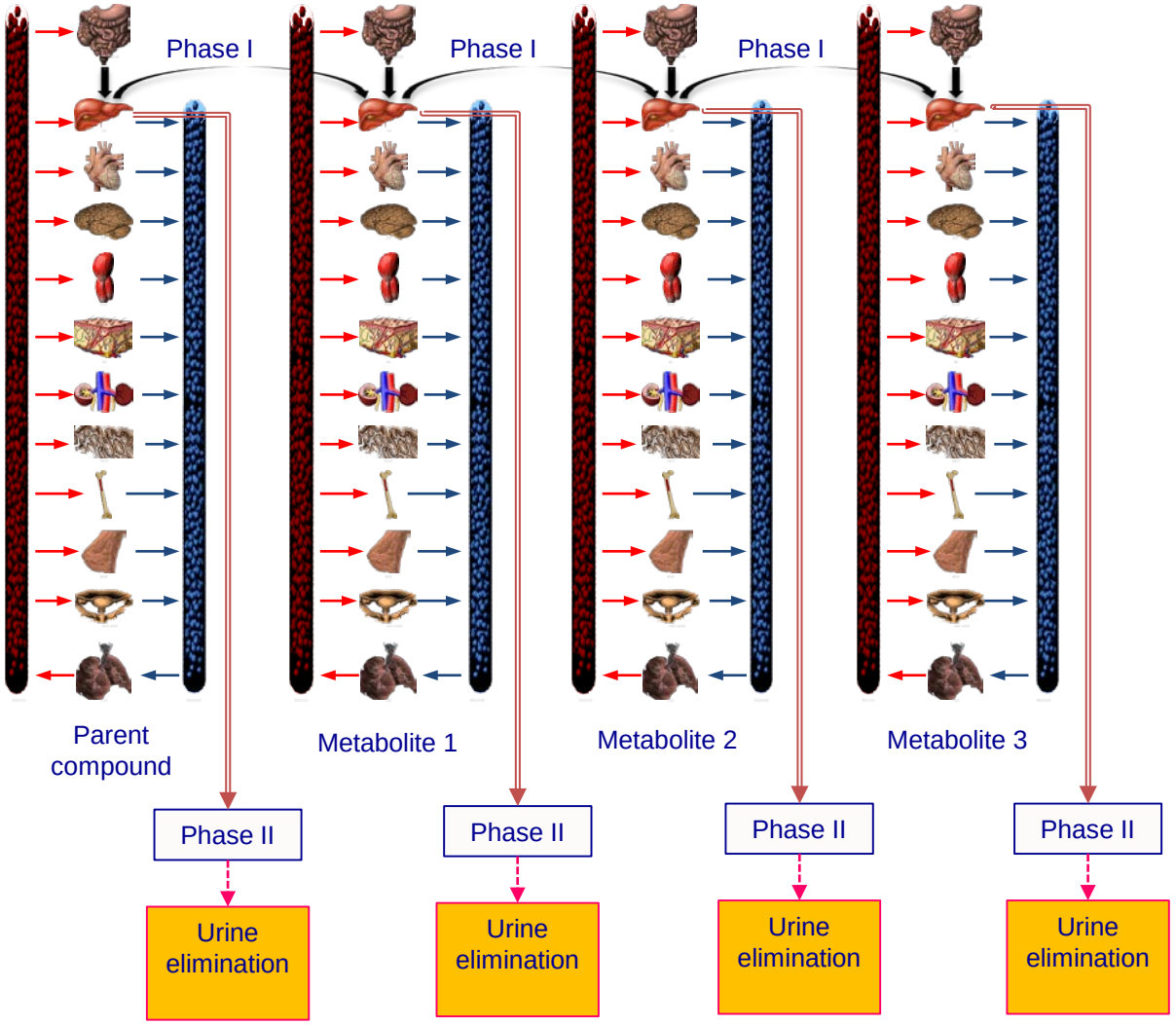

Development of generic multi-route lifetime PBPK model

NEUROSOME

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NEUROSOME: First training event

Heraklion, Crete, May 2019

Organ volumes (***V***) and blood flows (***Q***) were taken from the ICRP (2002) report and the obtained data were fitted to time (***T***) in order to exclude continuous time dependent non-lineal polynomial formulas in the form of:

$$V = a \cdot T^b + c \cdot T^d + e$$

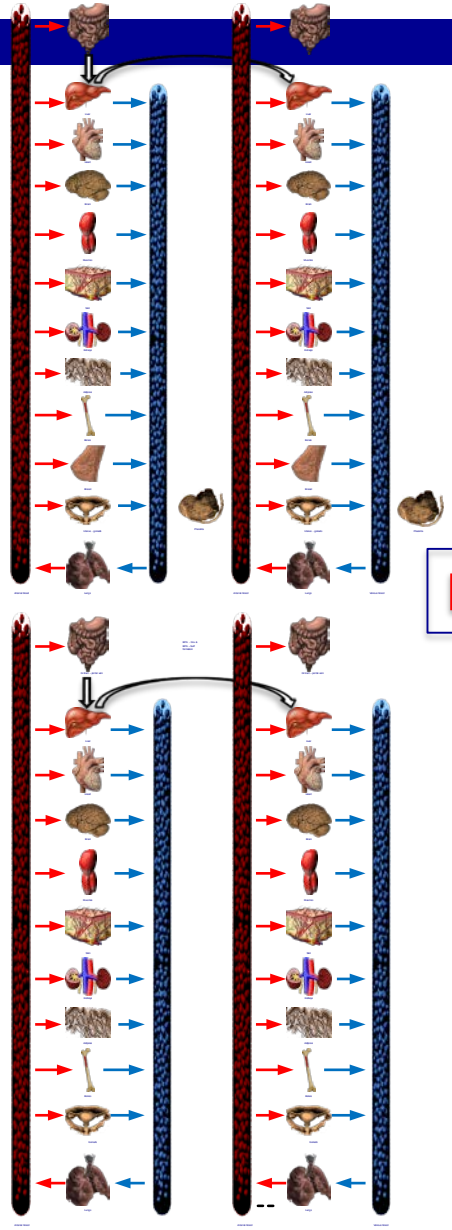
The permeability parameters PS were scaled according to the formula:

$$PS_{tissue\_child} = PS_{tissue\_adult} \left(\frac{V_{tissue\_child}}{V_{tissue\_adult}} \right)^{0.75}$$

Age dependent clearance:

$$CL_{INT} = \alpha_{ontogeny} \cdot CL_H \frac{Q_H}{Q_H - CL_H} \cdot \frac{1}{f_u}$$

where Q_H is the hepatic blood flow, CL_H is the plasma clearance, CL_{INT} is the intrinsic hepatic clearance per gram of liver weight and f_u is the fraction unbound in plasma, $\alpha_{ontogeny}$ is an ontogeny factor that represents the activity of the specific enzyme in relation to the age



Breast feeding link

$$V \frac{dC_{\_breast}}{dt} = PS_{\_cell\_breast} \cdot fu \cdot \left(C_{\_int\_breast} - \frac{C_{\_breast}}{K_{\_breast}} \right) - L_{excr}$$

$$L_{excr} = Q_{\_milk} \cdot \frac{C_{\_breast}}{K_{\_breast}} \cdot P_{\_milk/blood}$$

$$P_{\_milk/blood} = \frac{K_{ow} \cdot Fl_{\_tissue} + Fw_{\_tissue}}{K_{ow} \cdot Fl_{\_blood} + Fw_{\_blood}}$$

Mother – Fetus interaction

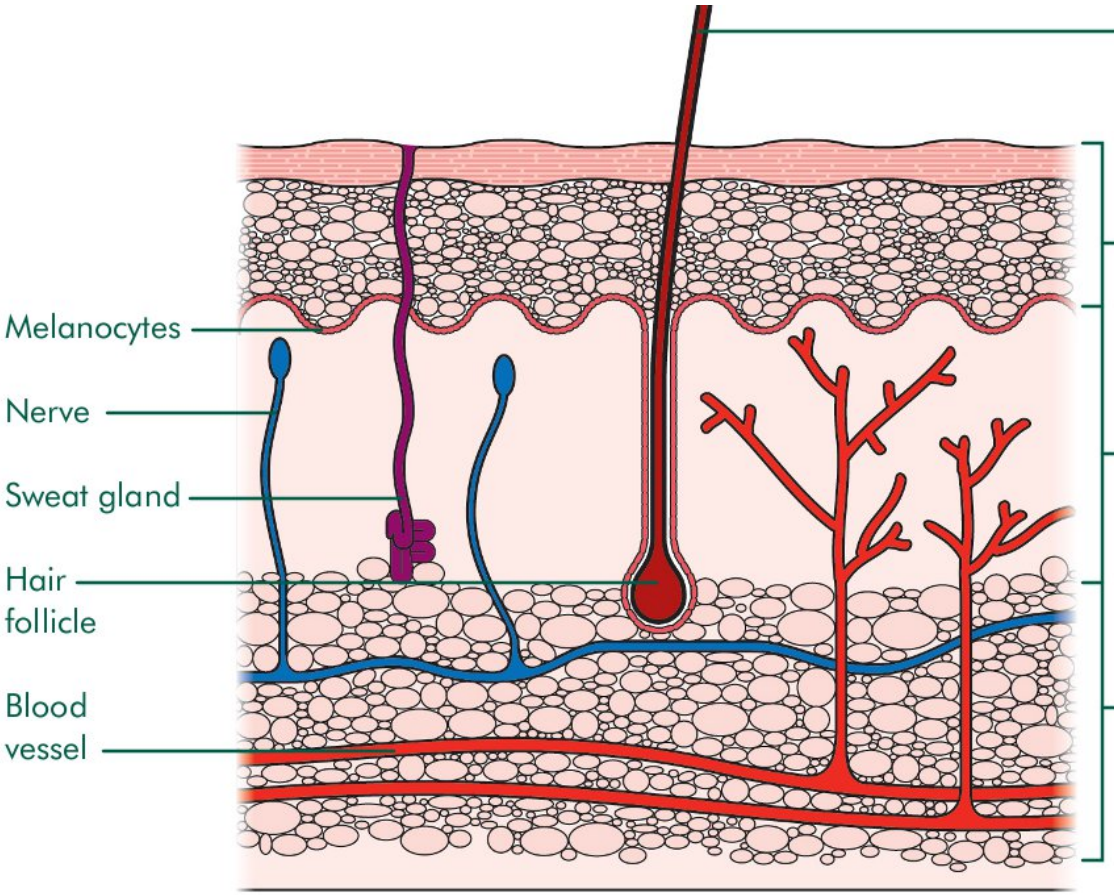
$$\frac{\partial Q_{uterus\_M}}{\partial t} = F_{uterus\_M} \times \left(C_{art\_M} - \frac{C_{uterus\_M}}{P_{uterus}} \right) - K_{d\_uter\_pla} \times \left(C_{placenta} - C_{uterus\_M} \right)$$

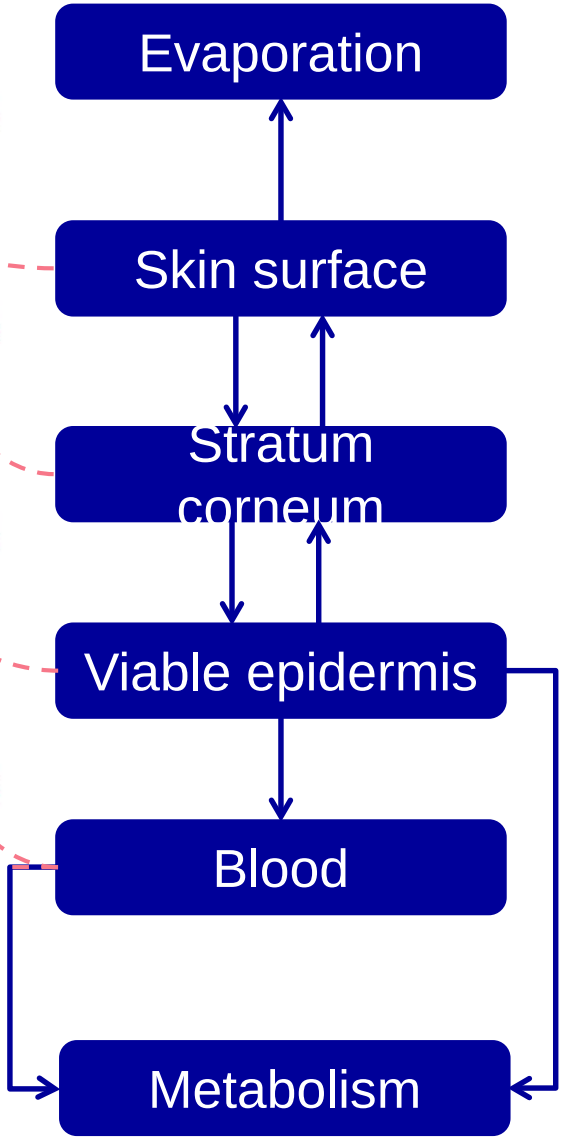
$$\frac{\partial Q_{placenta}}{\partial t} = K_{d\_uter\_pla} \times \left(C_{placenta} - C_{uterus\_M} \right) + F_{placenta\_B} \times \left(C_{art\_B} - \frac{C_{placenta}}{P_{placenta}} \right)$$

$$- K_{d\_pla\_amniot} \times \left(C_{placenta} - C_{amniot} \frac{P_{placenta}}{P_{amniot}} \right) - K_{m\_placenta} \times C_{placenta}$$

$$\frac{\partial Q_{amniot}}{\partial t} = K_{d\_pla\_amniot} \times \left(C_{placenta} - C_{amniot} \frac{P_{placenta}}{P_{amniot}} \right) + K_{e\_gut\_B} \times C_{gut\_B}$$

$$+ K_{e\_bile\_B} \times C_{liver\_B} - K_{a\_amniot\_B} \times C_{amniot}$$


Hair
Epidermis
Melanocytes
Nerve
Sweat gland
Dermis
Hair follicle
Blood vessel
Fat


Evaporation
Skin surface
Stratum corneum
Viable epidermis
Blood
Metabolism

$$D_1, D_2 = f(\text{Geometry of stratum corneum, area, solvent / SC partion coefficient})$$

$$\frac{dC_s}{dt} = -D_1 C_c + D_2 C_{sc} - evap$$

$$evap = f(MW, V_p, R, T, \beta, V, D_g, v, X)$$

$$\frac{dC_{sc}}{dt} = D_1 C_s - D_2 C_{sc} - D_3 C_{sc} + D_4 C_{ve}$$

$$D_3, D_4 = f(\varphi_{cor}, \varphi_{lip}, K_{lip/cor}, K_{cor/w}, K_{o/w})$$

$$\frac{dC_{ve}}{dt} = D_3 C_{sc} - D_4 C_{ve} - M - Q_b C_{ve}$$

$$M = \frac{V_{max} C_{ve}}{K_m + C_{ve}}$$

Evaporation

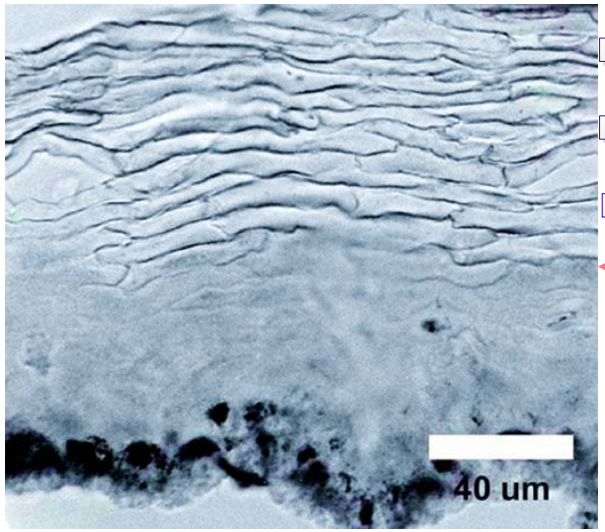
Skin surface

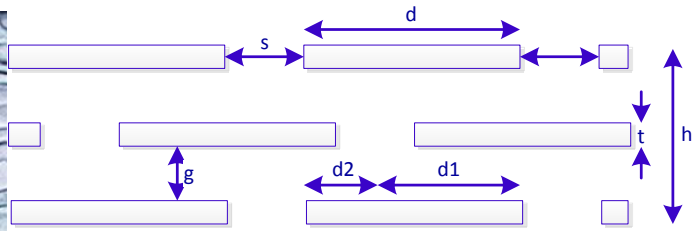
Stratum corneum

Viable epidermis

Blood

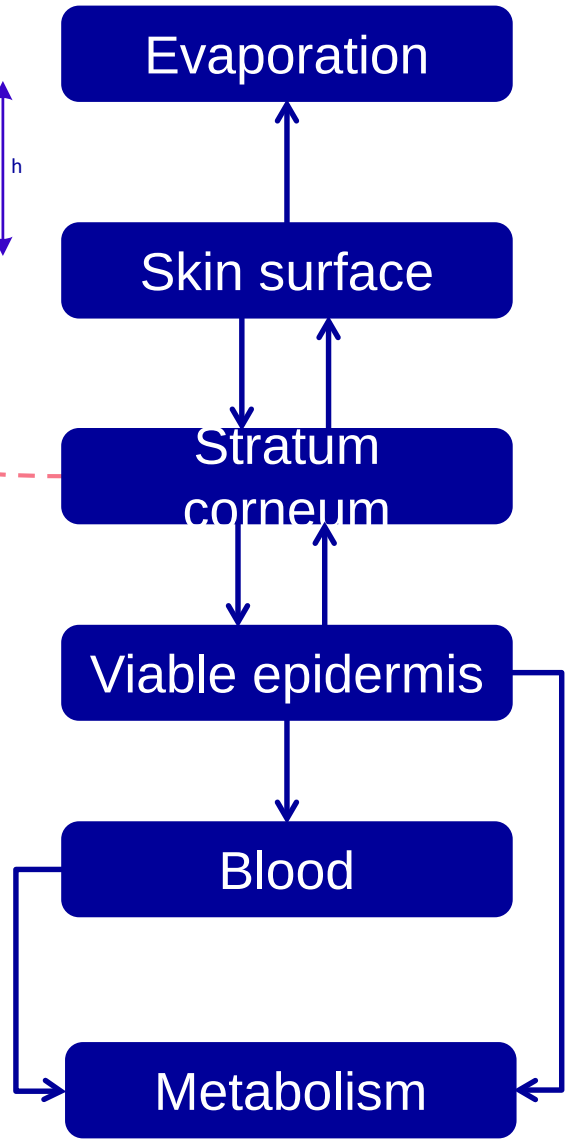
Metabolism



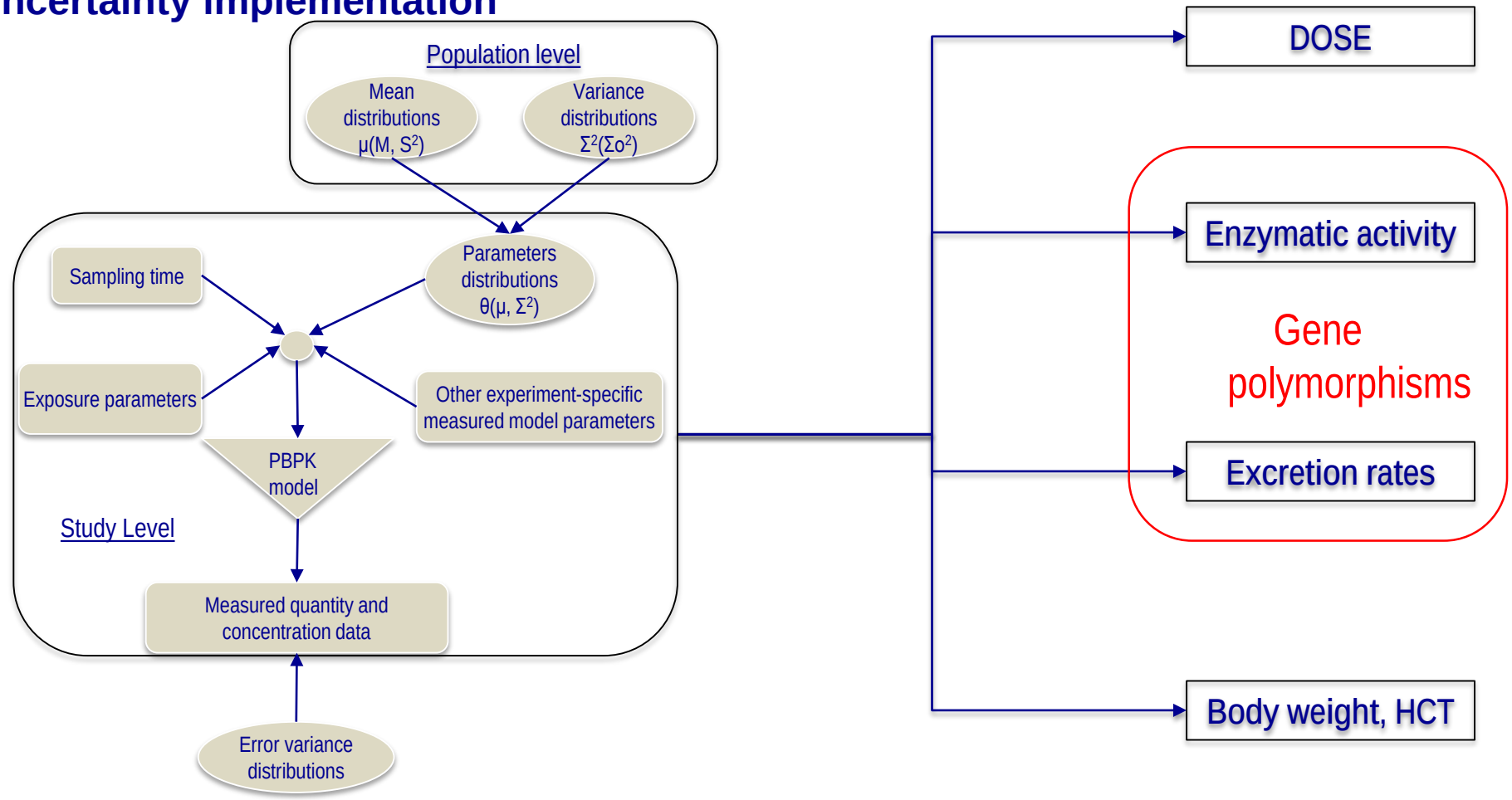


$$t = 1 + \frac{2g}{h}\ln\left(\frac{d}{2s}\right) + \frac{N \cdot d \cdot t}{s \cdot h} + \left(\frac{d}{1+\omega}\right)^2 \frac{\omega \cdot (N-1)}{h \cdot g}$$

Description	Symbol	Value	Unit
Number of layer	N	15	-
Length of corneocyte	d	30	um
Thickness of corneocyte	t	10	um
Length of path 1	d_1	20	um
Length of path 2	d_2	10	um
Vertical gaps	s	0,03	um
Horizontal gaps	g	0,03	um
corneocyte edge angle	φ	90º	degrees
Effective Diffusivity f(φ)	D_{ef}	0.002	cm^2/m



Uncertainty implementation



Hierarchical population model used in Bayesian analysis (Gelman et al, 1996).
Circles represent distributions and squares/rectangles represent known entities

μ: prior mean distribution

Σ^2: prior variance distribution

θ: study level distributions for each of the parameters based on randomly selected values for the mean and variance from the population distributions μ and Σ^2

Coupling biokinetics and metabolic regulation

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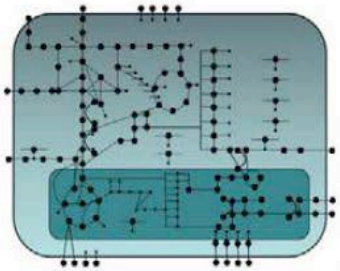
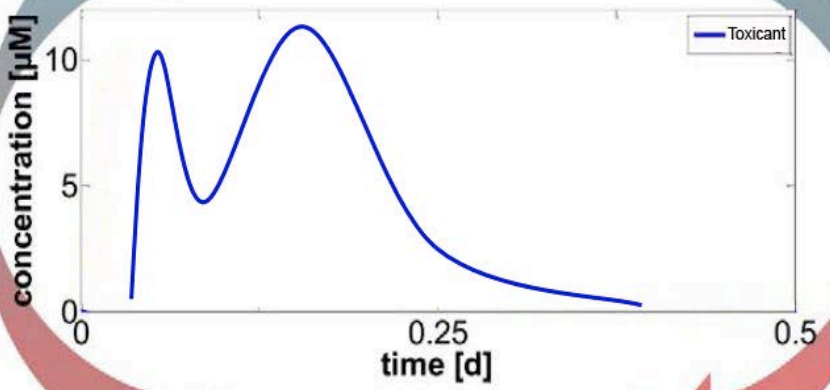


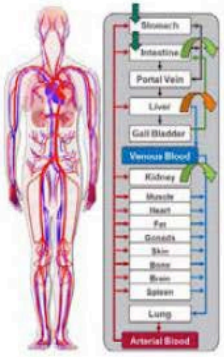
(3) Calculate flux distribution at cellular scale

FBA



(2) Use PBPK metabolization rate as upper bound for FBA

(4) Use FBA uptake as upstream PBPK metabolization rate



PBPK

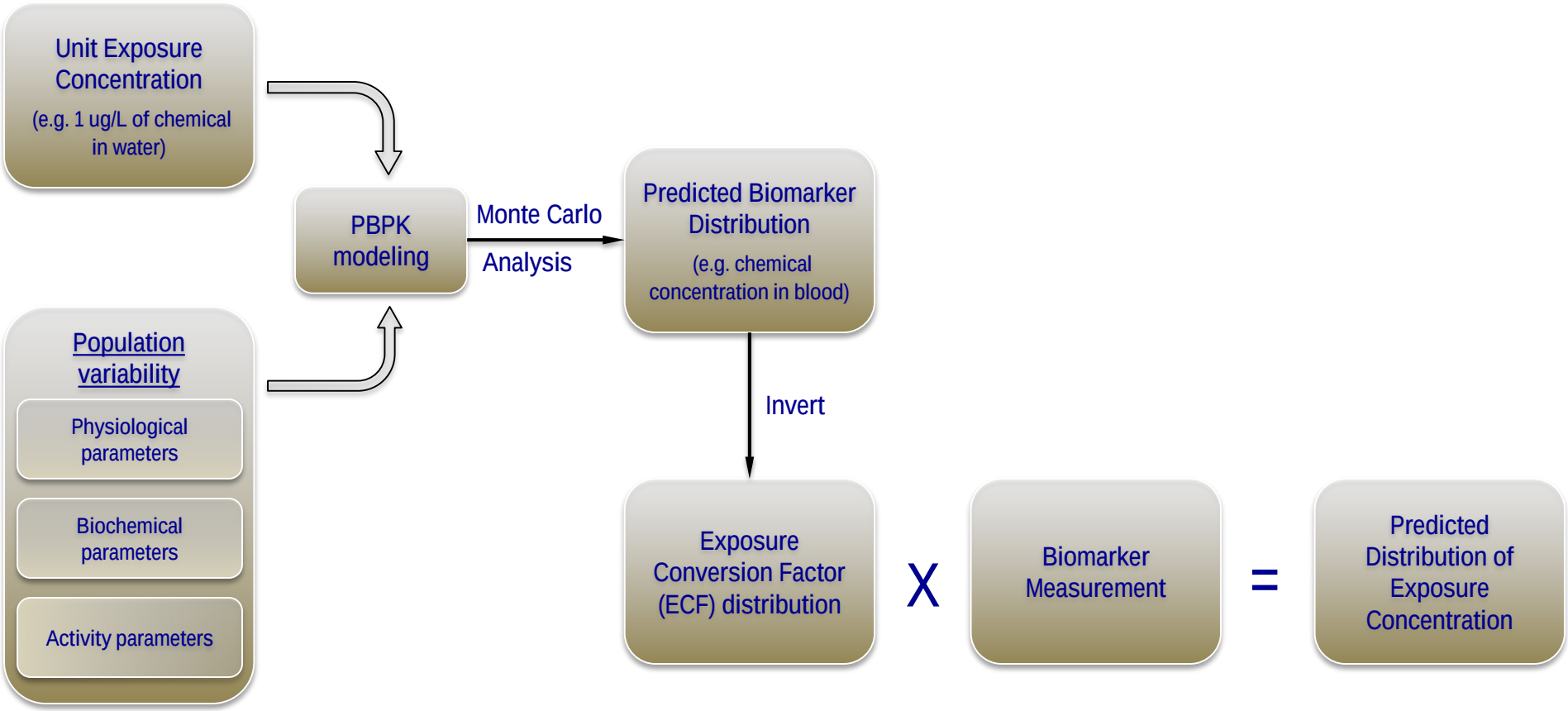
(1) Update PBPK metabolization rate from tissue concentrations

(5) Simulate whole-body concentrations for the next time step

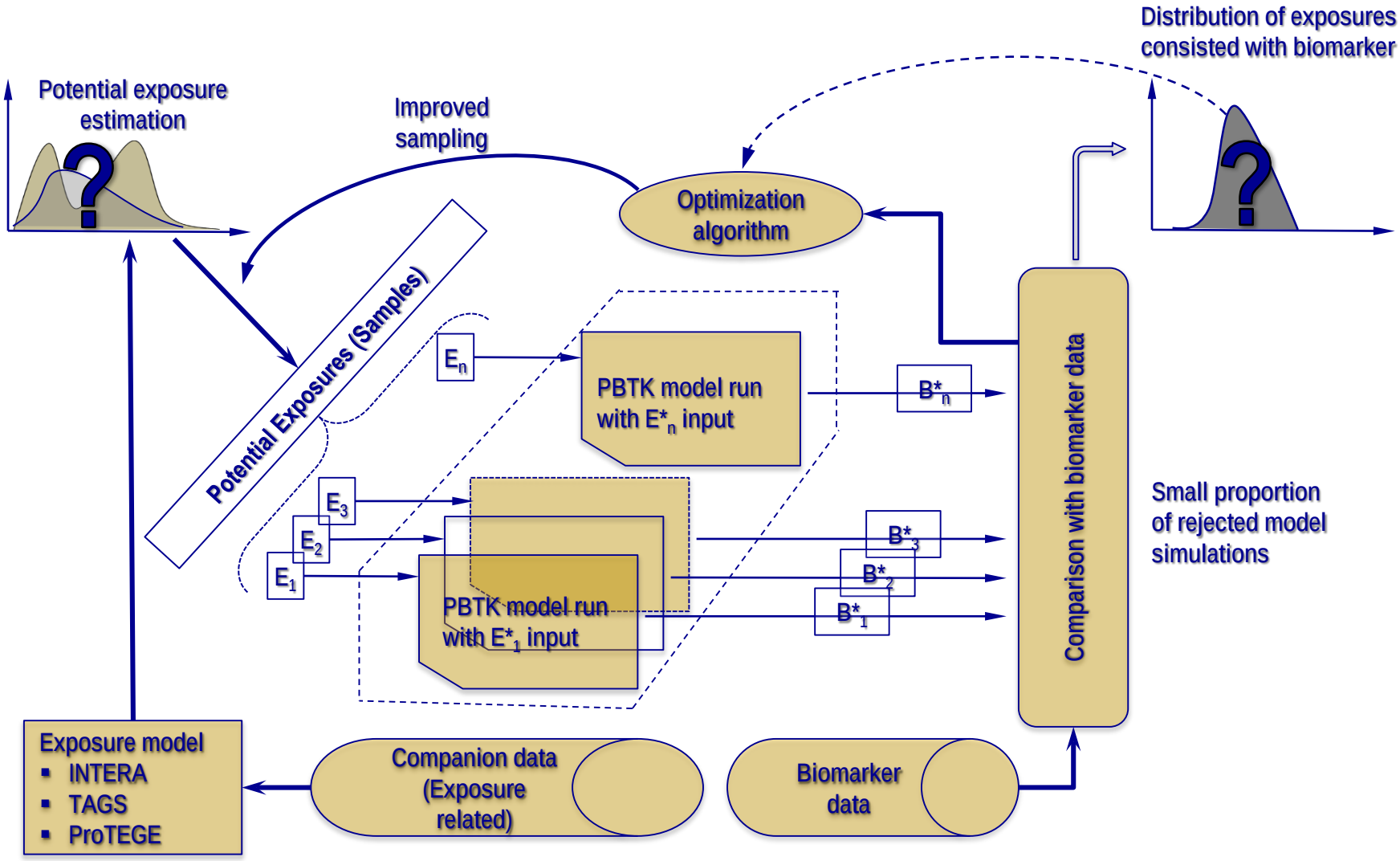
Exposure Reconstruction Techniques

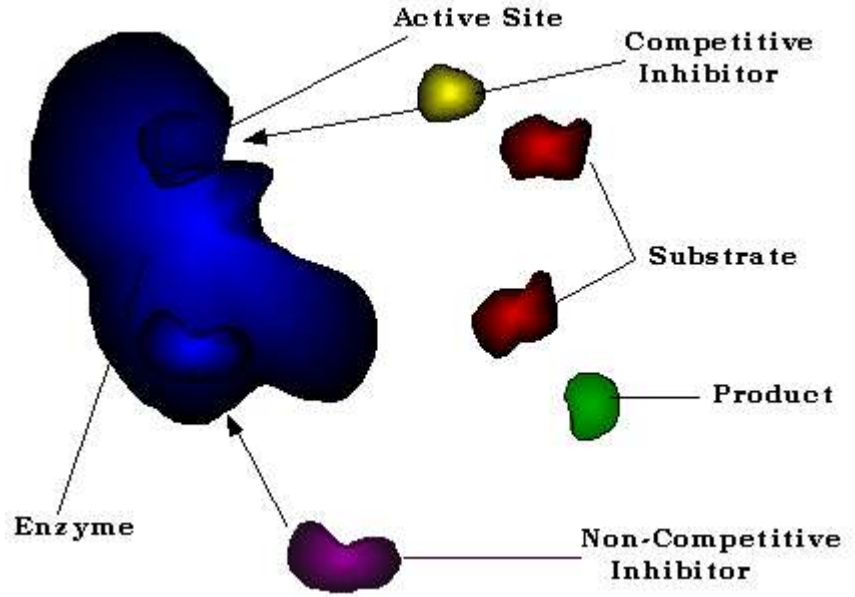
- Deterministic Inversion
- Stochastic Inversion/Bayesian Approach
- Exposure Conversion Factor Approach
- Discretized Bayesian Approach
- Bayesian Markov Chain Monte Carlo

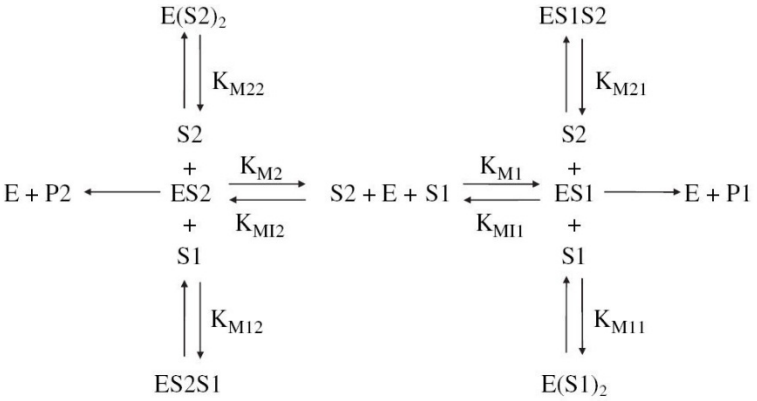
Exposure reconstruction trivial scheme



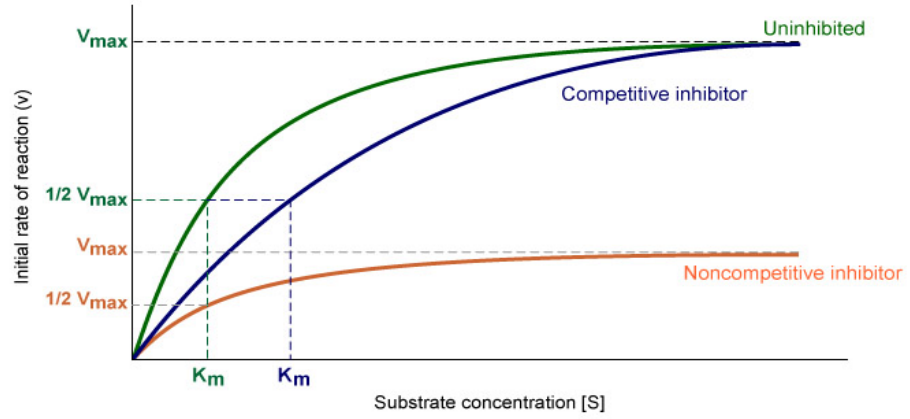
Exposure reconstruction







The Effects of Inhibition on Enzyme Kinetics

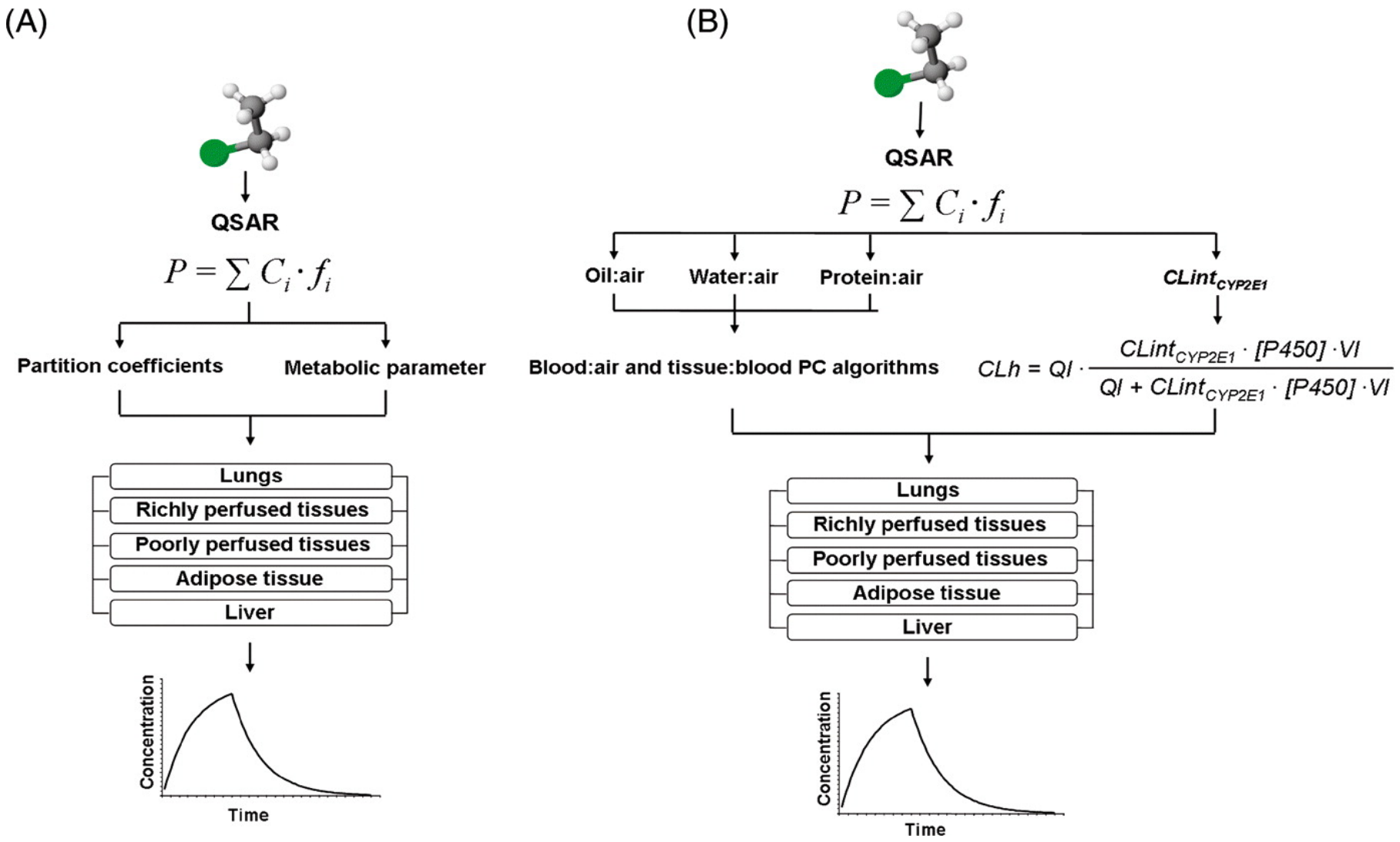


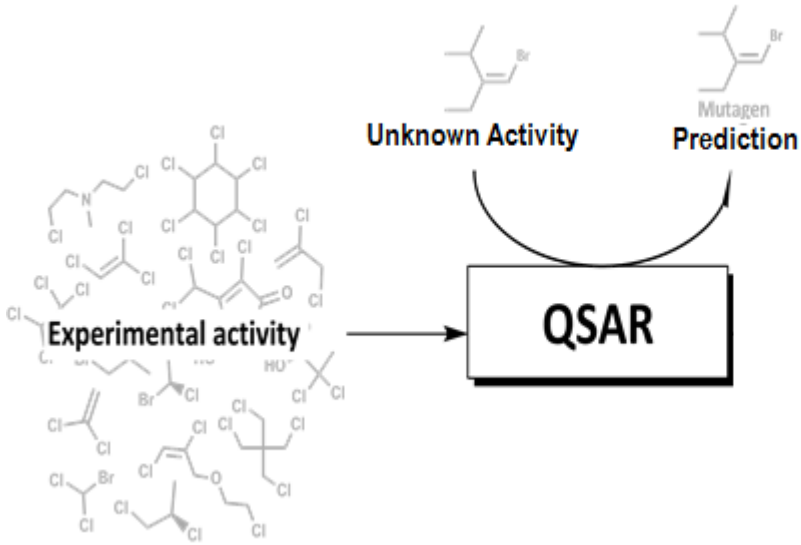
$$RAM_1 = k_1 \frac{V_{\max\_1} \times (S1)}{\left[S1(T_2) + K_{M1}(T2)\right]}$$

$$RAM_1 = \frac{V_{\max\_1} \cdot S1}{K_{M1}\left(1 + \frac{S2}{KM_{2-1}} + \ldots \frac{Sn}{KM_{n-1}}\right) + S1}$$

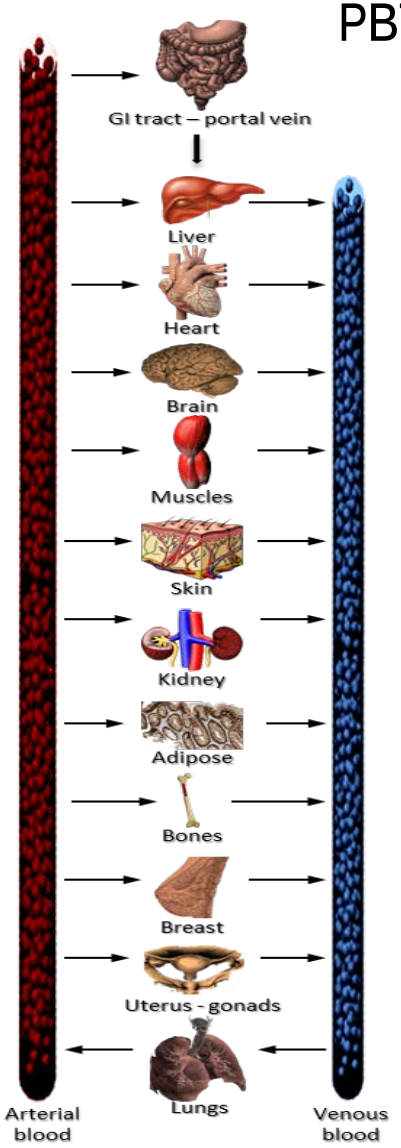
QSARs for biokinetic modelling

PBPK models based on QSARs




Unknown Activity
Mutagen
Prediction
Experimental activity
QSAR

PBTK


GI tract – portal vein
Liver
Heart
Brain
Muscles
Skin
Kidney
Adipose
Bones
Breast
Uterus - gonads
Lungs
Arterial blood
Venous blood

Overall Approach

- Literature Review

Algorithms using:

- Tissue Composition [1]
- Group Contribution Method [2]
- Linear Free Energy Relationship [3]

- Development of a QSAR model using LFER

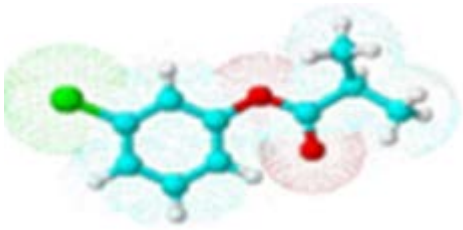
Application of the **LFER** to address **tissue/blood partition coefficients** and **constants of metabolism**

Kidney/blood PC
Heart/blood PC
Muscle/blood PC
Adipose/blood PC
Brain/blood PC
Lung/blood PC
Liver/blood PC

Maximal Velocity of Metabolism, V_{maxc}
Michaelis – Menten Constant, K_m

[1] Peyret T, Poulin P, Krishnan K. A unified algorithm for predicting partition coefficients for PBPK modeling of drugs and environmental chemicals. Toxicology and Applied Pharmacology 2010; 249: 197-207.
[2] Gao C, Goind R, Tabak HH. Application of the group contribution method for predicting the toxicity of organic chemicals. Environmental Toxicology and Chemistry 1992; 11: 631-636.
[3] Abraham MH. Application of solvation equations to chemical and biochemical processes. Pure and Applied Chemistry 1993; 65: 2503-2512.

Overall Approach



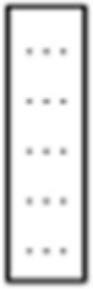
Molecular Structure

Y = f(X)
f(X) ?

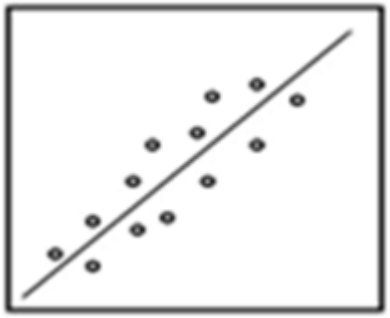
Activity

Validation of QSAR

X
Molecular
Descriptors



Y
Response
Variable



Statistical Analysis

1. Linear Free – Energy Relationship (LFER)

$$logSP = c + e \cdot E + s \cdot S + a \cdot A + b \cdot B + v \cdot V$$

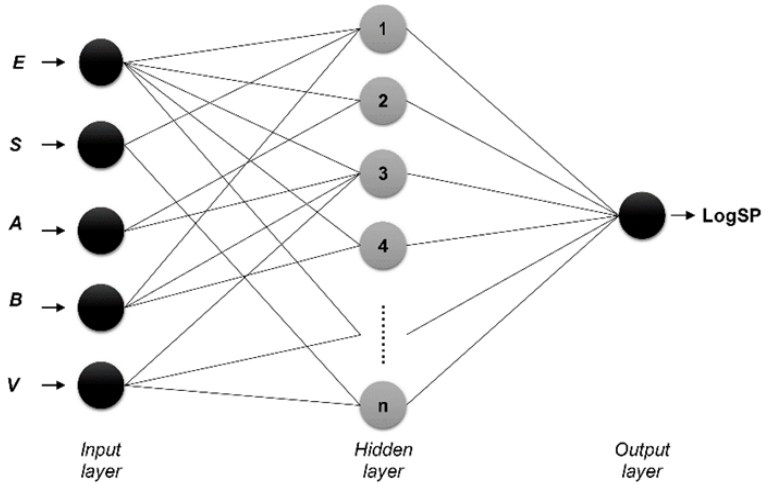
SP: biological property of a chemical (tissue/blood partition coefficients and parameters of metabolism)
E: excess molar refractivity of the chemical
S: chemical's dipolarity/polarizability
A: solute effective or summation hydrogen-bond acidity of the chemical
B: solute effective or summation hydrogen-bond basicity of the chemical
V: McGowan characteristic volume of the chemical
c, e, s, a, b, v: constants that reflect the properties of the chemical

2. Data collection

- Experimental values of $P_{tissue/blood}$ of 33 organic chemicals
- Experimental values of V_{maxc} and K_m of 29 organic chemicals
- Experimental and computed values of molecular descriptors (E, S, A, B, V)

3. Statistical Analysis

- a. Artificial Neural Networks (ANN)
  - Multi-Layer Perceptron (MLP) model using the scaled conjugate gradient back-propagation algorithm.
  - Input data divided into the training (70%), the validation (15%) and the testing (15%) data.



ANN example

- b. Non Linear Regression (NLR)
  - Form of the NLR model:
  - $$y = f(X, \beta) + \varepsilon$$

β: constants of LFER (c, e, s, a, b, v)

ε: error term

- Least Squares (LS) coupled with the Levenberg-Marquardt algorithm.

4. Expanding the Domain of Applicability

The QSAR model, derived from ANN analysis, was used:

- for the estimation of tissue/ blood partition coefficients for the main human tissues
- for several chemical compounds, categorized into chemical families, including hydrocarbons, aromatic and halogenated hydrocarbons, alcohols, ketones, ethers and esters.

The results were validated using the equation:

$$P_{tissue/blood} = \frac{P_{ow} \cdot Fl_{tissue} + P_{ow} \cdot Fw_{tissue}}{P_{ow} \cdot Fl_{blood} + P_{ow} \cdot Fw_{blood}}$$

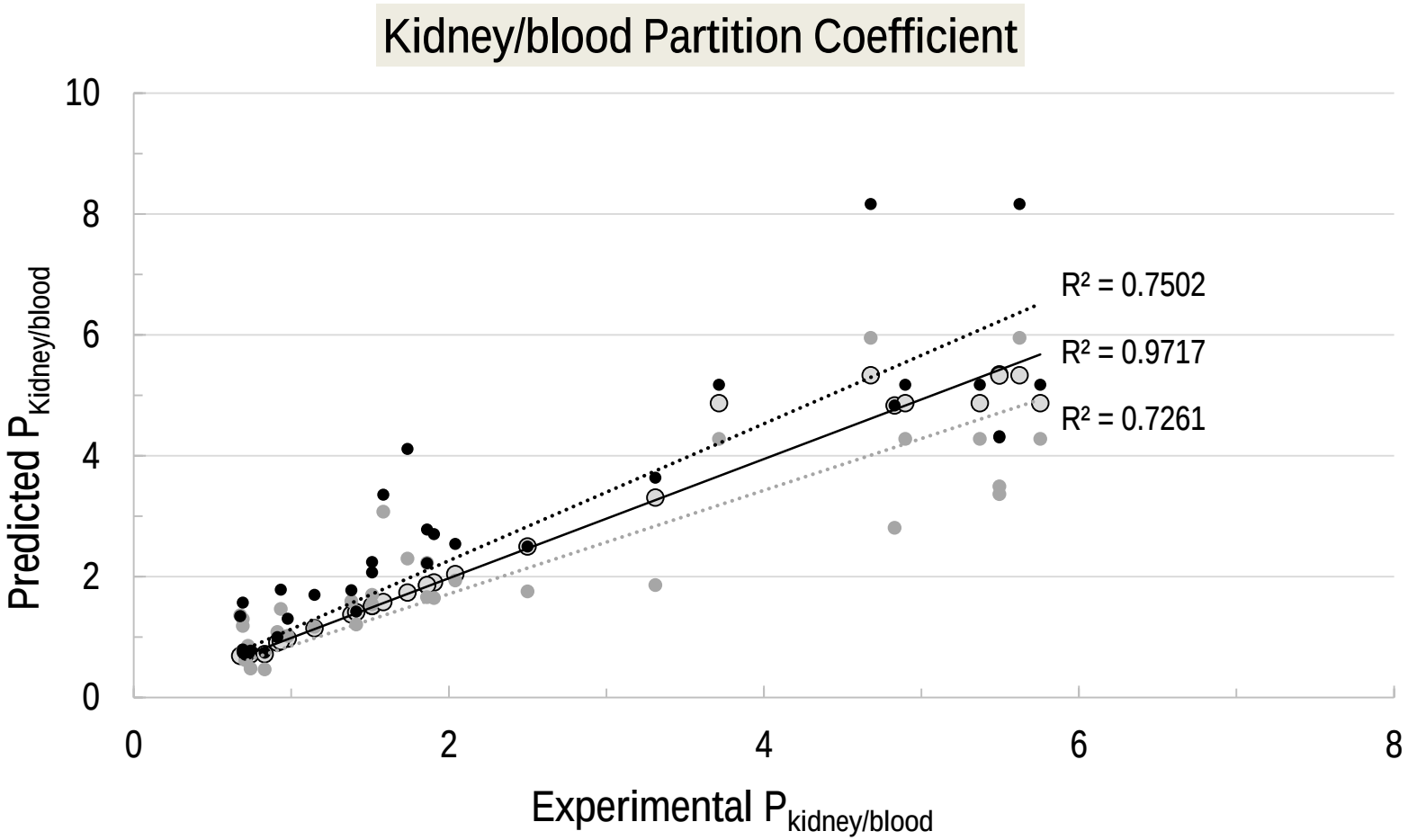
P_{ow}: octanol/ water partition coefficient,

Fl_{tissue} and Fw_{tissue}: fractional contents of lipids and water in tissue, respectively, and

Fl_{blood} and Fw_{blood}: fractional contents of lipids and water in blood, respectively [4].

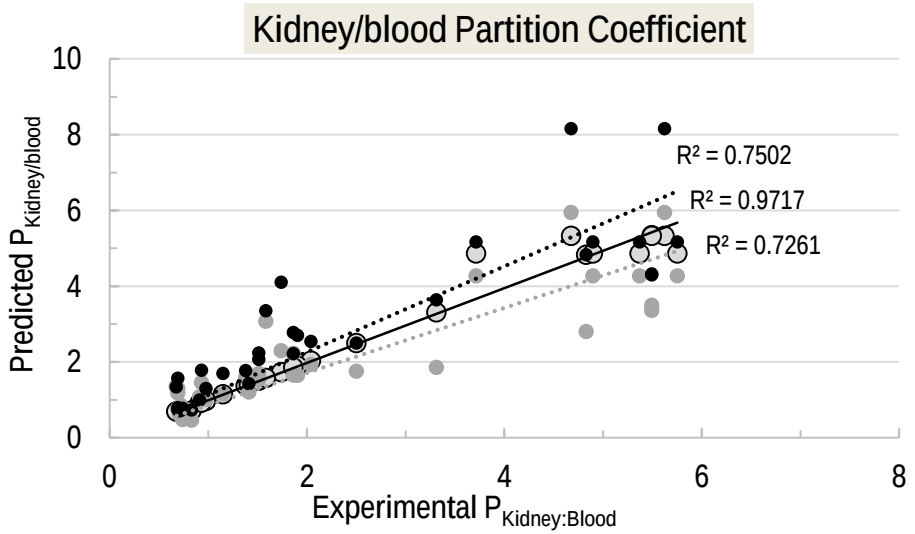
[4] Hayes AW, Principles and Methods of Toxicology, 5th Edition, CRC Press, 2007.

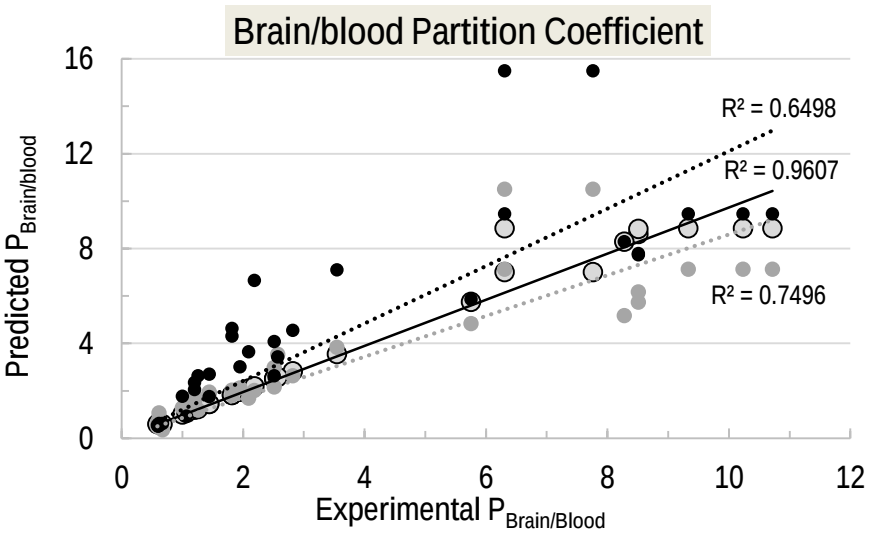
Results Tissue/blood Partition Coefficients

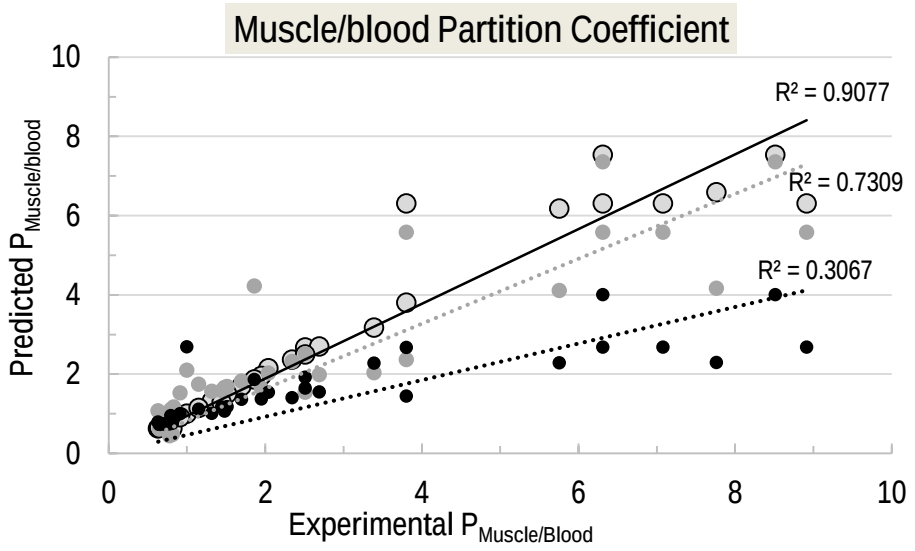


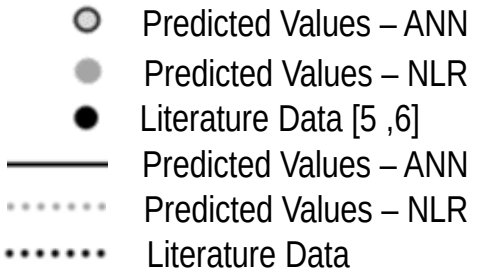
Results

Tissue/blood Partition Coefficients





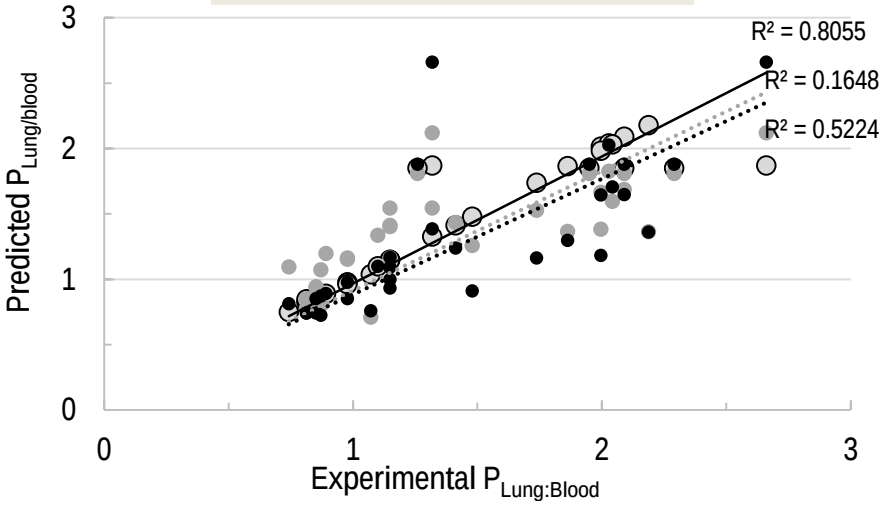




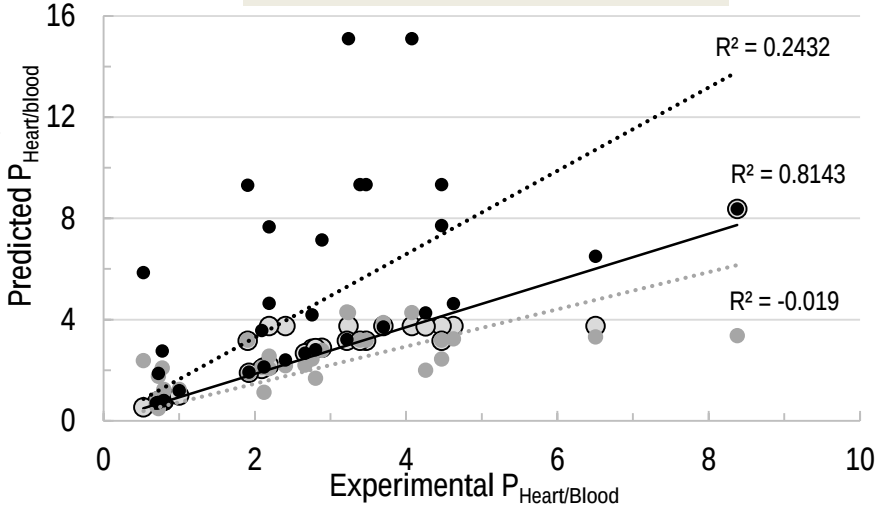
[5] Zhang H. A new nonlinear equation for the tissue/blood partition coefficients of neutral compounds. Journal of Pharmaceutical Sciences 2004; 93: 1595-1604.

[6] Price K, Krishnan K. An integrated QSAR-PBPK modelling approach for predicting the inhalation toxicokinetics of mixtures of volatile organic chemicals in the rat. SAR and QSAR in Environmental Research 2011; 22: 107-128.

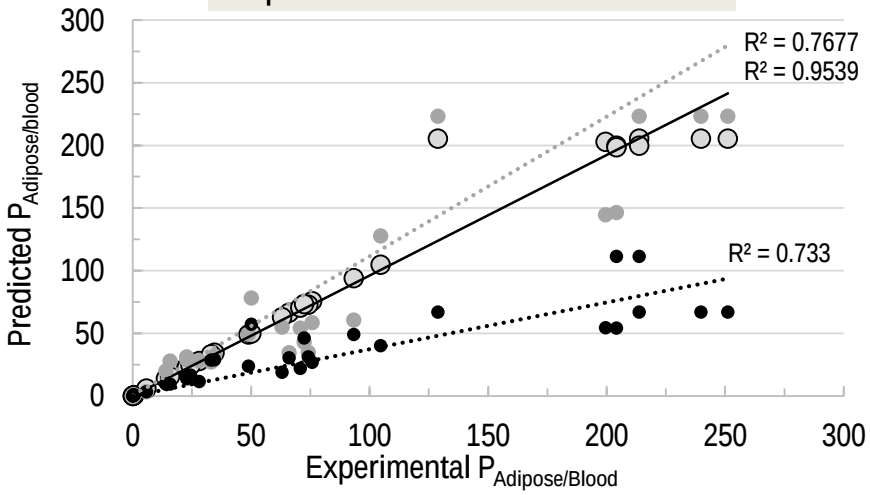
Lung/blood Partition Coefficient



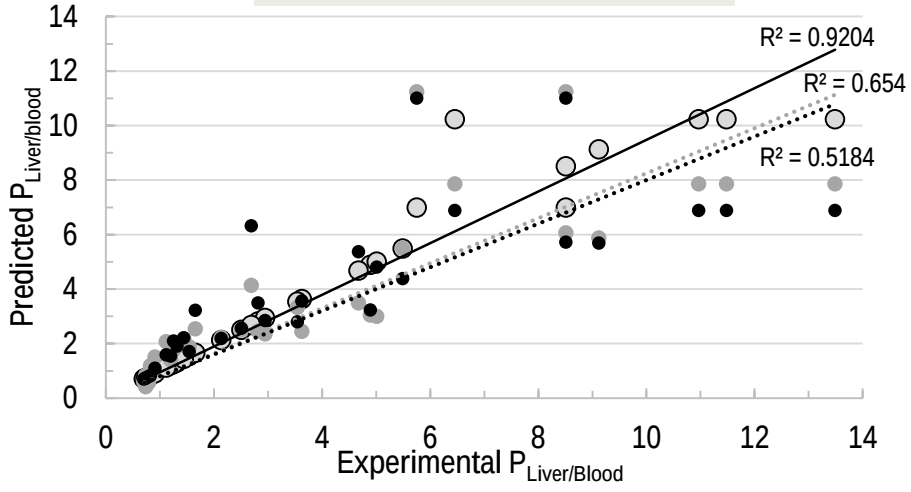
Heart/blood Partition Coefficient

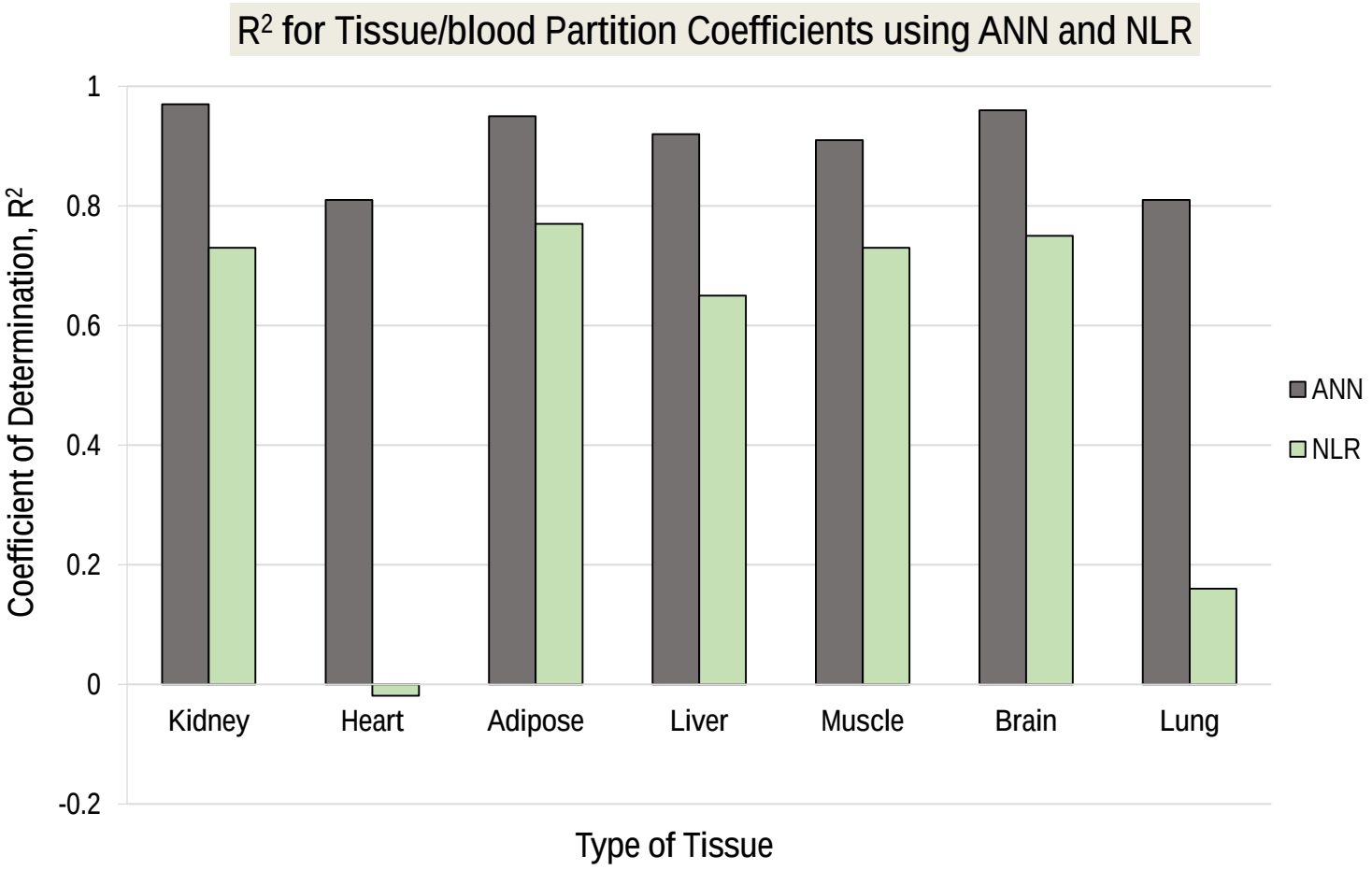


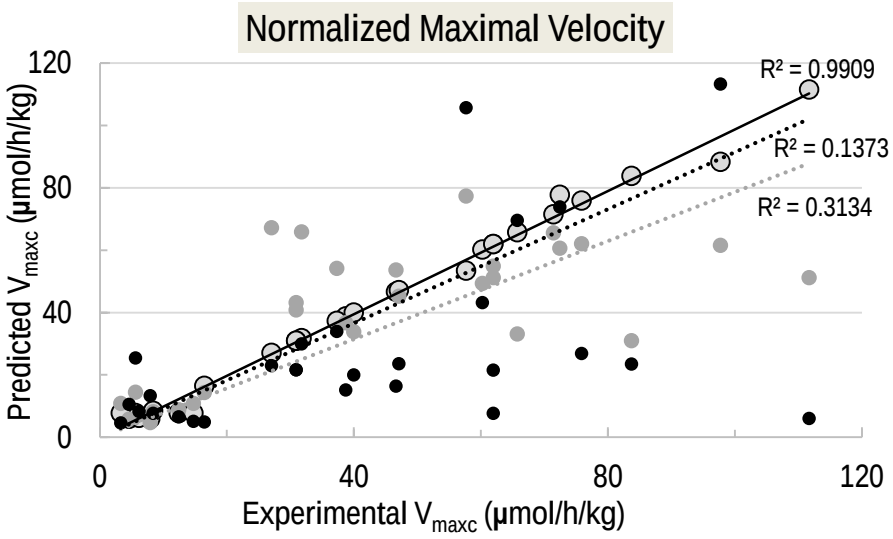
Adipose/blood Partition Coefficient

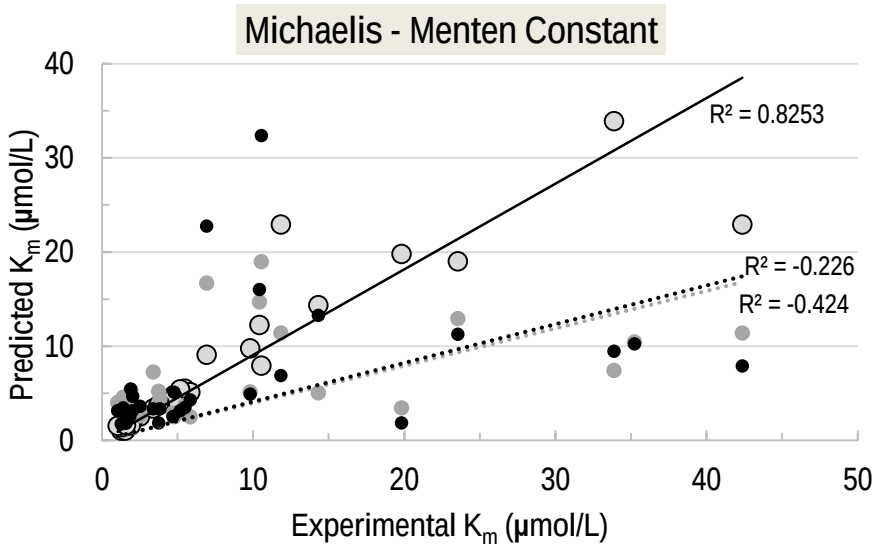


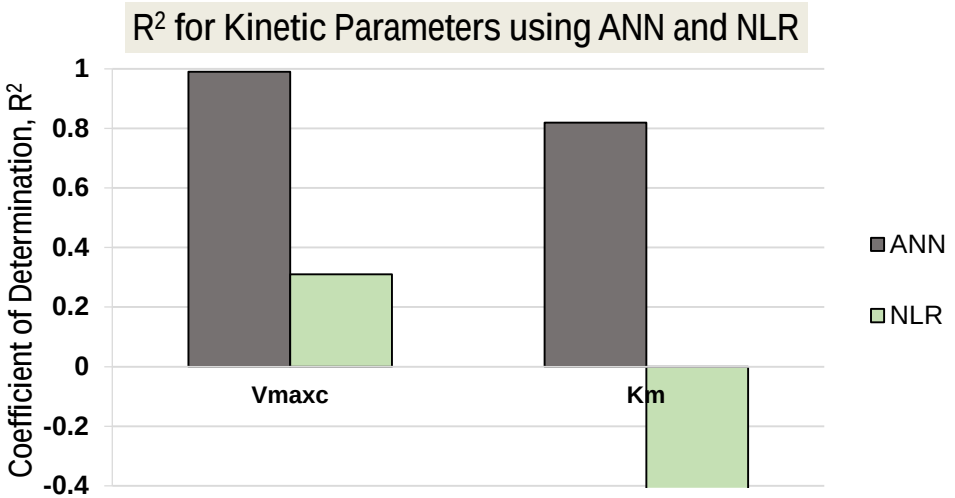
Liver/blood Partition Coefficient




R2 for Tissue/blood Partition Coefficients using ANN and NLR
Coefficient of Determination, R2
1
0.8
0.6
0.4
0.2
0
-0.2
Kidney
Heart
Adipose
Liver
Muscle
Brain
Lung
Type of Tissue
ANN
NLR


Normalized Maximal Velocity
R² = 0.9909
R² = 0.1373
R² = 0.3134
Predicted Vmaxc (μmol/h/kg)
Experimental Vmaxc (μmol/h/kg)
0
40
80
120


Michaelis - Menten Constant
R² = 0.8253
R² = -0.226
R² = -0.424
Predicted Km (μmol/L)
Experimental Km (μmol/L)
0
10
20
30
40
50


R2 for Kinetic Parameters using ANN and NLR
Coefficient of Determination, R2
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
Vmaxc
Km
ANN
NLR

Results

Relative Importance of Inputs to the Predictions

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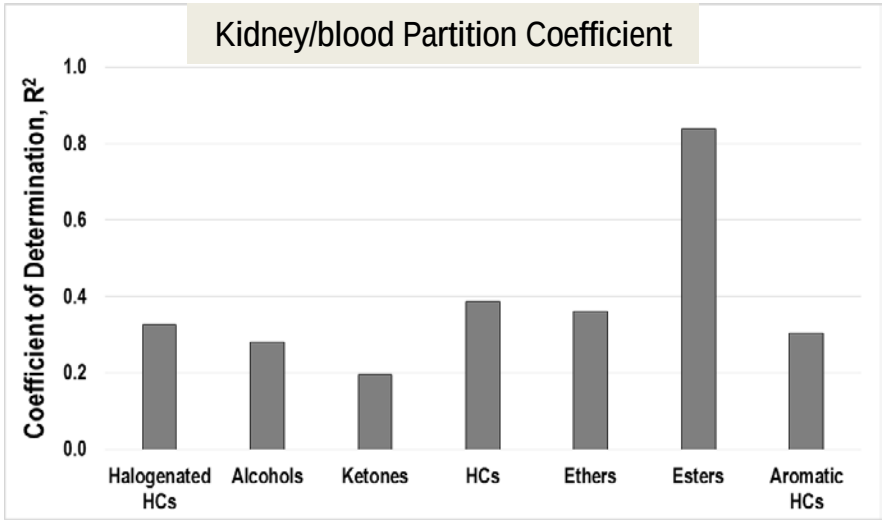
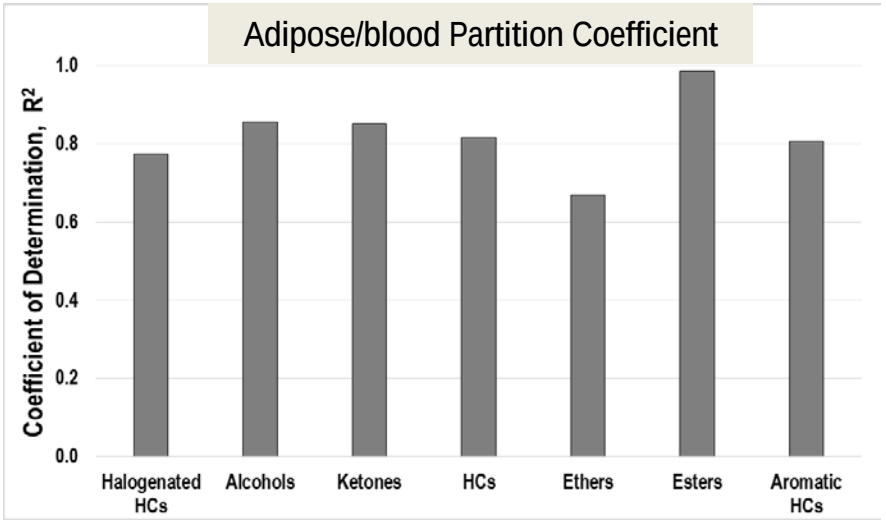
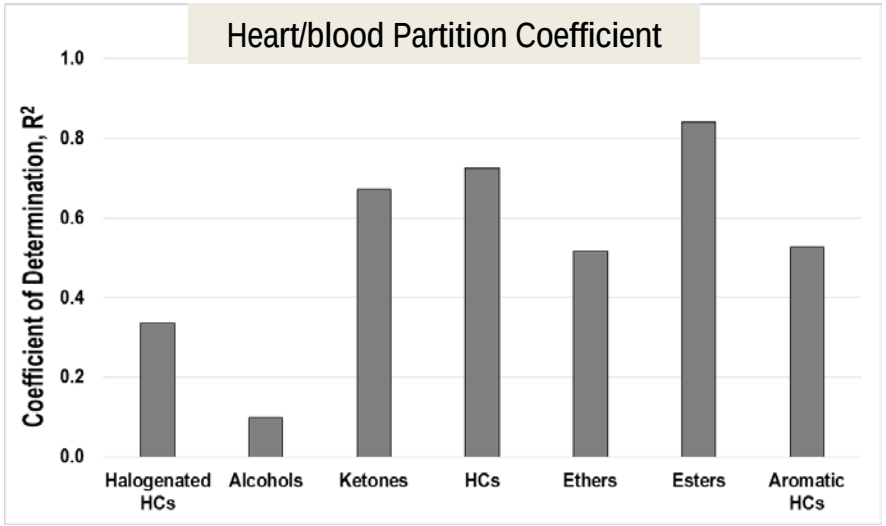
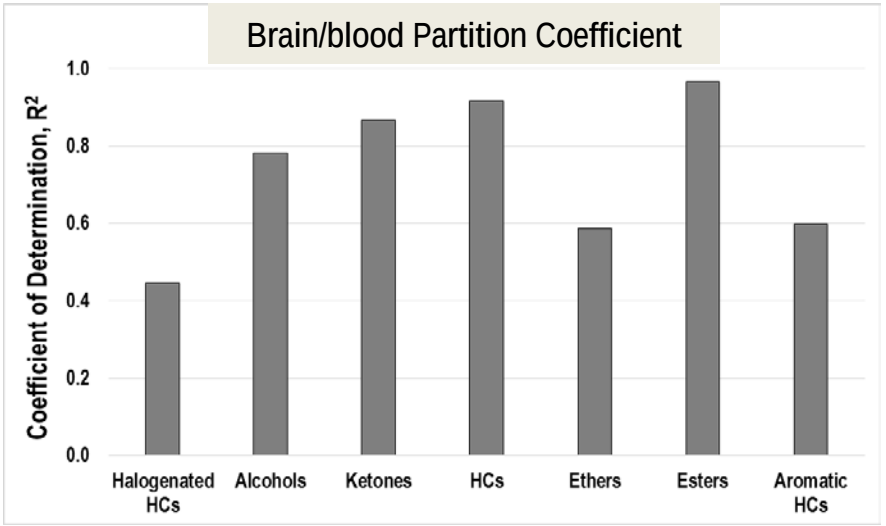
	E	S	A	B	V
log Kidney/blood partition coefficient	15.2	22.0	19.5	13.9	29.4
log Heart/blood partition coefficient	23.0	24.0	7.3	23.7	22.0
log Adipose/blood partition coefficient	10.2	8.3	13.5	28.5	39.5
log Liver/blood partition coefficient	8.9	16.0	31.2	10.1	33.8
log Muscle/blood partition coefficient	16.5	19.9	20.6	9.9	33.1
log Brain/blood partition coefficient	21.6	12.8	19.6	12.7	33.3
log Lung/blood partition coefficient	29.5	11.8	13.3	13.0	32.4
log V_{macx}	13.3	35.4	22.7	20.2	8.4
log K_m	23.5	21.5	11.3	13.6	30.1

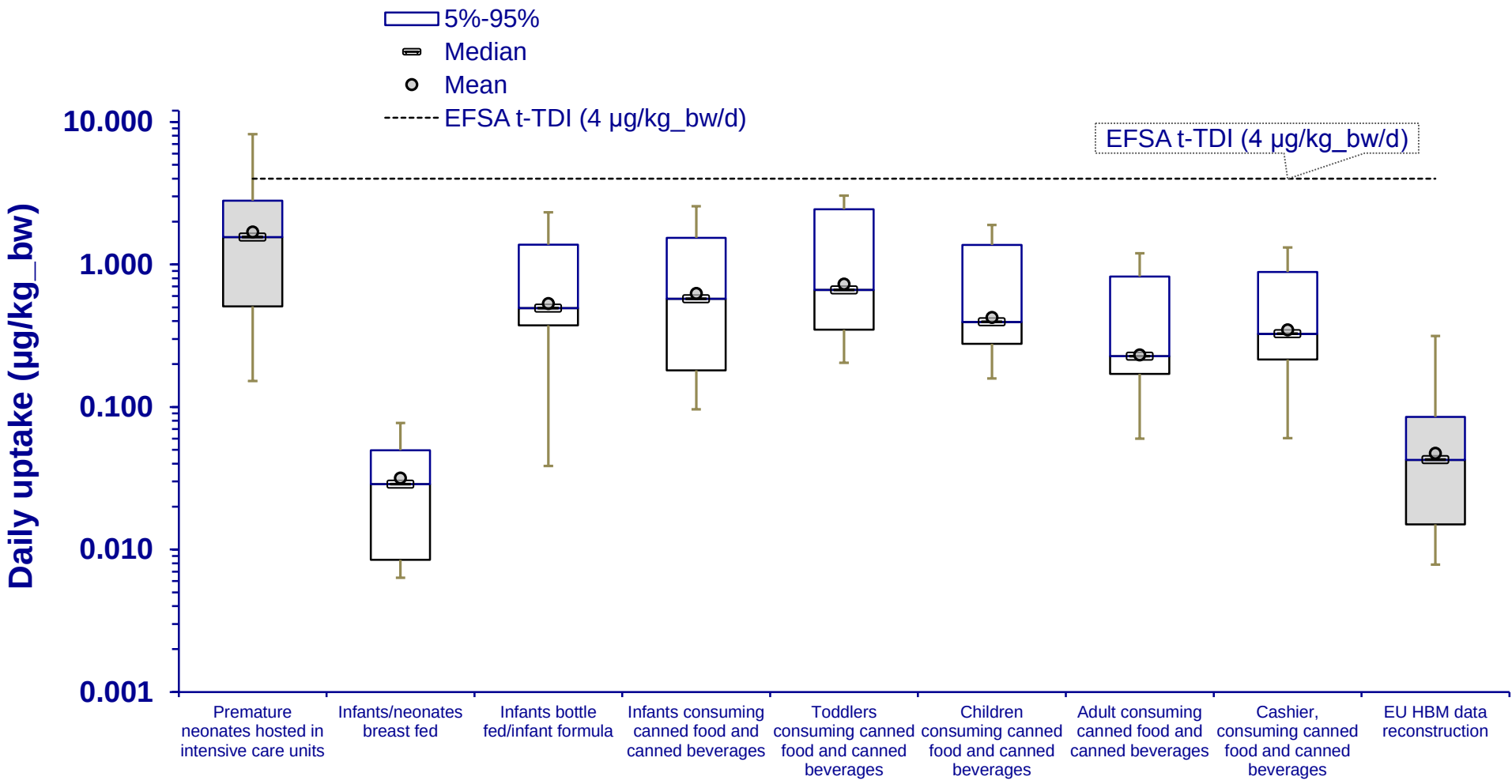

Kidney/blood Partition Coefficient
Coefficient of Determination, R²
1.0
0.8
0.6
0.4
0.2
0.0
Halogenated HCs
Alcohols
Ketones
HCs
Ethers
Esters
Aromatic HCs


Adipose/blood Partition Coefficient
Coefficient of Determination, R²
1.0
0.8
0.6
0.4
0.2
0.0
Halogenated HCs
Alcohols
Ketones
HCs
Ethers
Esters
Aromatic HCs


Heart/blood Partition Coefficient
Coefficient of Determination, R²
1.0
0.8
0.6
0.4
0.2
0.0
Halogenated HCs
Alcohols
Ketones
HCs
Ethers
Esters
Aromatic HCs


Brain/blood Partition Coefficient
Coefficient of Determination, R²
1.0
0.8
0.6
0.4
0.2
0.0
Halogenated HCs
Alcohols
Ketones
HCs
Ethers
Esters
Aromatic HCs

External exposure assessment



Internal dosimetry aspects of BPA toxicokinetics

- Wider inter-individual variability regarding glucuronidation capacity (significantly lower clearance for neonates/infants)
- Very strong plasma protein binding
- First-pass metabolism decisive for clearance – wide bioavailability differences are expected from routes beyond oral (up to six times higher internal dose concentrations for inhalation compared to oral)
- BPA-GLU de-conjugates to BPA in the stomach, increasing the actual dose during breast feeding, thus, the sum of BPA and BPA-GLU needs to be taken into account as BPA dose during breast feeding
- BPA-GLU de-conjugates to BPA in the placenta, increasing the actual dose during pregnancy

- The EFSA t-TDI of 4 μg/kg_bw/d was translated into internal exposure, found to correspond to a concentration of 0.013 μg/L of free plasma BPA (in adults).
- The use of internal dosimetry metrics allows the use of in vitro toxicological data for risk characterization. The ToxCast BPA *in vitro* assays provided six ER agonist or binding AC50 values for BPA, ranging from 0.6 to 1.7 μM. To calculate a conservative Biological Pathway Altering Dose (BPAD), the lowest ToxCast AC50 was selected, which is 0.64 μM for Attagene Factorial cis ERE assay.

Incorporating the uncertainty factors related to population response to xenobiotics, two different values are produced, namely the BPAD99, which is the permissible exposure level that accounts for population variability, and BPADL99, which is the permissible exposure level additionally accounting for uncertainty.

By using the reverse toxicokinetic approach that accounts for the concentration at steady state divided by the dose rate, the respective the estimated population parameters gives a BPAD99 of 0.44 μg/kg_bw/d, with lower one-sided confidence limit, BPADL99, of 0.16 mg/kg/day.

Using these external exposure values in our PBTK model, we derive equivalent internal dose of 1.44 and 0.52 μg/L respectively. These concentrations are almost 2 orders of magnitude higher than the BED derived from the EFSA t-TDI (0.013 μg/L).

Bisphenol A risk characterization

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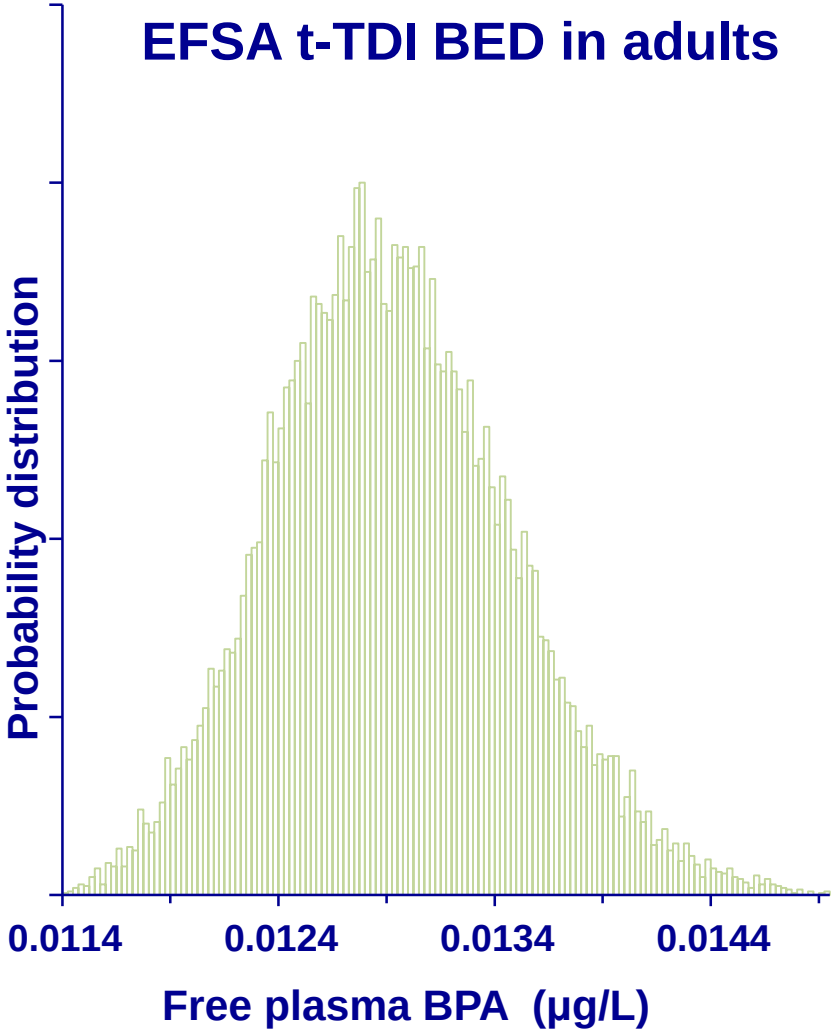
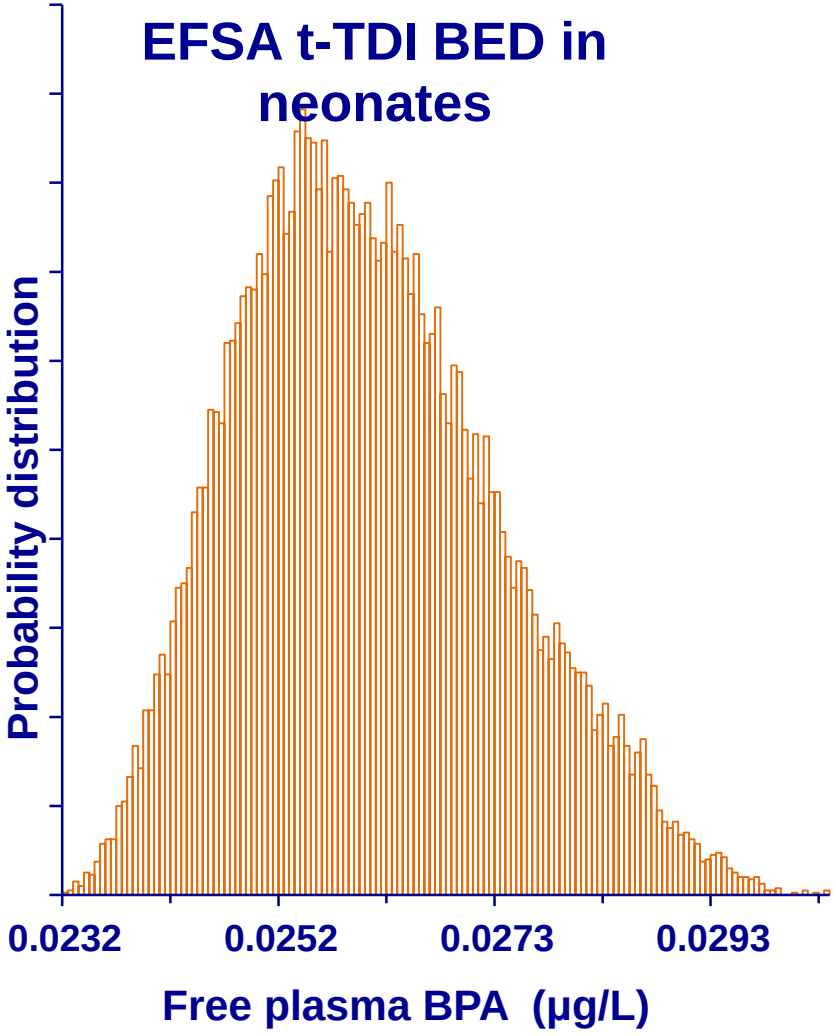
Translating external reference value into internal reference value

EFSA t-TDI BED in adults



EFSA t-TDI BED in neonates



External to internal

Exposure to BPA at EFSA t-TDI (4 µg/kg_bw/d)

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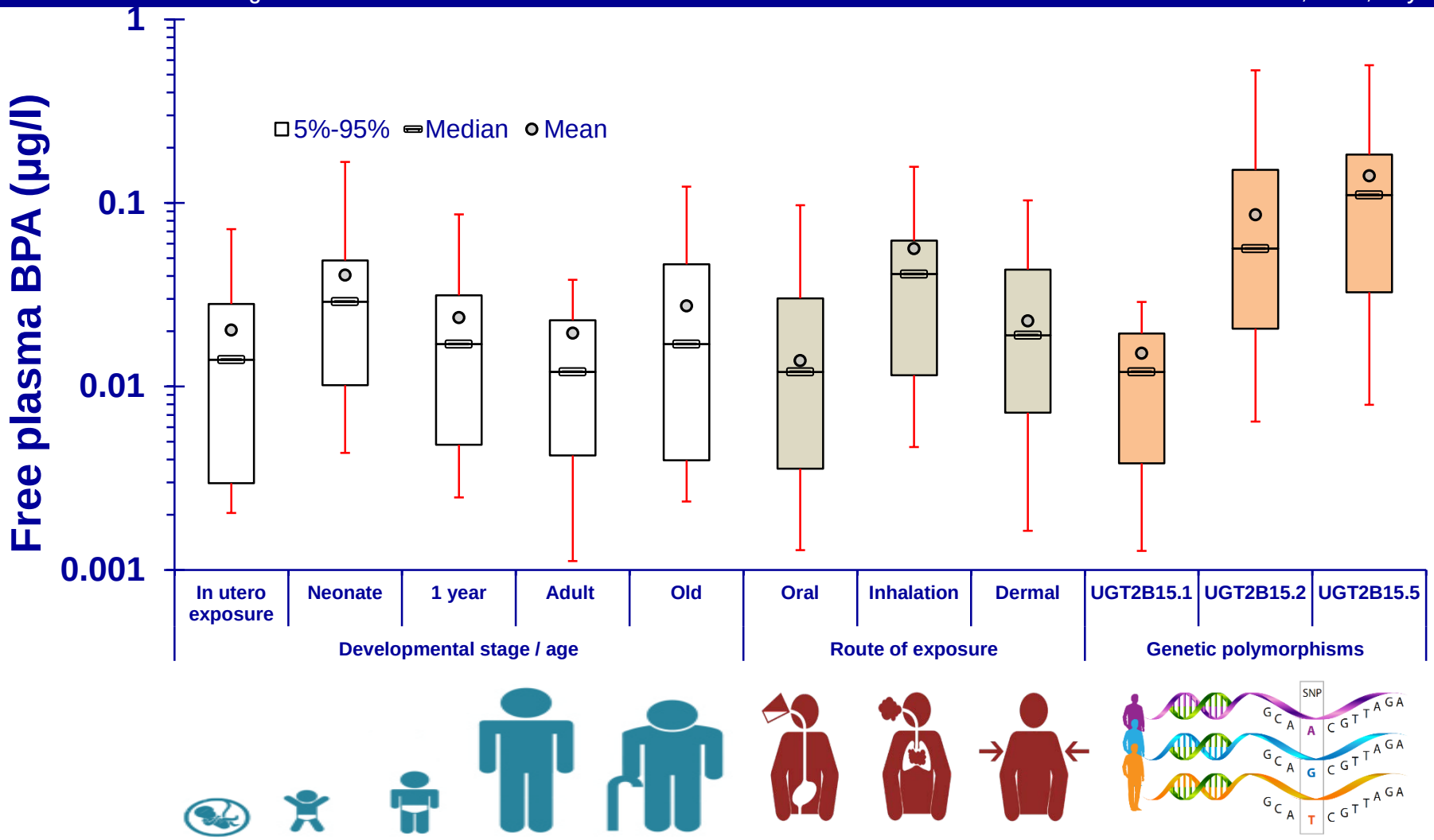
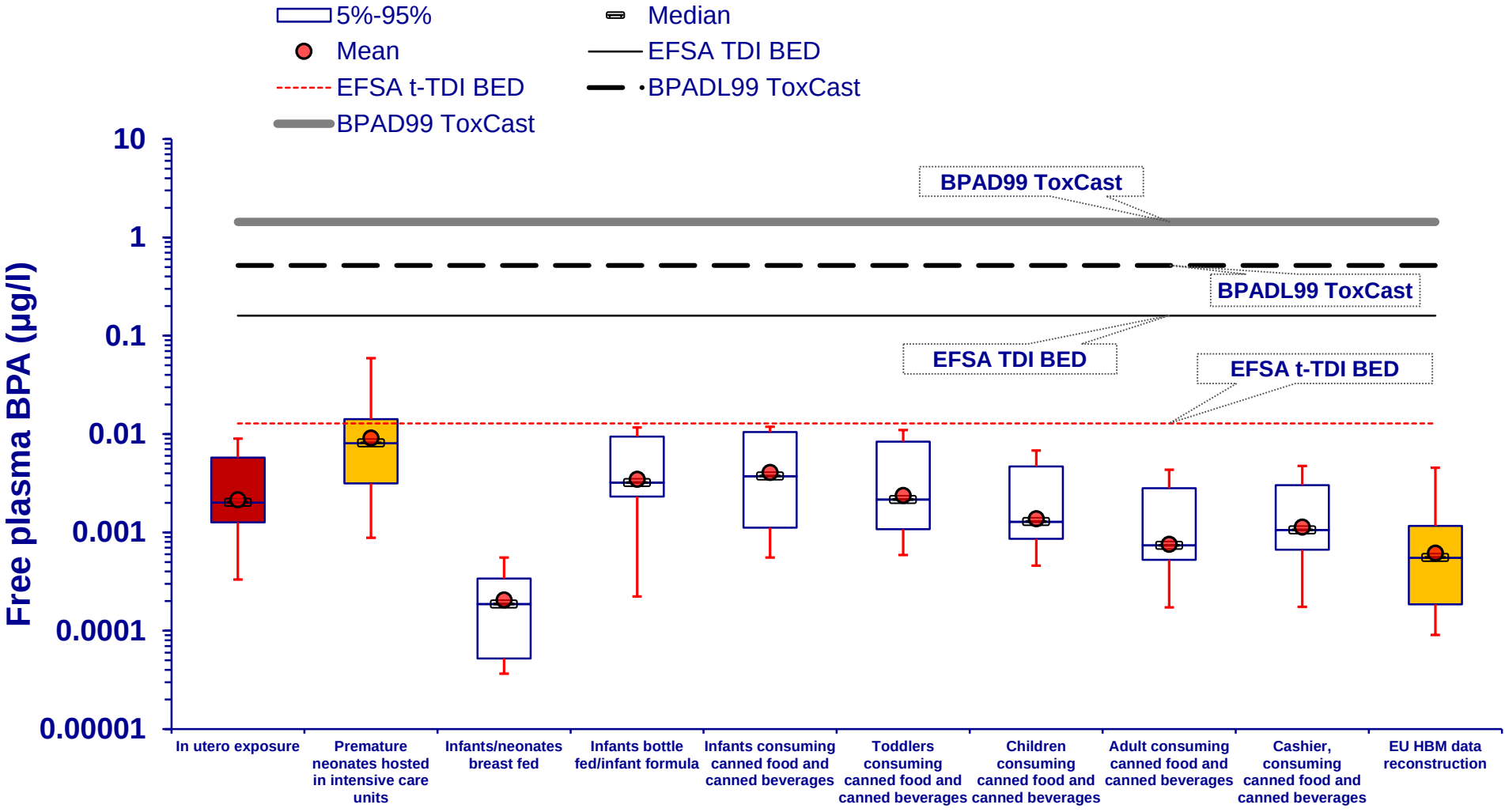


Translating external into internal exposure assessment



Mechanism hypothesis

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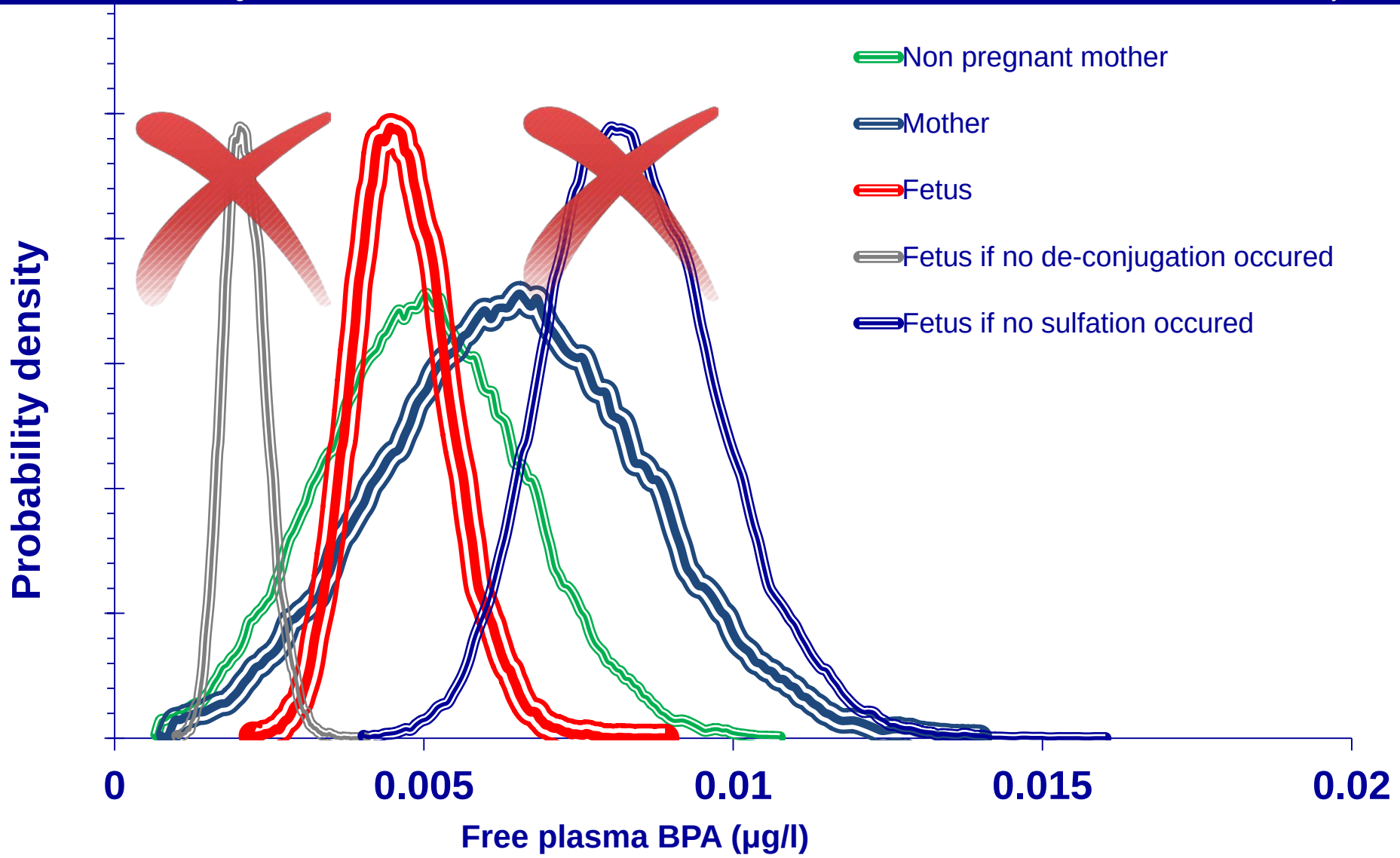

Exposure reconstruction based on HBM data

Reconstructing exposure from TCM spot samples

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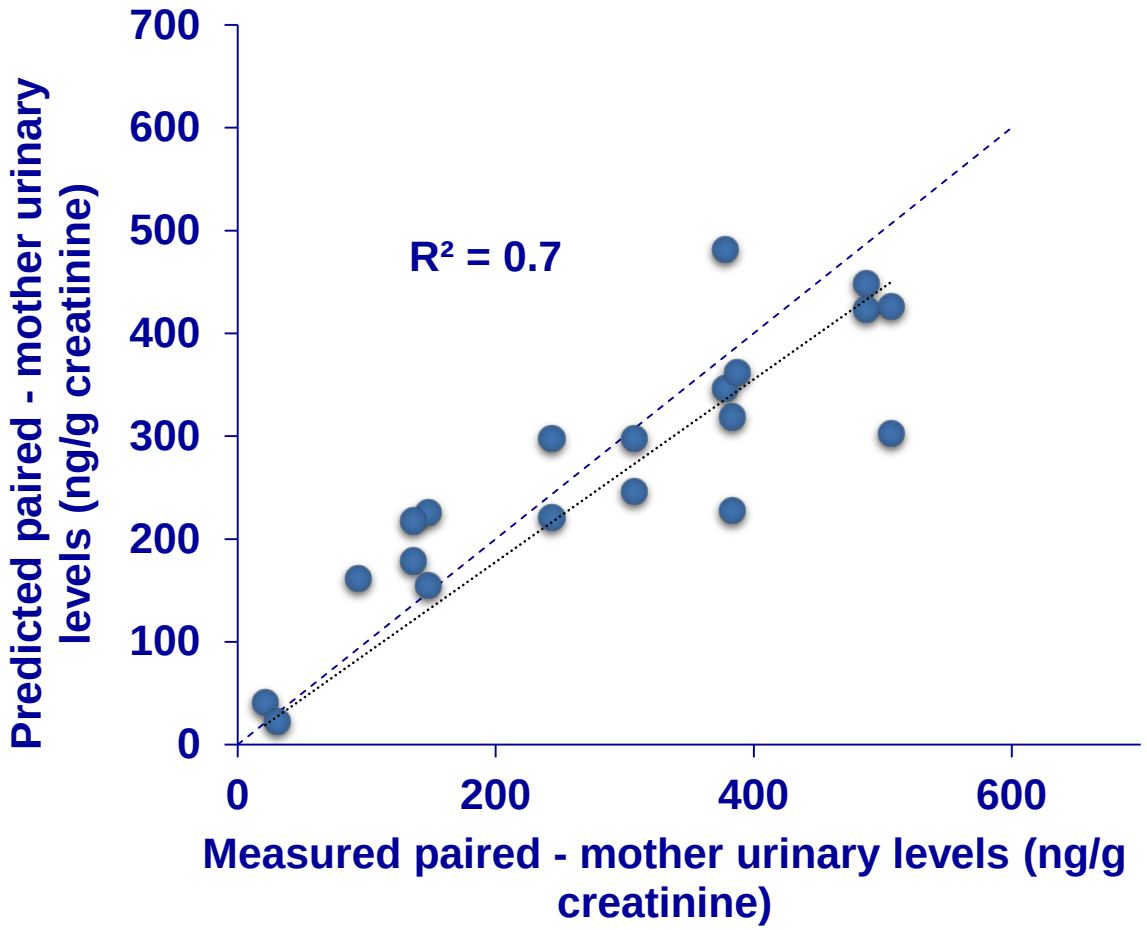
- Urinary TCM (morning voids) was measured in 20 matched mothers and children (paired)
- Using the children urinary TCM levels, indoor air background TCM concentrations were reconstructed
- These concentrations were used for estimating mother exposure

↓

Urinary TCM was predicted for the paired others (nested reconstruction)

↓

Re-running forward the model we estimated TCM blood levels (internal exposure)



Andra SS, Charisiadis P, Karakitsios S, Sarigiannis DA, Makris KC. Passive exposures of children to volatile trihalomethanes during domestic cleaning activities of their parents. Environmental Research 2015; 136: 187-195.

Reconstructing exposure from time-dynamic data

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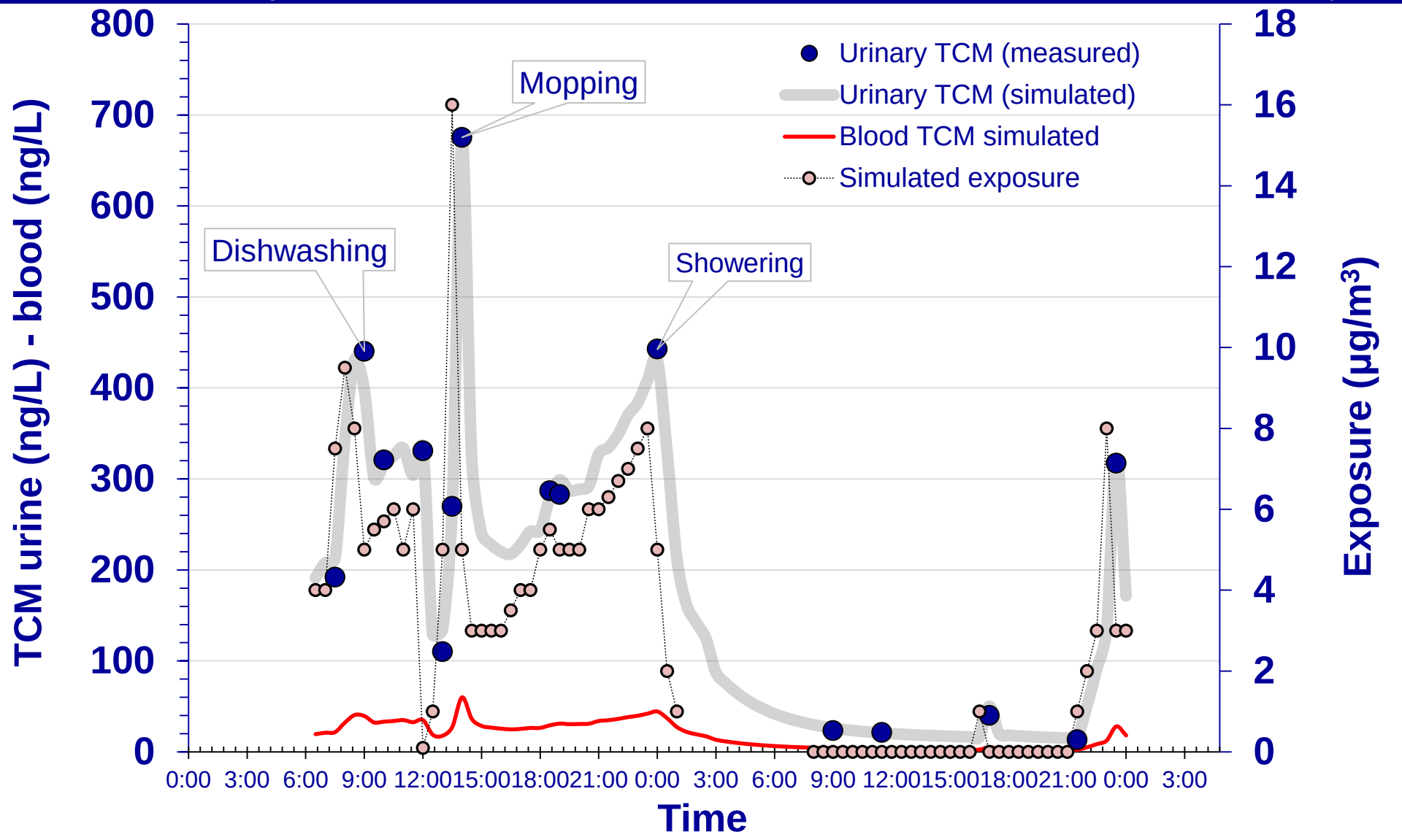

Reconstructing exposure from time-dynamic data

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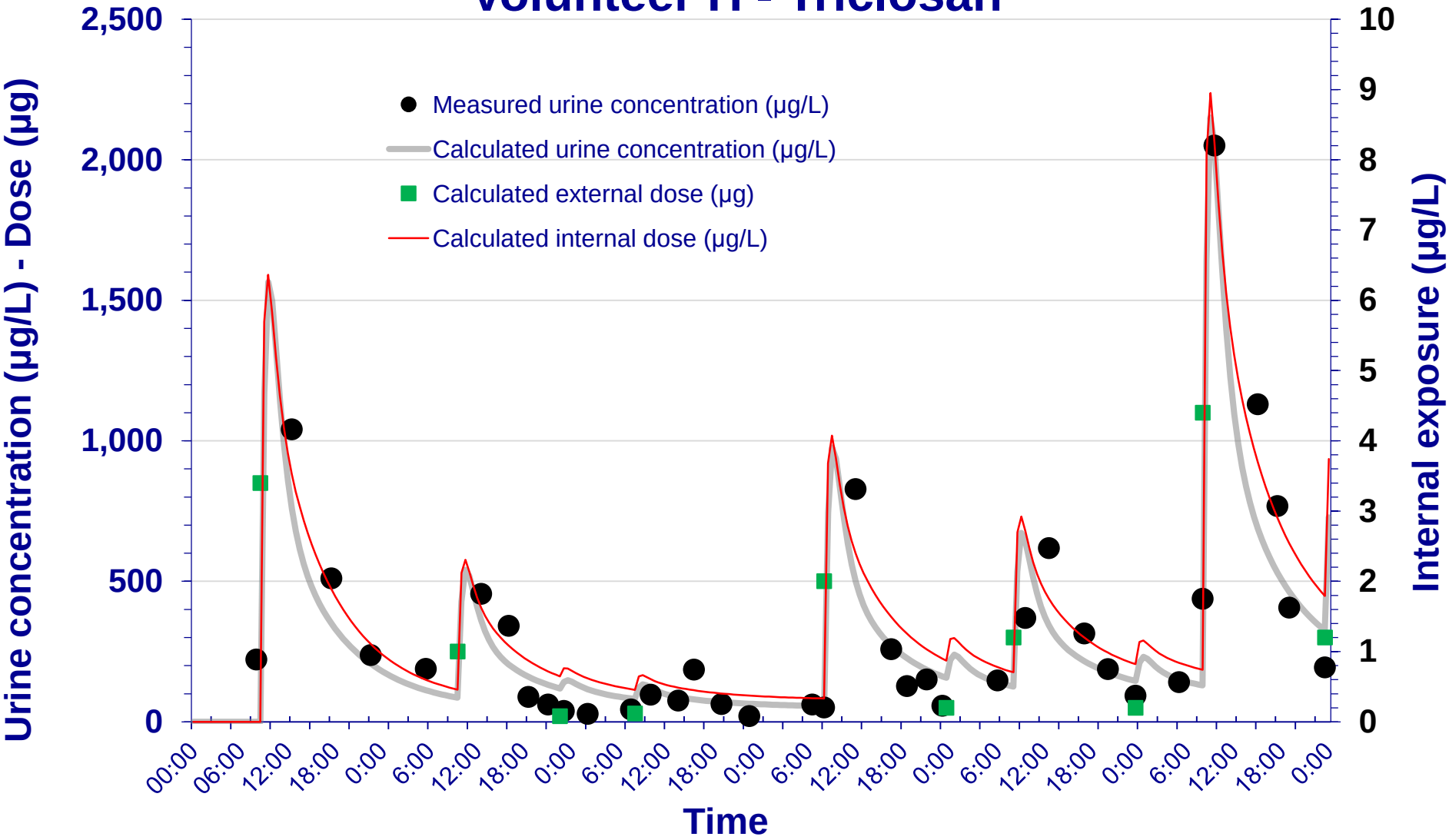
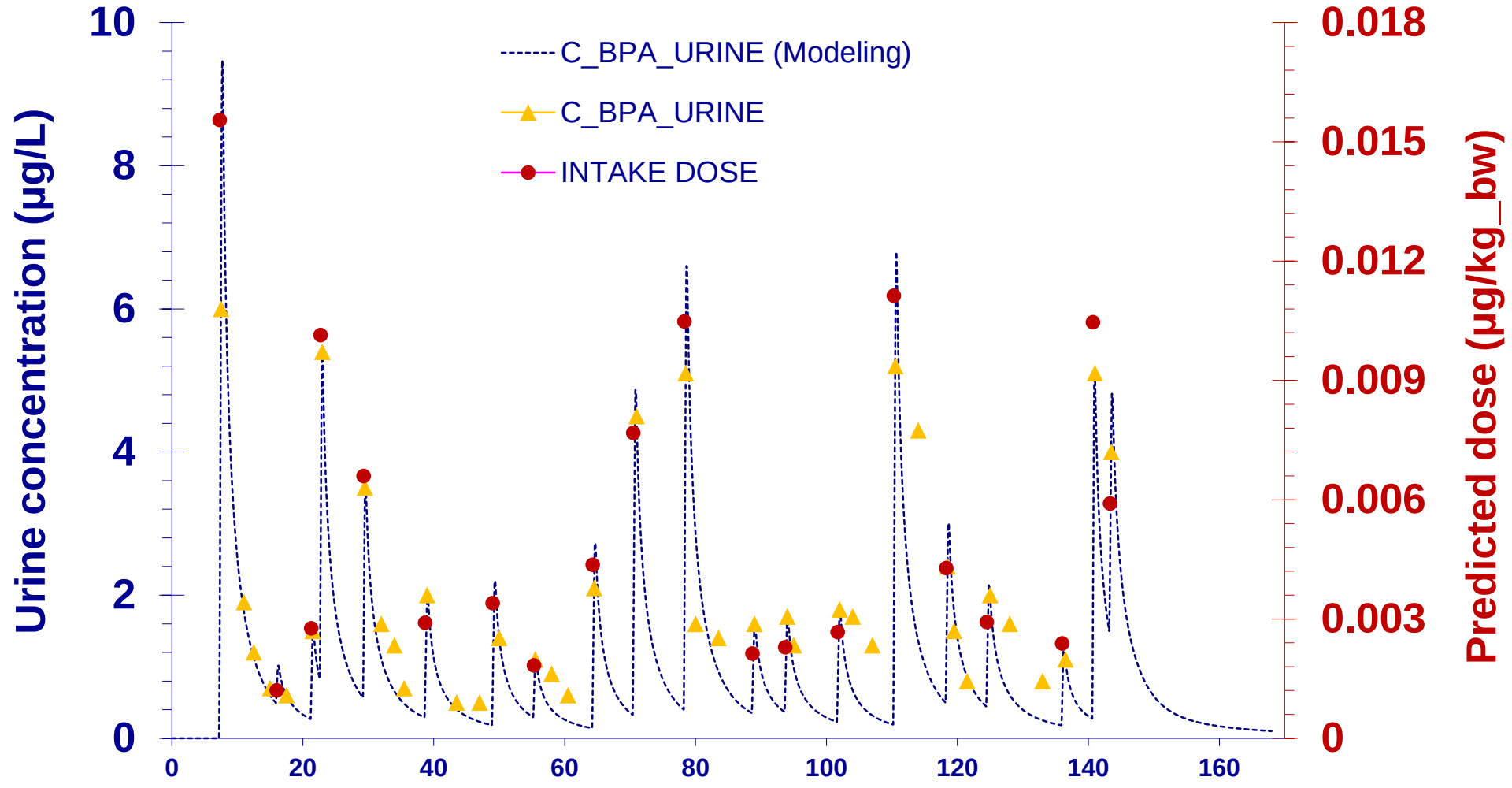
Volunteer H - Triclosan



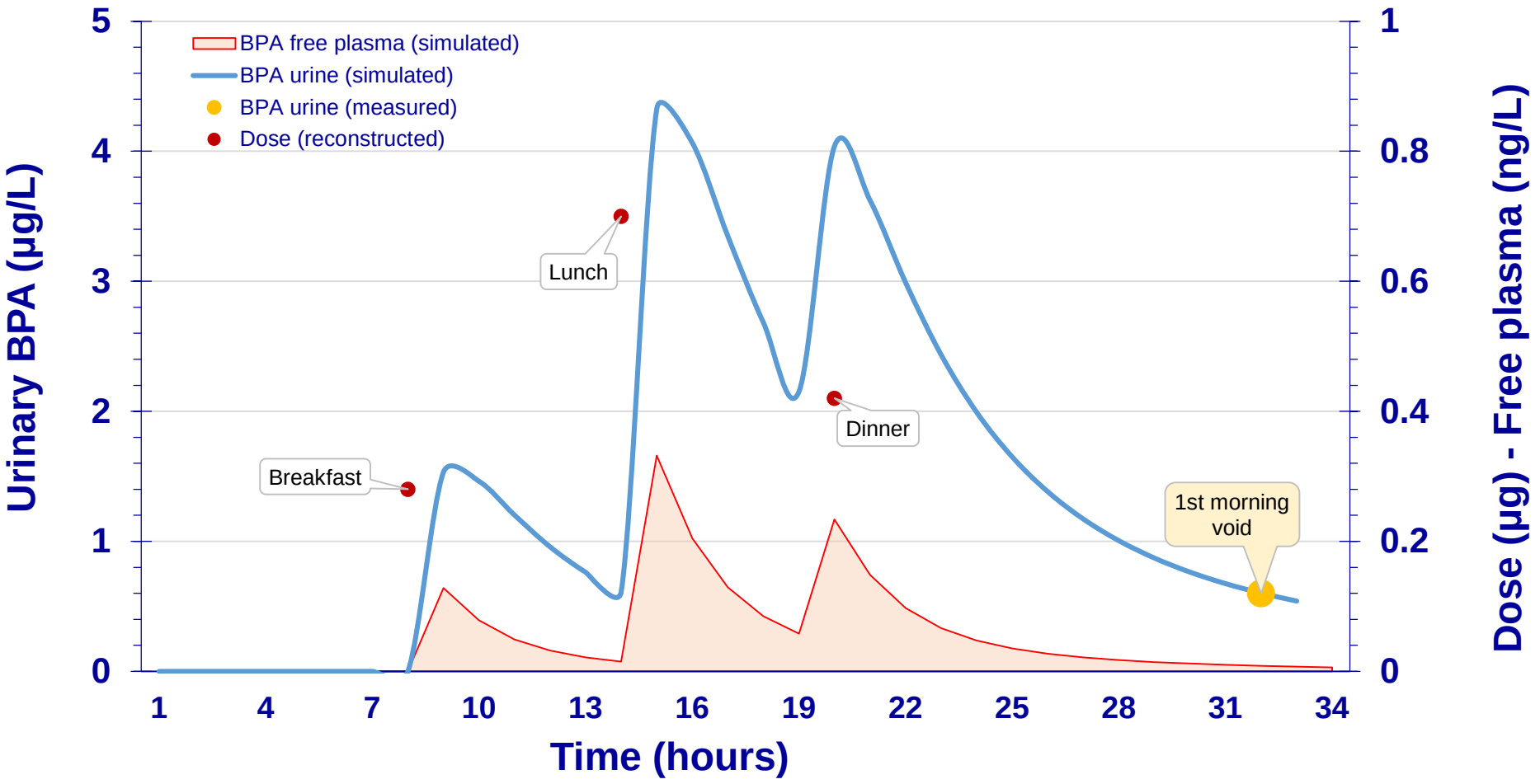
Exposure reconstruction

H2020-MSCA-ITN-2017 GA - 766251



Exposure reconstruction

H2020-MSCA-ITN-2017 GA - 766251



Bertold Brecht's *Life of Galileo*:
"*The main objective of science is not to open the door to infinite wisdom but to roll back the boundaries of infinite error*.

Thank you for your attention

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A connectivity perspective to environmental health