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2 Physiology-based toxicokinetic modeling in the frame of the European Human Biomonitoring Initiative

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3 Abbreviations

2,6-DMA	2,6-Dimethoxyamphetamine
3-OH-BaP	3-hydroxybenzo(a)pyrene
5-cx MEPP	Mono(2-ethyl-5-carboxypentyl) Phthalate
5-OH MEHP	Mono-(2-ethyl-5-hydroxyhexyl) Phthalate
5-oxo-MEHP	Mono-(2-ethyl-5-oxohexyl) Phthalate
ACAT	Advanced Compartmental Absorption and Transit model
AChE	Acetylcholinesterase
ADME	Absorption, Distribution, Metabolism, Excretion
AFE	Average Fold Error
AUC	Area Under the Curve
BaP	Benzo(a)pyrene
BD	1,3-butadiene
BDE-47	2,2',4,4'-tetrabromodiphenyl ether
BDEs	Brominated Diphenyl Ethers
BFRs	Brominated Flame Retardants
BMI	Body Mass Index
BPA	Bisphenol A
BPAG	Bisphenol A Glucuronide
BPAS	Bisphenol A Sulfate
BPF	Bisphenol F
BPS	Bisphenol S
BTEX	Benzene, Toluene, Ethylbenzene, Xylene
BuChE	Butyrylcholinesterase
BW	Body Weight
CAE	Chloracetate Esterase
ChE	Cholinesterase
CO	Cardiac Output
CPF	Chlorpyrifos
CV	Coefficient of Variation
DEHP	Di(2-ethylhexyl) Phthalate
DINCH	1,2-cyclohexane dicarboxylic acid diisononyl ester

DMA	Dimethylarsinic acid
DMT-1	Divalent Metal Transporter 1
DnBP	Di-n-Butyl Phthalate
EHR	Enterohepatic Recirculation
EPA	Environmental Protection Agency
ER	Estrogen Receptor
ERDEM	Exposure Related Dose Estimating Model
FDA	Food and Drug Administration
GEC	Gastric Emptying Constant
GFR	Glomerular Filtration Rate
GI	Gastrointestinal
HBM	Human Biomonitoring
IV	Intravenous
IVIVE	In Vitro to In Vivo Extrapolation
MAPE	Median Absolute Performance Error
MBP	Monobutyl Phthalate
MBP-G	Monobutyl Phthalate Glucuronide
MC	Markov Chain
MCMC	Markov Chain Monte Carlo
MDSs	Model Data Sets
MEHP	Mono(2-ethylhexyl) Phthalate
MLR	Multiple Linear Regression
MMA	Methylarsonic Acid
MMAD	Mass Median Aerodynamic Diameter
MOCA	4,4'-Methylenebis(2-chloroaniline)
MRD	Mean Relative Deviation
MSP	Microsomal Protein
MTBE	Methyltert-butylether
NHANES	National Health and Nutrition Examination Surveys
NHEXAS	National Human Exposure Assessment Survey
NMP	N-methyl-pyrrolidone
NSC	Normalised Sensitivity Coefficient
OP	Organophosphate
o-TOL	o-toluidine
PAHs	Polycyclic Aromatic Hydrocarbons

PBBK	Physiologically Based Biokinetic models
PBPK	Physiologically Based Pharmacokinetic models
PBTK	Physiologically Based Toxicokinetic models
PC	Partition Coefficient
PCBs	Polychlorinated Biphenyls
PCDDs	Polychlorinated Dibenzo-p-Dioxins
PE	Performance Error
PFAA	Perfluoroalkyl acid
PFASs	Per- and polyfluoroalkyl substances
PFCs	Perfluorinated Compounds
PFOA	Perfluorooctanoic acid
PFOS	Perfluorooctanesulfonic acid
P-PBPK	Pregnancy-Physiologically Based Pharmacokinetic model
QSARs	Quantitative Structure-Activity Relationships
QSPRs	Quantitative Structure-Property Relationships
RMSEP	Root Mean Square Error of Prediction
SD	Standard Deviation
SHEDS-HT	Stochastic Human Exposure and Dose Simulation-High Throughput
SR	Sensitivity Ratio
SRCs	Standardised Regression Coefficients
SVHC	Substances of Very High Concern
TCDD	2,3,7,8-tetrachlorodibenzo-p-dioxin
TCP	3,5,6-trichloropyridinol
TCPY	3,5,6-trichloro-2-pyridinol
TLV	Threshold Limit Value
UGT2B7	UDP-Glucuronosyltransferase-2B7
UWW	Uterine Wet Weight
VOCs	Volatile Organic Compounds

4 Abstract

Given the opportunities provided by internal dosimetry modelling in the interpretation of HBM data, the assessment of the links between exposure to chemicals and observed HBM data can be effectively supported by PBTK modelling. This paper gives a comprehensive review of available human PBTK models for compounds selected as a priority by the European Human Biomonitoring Initiative. We highlight their advantages and deficiencies and suggest steps for advanced internal dose modelling. The review of the available PBTK models highlighted the conceptual differences between older models compared to the ones developed recently, reflecting commensurate differences in research questions. Due to the lack of coordinated strategies for deriving useful biomonitoring data for toxicokinetic properties, significant problems in model parameterisation still remain; these are further increased by the lack of human toxicokinetic data due to ethics issues.

Finally, questions arise as well as to the extent they are really representative of interindividual variability. QSARs for toxicokinetic properties is a complementary approach for PBTK model parameterisation, especially for data poor chemicals. This approach could be expanded to model chemico-biological interactions such as intestinal absorption and renal clearance; this could serve the development of more complex generic PBTK models that could be applied to newly derived chemicals.

Another gap identified is the framework for mixture interaction terms among compounds that could eventually interact in metabolism. From the review it was concluded that efforts should be shifted toward the development of generic multi-compartmental and multi-route models, supported by targeted biomonitoring coupled with parameterisation by both QSAR approach and experimental (*in-vivo* and *in-vitro*) data for newly developed and data poor compounds.

Keywords: PBTK modelling, internal dose, human biomonitoring

5 Introduction

PBTK models are continuously gaining ground in regulatory toxicology, describing in quantitative terms the absorption, metabolism, distribution and elimination processes in the human body, with a focus on the effective dose at the expected target site (Bois et al., 2010). Considering the growing interest that PBTK models find in the risk assessment process, guidelines for proper species, doses, and exposure scenarios extrapolations have been proposed by Clewell and Clewell (2008), while the steps towards good modelling practice have been explicitly described by Loizou et al. (2008). The need for the widespread use of PBTK models development is further amplified by the increasing scientific and regulatory interest about aggregate and cumulative exposure. PBTK models translate external exposures from multiple routes (Yang et al., 2010) into internal exposure metrics, addressing the importance of different exposure routes in the overall bioavailability (Sarigiannis and Karakitsios, 2011; Valcke and Krishnan, 2011) or the dependence on critical developmental windows of susceptibility, such as pregnancy (Beaudouin et al., 2010), lactation (Verner et al., 2008) and infancy (Edginton and Ritter, 2009b). With regard to cumulative exposure, PBTK models offer a framework for including the effect of the interactions among the mixture compounds on metabolism. However, due to inherent difficulties, the existing applications are currently limited mainly to VOCs (Haddad et al., 2000; Sarigiannis and Gotti, 2008) and metals (Sasso et al., 2010). Recently, efforts have shifted towards the integration of whole-body physiology, disease biology, and molecular reaction networks (Eissing et al., 2011), as well as integration of cellular metabolism into multi-scale whole-body models (Krauss et al., 2012).

The use of internal dose modeling aims at integrating exposure data and modeling output with Human Biomonitoring data. Its goals are to (a) provide the time history of the exposure profile, focusing on susceptible developmental stages; (b) assimilate biomonitoring data to estimate the individual exposome; and (c) derive reliable biologically effective dose values for the compounds of interest so that they can be associated to observed health outcomes. The key component of the above is the development of a lifetime (including gestation and breastfeeding) generic PBTK model (Sarigiannis and Karakitsios, 2012; Sarigiannis et al., 2016a) incorporating mixture interaction (Sarigiannis and Gotti, 2008) and a framework for biomonitoring data assimilation (Georgopoulos et al., 2008a). Aiming to expand the applicability of the generic PBTK model, parameterisation of the model for known and new chemicals with limited information is done through the development of QSAR models.

A generic PBTK model could also be used to reconstruct exposure from Human Biomonitoring data (Andra et al., 2015). Towards this aim, a tiered approach would be followed as a function of data availability (periodicity and size of sampling, specimen type) and requirements of the exposure reconstruction analysis (temporal analysis of exposure, contribution from different routes), ranging from Exposure Conversion Factors (Tan et al., 2006), up to Markov Chain Monte Carlo analysis. Inputs involve spatial and temporal information on media concentrations of xenobiotics and corresponding information on human activities, food intake patterns or consumer product use. Outputs are the observed biomarkers. The error metric can be defined in terms of population variation (the latter has to be lower than the intra-individual variation, which may be associated with measurement or other random error source). PBTK could be combined with multimedia models and survey questionnaires to identify exposure sources. PBTK modeling may also be used to estimate the internal doses of xenobiotics that exceed levels associated with biological alterations (Judson et al., 2011) and, eventually, health risk. The latter can involve the use of specific omics results (e.g., metabolomics analysis) and associations of biologically effective doses to early biological responses (toxicodynamics). In addition, biologically effective doses would be used to quantify the effect of compound-induced extracellular perturbations on metabolism, so as to directly couple the PBTK model with metabolic regulatory networks. Direct coupling defines a

feedback loop that connects clearance and metabolite production rates to metabolism regulation (Eissing et al., 2011) via dynamic flux balance analysis (Krauss et al., 2012).

Considering the opportunities offered by the use of PBTK models in exposure/risk characterisation, several research groups are developing generic PBTK models, either as stand-alone models such as PK-Sim (Willmann et al., 2003a), Indus-Chem (Jongeneelen and Berge, 2011) or PoPGen (McNally, 2014), or incorporated within integrated computational platforms for exposure assessment such as INTERA (Sarigiannis et al., 2011) and MENTOR (Georgopoulos et al., 2008b). The development of generic PBTK models is substantiated by recent advances in quantitative structure–activity relationships (QSARs) and quantitative structure–property relationships (QSPRs) (Peyret and Krishnan, 2011; Price and Krishnan, 2011), providing the basis for development of relevant PBTK models for data-poor or new chemicals (Papadaki et al., 2017; Sarigiannis et al., 2017).

Recognising key gaps in the knowledge required to support actions on chemicals within the 7th Environmental Action Programme, as well as the need to address these gaps Human Biomonitoring (HBM) was identified as a tool that can serve the chemicals agenda. As a response to these needs, the European Human Biomonitoring Initiative (HBM4EU) aims at generating knowledge to inform the safe management of chemicals and so protect human health (Ganzleben et al., 2017). As an overarching aim, is the acquisition of HBM data on the exposure of the EU population to prioritised chemicals, and to derive European Health based guidance values and statistically derived reference values for bisphenols (A, S, F), phthalates and DiNCH, new generation flame retardants, cadmium, chromium, PAHs, Anillin derivates, and short chain perfluorinated compounds in a first round.

Given the opportunities provided by internal dosimetry modelling in the interpretation of HBM data, the assessment of the links between exposure to chemicals and observed HBM data can be effectively supported by PBTK modelling. To summarise, the aim of this paper is to provide a comprehensive review of human PBTK models available for the HBM4EU prioritised compounds, to highlight their advantages and deficits and to provide steps for increasing the predicting accuracy.

6 Methodology

6.1 Selection of priority compounds

The compounds that will be dealt with priority in the HBM4EU project, were selected in consortium with primarily policy makers and regulators in chemical/food safety and occupational health in European Union Member States, European institutions responsible for policy making and agencies responsible for implementing EU regulations. The criteria used comprised public concern, scientific evidence and urgency to regulate in order to safeguard occupational and consumer health while fostering industrial competitiveness and innovation.

Keywords
Physiologically based pharmacokinetic (or toxicokinetic or biokinetic) model + PBPK (or PBTK or PBBK) + anilines + human
Physiologically based pharmacokinetic (or toxicokinetic or biokinetic) model + PBPK (or PBTK or PBBK) + bisphenols + human
Physiologically based pharmacokinetic (or toxicokinetic or biokinetic) model + PBPK (or PBTK or PBBK) + bisphenol A + BPA + human
Physiologically based pharmacokinetic (or toxicokinetic or biokinetic) model + PBPK (or PBTK or PBBK) + bisphenol S + BPS + human
Physiologically based pharmacokinetic (or toxicokinetic or biokinetic) model + PBPK (or PBTK or PBBK) + bisphenol F + BPF + human
Physiologically based pharmacokinetic (or toxicokinetic or biokinetic) model + PBPK (or PBTK or PBBK) + phthalates + human
Physiologically based pharmacokinetic (or toxicokinetic or biokinetic) model + PBPK (or PBTK or PBBK) + pahs + human
Physiologically based pharmacokinetic (or toxicokinetic or biokinetic) model + PBPK (or PBTK or PBBK) + polycyclic aromatic hydrocarbons + human
Physiologically based pharmacokinetic (or toxicokinetic or biokinetic) model + PBPK (or PBTK or PBBK) + pesticides + human
Physiologically based pharmacokinetic (or toxicokinetic or biokinetic) model + PBPK (or PBTK or PBBK) + perfluorinated compounds + human
Physiologically based pharmacokinetic (or toxicokinetic or biokinetic) model + PBPK (or PBTK or PBBK) + PFOA + PFOS + human
Physiologically based pharmacokinetic (or toxicokinetic or biokinetic) model + PBPK (or PBTK or PBBK) + metals + human
Physiologically based pharmacokinetic (or toxicokinetic or biokinetic) model + PBPK (or PBTK or PBBK) + chromium + human

Keywords
Physiologically based pharmacokinetic (or toxicokinetic or biokinetic) model + PBPK (or PBTK or PBBK) + cadmium + human
Generic + Physiologically based pharmacokinetic (or toxicokinetic or biokinetic) model + PBPK (or PBTK or PBBK) + human

The wide spectrum of chemicals that were proposed as candidates to consider in the frame of the European Human Biomonitoring initiative were classified in three clusters on the basis of the criteria outlined above. Group A includes compounds for which there is enough information, policy relevance, regulatory expediency and/or public concern to warrant successful collection and interpretation of biomonitoring data in Europeans. Group B includes compounds for which data gaps were identified already during preliminary prioritisation but public concern is such that warrants focus right after Group A. Group C includes substances for which the available information is limited and there is no significant urgency to deal with. During the initial 2-3 years of HBM4EU the project puts its main focus on the chemicals in Group A. These include phthalates and DiNCH, anilines and MOCHA, bisphenols, polyaromatic hydrocarbons and airborne chemicals, flame retardants, perfluorinated compounds, cadmium and hexavalent chromium. In addition, HBM4EU will address the issue of chemical mixtures; in this context, co-exposure of consumers to mixtures of plant protection products will be addressed as a part of Group A.

6.2 Review method

The review was based on keyword research in three different scientific libraries: Web of science, Scopus and PubMed. The keywords, which were used referred to the classes of chemicals that are included in the 1st set of priority compounds. Furthermore, generic PBTK models were included in the search criteria as they can simulate a wide range of chemicals during different life stages. The findings that corresponded to PBTK models for estimating ADME properties of several chemical compounds using directly human data or extrapolated data from animals to humans were included in the review. The studies that referred only to animal species and not to humans were excluded. For flame retardants, the only PBTK model that was identified was the one for BDE-47 in rats. Considering the lack of a human PBTK model, we decided (exceptionally) to include this model in the review.

Different combinations of keywords used are presented in the following table.

7 Human PBTK models identified for the priority compounds

7.1 Anilines

Aniline is the prototypical aromatic amine and is predominantly used as a chemical intermediate for the dye, agricultural, polymer, and rubber industries (ATSDR, 2002). The general population may be exposed to aniline via inhalation through tobacco smoke, orally through diet or drinking water containing aniline in small amounts and rarely by living in uncontrolled hazardous waste sites. It has been reported that aniline causes methemoglobinemia (Harrison and Jollow, 1987; Kearney et al., 1984; Lee et al., 2013). Exposure to aniline can also provoke dizziness, headaches, irregular heartbeat, convulsions and coma.

One PBTK model that generated toxicity exposure distributions for a series of substituted anilines in rats and human was found in literature (Nguyen et al, 2015). The substituted anilines were chosen because of their structural similarity to aniline. This model consisted of two major sub-models that described disposition and input. In the disposition model, the relevant organs or tissues were selected. 14 compartments, including those for lungs, adipose, heart, brain, muscle, spleen, pancreas, stomach, gut, kidney, bone, skin, and thymus and two blood compartments (arterial and venous blood) were included. The input model was adapted from the advanced compartmental absorption and transit model (ACAT) (Agoram et al., 2001) originally developed by Yu et al (1999). It consisted of nine compartments, including stomach, large intestine, seven segments of small intestine, and corresponding enterocyte or GI wall. Each tissue was assumed to be perfusion-rate limited, as the compounds were reported to be rapidly absorbed from the small intestine, and passively permeated through tissue and cellular membranes with no known transporter. Finally, aniline was reported to be metabolised in liver by acetylation and hydroxylation pathways. The model was validated by comparing the whole blood concentration–time profiles for the five model compounds after an oral solution dose using the rat PBPK model. Different doses of aniline were simulated and compared with reported *in vivo* data of Harrison and Jollow (1987). The shape and the magnitude of predicted blood concentration–time course was in agreement with the observed data.

7.2 Bisphenols

The bisphenols are a group of chemical compounds with two hydroxyphenyl functionalities. Bisphenol A (BPA) is the most popular representative of this group and has been listed as endocrine disruptor by U.S. Environmental Protection Agency (EPA), as well as lately by ECHA (2018); although BPA was already in the REACH candidate list of substances of very high concern (SVHC), the entry was updated, to reflect its endocrine disrupting properties. BPA is used primarily as a monomer in the industrial production of epoxy resins and polycarbonate plastics (Keith, 1997). Thus, it is present in a wide range of consumer products, such as food and drink containers, as well as medical devices (EFSA, 2015; FDA, 2014; Willhite et al., 2008). There are several PBTK models in literature regarding human exposure to BPA.

The first model for BPA (for both rats and humans) was developed by Shin et al (2004a), where input parameters regarding human PBPK model were found using scaling methods from rat data. The compartments were divided into a) non-eliminating organs, which included spleen, kidneys, heart, testes, brain, muscle, adipose tissue, stomach and small intestine, b) an eliminating organ (liver), c) lungs, d) blood (vein and artery), e) lumen and f) small intestine. Differential mass balance equations were used for each individual compartment. For parameterisation and validation of the model, multiple intra-venous injections to rats and single intra-venous injection (5mg dose) and multiple oral administrations to steady state (100mg doses every 24h) to a 70kg human were

used. The same was also used for predicting time courses of BPA in blood and various human tissues. Observed concentrations of bisphenol A in blood and other tissues, testis, brain, muscle, adipose tissue, stomach, and small intestine, were found after multiple iv injections to rats, together with the simulated individual time courses using the PBPK model. The average steady-state concentration of bisphenol A in all tissues except adipose tissue were higher than the corresponding blood levels. Good agreement was noted between predicted and observed concentration–time profiles for blood and all tissues despite the varying steady state concentrations.

Teeguarden et al. (2005a) developed a PBTK model for the evaluation of toxicokinetics of BPA for rats and human. Two sub models were established; one for BPA, consisting of the five compartments of gastrointestinal (GI) lumen, liver, blood, uterus and the remaining tissues and one for its metabolite glucuronide BPA (BPAG) including plasma and GI lumen. Tissue distribution was represented as perfusion-limited in all the compartments, while no blood flow distribution was represented to the GI lumen. This tissue was represented only as a compartment of absorption of BPA and of elimination and reabsorption of BPAG in the bile. Hepatic metabolism from BPA to BPAG was considered as second order kinetics. The metabolised BPA was transferred to the BPAG sub-model. A fraction of the formed BPAG was transferred to the GI lumen and then was eliminated via the bile. The rest was transferred to the plasma compartment and was eliminated via urine. Another fraction of the BPAG eliminated to the GI lumen was hydrolysed to BPA and reabsorbed from the GI lumen to the liver at a first order rate. The extensive binding of BPA to plasma proteins in different species (including humans) in a percentage of ~90–95% of the total (Csanady et al., 2002; Kurebayashi et al., 2002) was in general comprised in the partition coefficient values from Csanady et al. (2002). Assessment of the model was carried out with BPA plasma and blood concentration data in rats, BPAG blood concentration and cumulative excretion of BPAG in urine and feces in rats, time course data of BPAG concentration in plasma in men and women after oral exposure to BPA as well as cumulative BPAG excretion in urine and feces in men and women. The error in the estimations was not explicitly quantified by the authors and the results were commented from graphic representations. The human assessment showed a good agreement of the simulated vs. the observed data from plasma at the beginning of the depuration (<12 h post-exposure) in men, while the data for women were scarce. An underestimation of the concentrations at later points of the time course, for both genders was noticed. A good agreement of the simulated vs. the observed excretion data in human was observed.

Based on the structure of the PBTK model with the BPA sub model coupled to a BPAG sub model, proposed by Teeguarden et al. (2005a), Edginton and Ritter (2009b) developed a model for predicting plasma concentration of BPA in children younger than 2 years old. The model included 15 organs as well as arterial, venous, and portal blood compartments. The organs were connected via blood flows, and the circulation system was closed via the lung. The oral absorption model was that of Willmann et al. (2004a) providing BPA input to the portal vein. Scaling the gastrointestinal parameters (gastrointestinal geometry, gastric emptying time, intestinal permeability, gastric and intestinal pH, small intestinal transit time and intestinal surface area) to children between 0 and 2 years of age was also considered. The elimination of the total BPA was attributable to its metabolism to BPAG via glucuronidation by the enzyme UGT2B7. The intrinsic clearance of BPA to BPAG from adults to children was scaled. In general, it is noted that UGT2B7 activity in term neonates is only 5% that of adults, increases to 30% by 3 months of age and reaches adult levels by 1 year of age (Edginton et al., 2006a). It has to be noted that clearance was parameterised in a way that the observed blood time course of an adult fitted well the toxicokinetic profile of single BPA dose provided by Völkel et al. (2002).

Mielke and Gundert-Remy (2009) used a PBTK model allowing the simulation of blood concentrations of bisphenol A at various life stages and the intake of bisphenol A as a

discontinuous process thus mirroring the intake of the substance with meals. The basic model was similar to the model by Ramsey and Andersen (1984) but with some modifications for various life stages, including the newborn (Abraham et al., 2005). Excretion was modelled by metabolism in the liver to glucuronides and sulfate conjugated metabolites. Also this model was validated using the human voluntary data provided by Völkel et al. (2002). The predicted value of 2.6 ng/ml was somewhat higher than the experimental highest measured value of 2.3 ng/ml, however it was considered as good, supporting the credibility of the model results. This model was further developed including the addition of skin absorption (Mielke et al., 2011), for the assessment of the contribution of dermal exposure to the internal exposure of bisphenol A in man.

In addition, a PBTK model was developed by Yang et al. (2015) in order to assess the human exposure to BPA and its phase II conjugates BPAG and BPA sulfate (BPAS) in adult humans following oral ingestion. An eight-compartment PBTK model for BPA, including serum, liver, fat, gonads, richly perfused tissues, slowly perfused tissues, brain, and skin, and two single-compartment (volume of distribution, V_{body}) sub-models for BPAG and BPAS were constructed. According to the original model proposed by Fisher et al. (2011), the compartments were selected based on kinetic considerations (e.g. liver) and the model's potential use for internal dose metrics estimation and dermal exposure assessment (e.g. brain and gonads, skin). The uptake of BPA and BPAG in the tissues was described as a first order process. The phase II metabolites, BPAG and BPAS, were simply described as a single non-physiological compartment given that these conjugates display no known estrogenic activity. An In Vitro to In Vivo Extrapolation (IVIVE) approach was employed to derive model parameters representing hepatic glucuronidation and sulfation of BPA that were described using Michaelis–Menten equations. BPA glucuronidation occurred in the liver and the small intestine, while the formation of BPAS was assumed to occur only in the liver (Kurebayashi et al., 2010). Ten percent of BPAG derived from the small intestine and the liver was assumed to be secreted into the gut through the bile and undergo enterohepatic recirculation (EHR), whereas the remaining 90% of BPAG was taken up via the systemic circulation in the BPAG sub-model. The overall toxicokinetic behavior of the model was validated using the human volunteer data delivered by Völkel et al. (2002), who reported plasma concentration and urinary excretion-time profiles of d_{14}-BPAG in adult humans after a single oral dosing of 5 mg d_{16}-BPA over a period of up to 42 h. These toxicokinetic data were used to optimise the parameterisation of key kinetic parameters. Simulations of cumulative excretion of total d6-BPA in urine were also in line with collected data, with MRD of 2.7 (1.6–6.4) and AFE of 1.5 (1.1–2.0).

Lately, a generic PBTK model that captures satisfactorily life stage changes and physiological and metabolic efficiency change over an individual's lifetime (from conception till 80 years of age) was developed in INTEGRA European project and was used for the estimation of BPA toxicokinetics (Sarigiannis et al., 2016b). Furthermore, special attention was paid on the assessment of exposure to BPA during critical developmental stages such as gestation by modelling the mother-fetus toxicokinetic interaction. Arterial, venous and portal blood compartments, as well as all major human organs were included in the model. The main routes of exposure were described in detail and all the age and gender exposure modifiers were taken into account. To estimate the total amount of BPA to which the infant is orally exposed, the sum of free BPA and BPAG was considered, since all conjugated BPA is cleaved in the gastrointestinal tract. Three mass balance equations for a) red blood cells, b) plasma and interstitial tissue and c) cells were written regarding each tissue, allowing the application of the model to both flow limited and membrane-limited compounds. In this model, the parent compound (BPA) and the metabolite BPAG and BPAS (for fetus and early infancy) were taken into account, as the main detoxification pathway of BPA is phase II glucuronidation and sulfation at early developmental stages. Free BPA and BPAG were excreted through lactation, while BPAG was eliminated via urine for humans. This model was also

validated with the human volunteer data from the Völkel et al. (2002) study for both BPA and BPA-glu in urine and the results fitted the experimental values with R^2 of 0.82 and 0.78 respectively.

Finally, a model has been recently presented by Sharma et al. (2018b) that has taken stock from the advances and the parameterisation provided by the existing models. Metabolism in pregnancy was introduced via scaling of the *in vitro* Vmax for glucuronidation and sulfation, considering the pre-pregnancy body weight. The BPA metabolism data for the fetus was scaled using human *in vitro* data and fetus microsomal protein content, and, growing fetus liver and body weight. Two metabolic kinetic parameters namely V_{max} (maximum rate of reaction) and K_m (affinity of the substrate for the enzyme), for mother and fetus, were taken from *in vitro* studies and scaled to *in vivo*. Validation of the developed adult PBPK model was performed by comparing the model predictions with plasma data obtained from the human study by Thayer et al. (2015), in which volunteers were orally administered 100 µg/kg BW dose of deuterated BPA. The observed concentration in different cohorts during pregnancy was used for P-PBPK model evaluation. For instance, maternal blood concentration during pregnancy or at the delivery time was used for exposure estimation. Five biomonitoring cohort data on fetus plasma, liver, mother placenta and amniotic fluid were used for model calibration and evaluation purpose.

7.3 Phthalates and DiNCH

Phthalates is a huge class of chemicals used mainly as plasticizers in a wide variety of products, such as toys, vinyl flooring and wall covering, detergents, lubricating oils, food packaging, pharmaceuticals and personal care products (Heudorf et al., 2007; Kamrin, 2009). Humans are exposed through ingestion, inhalation, skin and eye contact. The primary route of exposure is through oral consumption mainly due to the transfer of substances from food packaging onto food stuff, as well as dust and soil ingestion (National Research Council, 2008). Phthalates have been reported to be responsible for several reproductive or developmental abnormalities (Meeker et al., 2009; Swan, 2008).

Clewell et al. (2008) developed a model for di-n-butyl phthalate (DBP) and its metabolites: monobutyl phthalate (MBP), MBP-glucuronide and oxidative metabolites of MBP in rat. Clewell et al. (2008) represented in detail the GI tract (upper, lower, wall), liver, plasma, certain reproductive tissues and either rest of the body or richly and slowly perfused tissues (depending on the sub-model), as well as feces and urine. The model of Gentry et al. (2011) for di(2-ethylhexyl) phthalate (DEHP) and its metabolites in human was based on the model by Clewell et al. (2008). The main structural differences in the model of (Gentry et al. 2011) compared to the model by Clewell et al. (2008) consisted in a simplified GI lumen, non-application of the glucuronidation pathway and detailed representation of the oxidative-metabolites-submodel. In the models of Clewell et al. (2008) and Gentry et al. (2011), the distribution of the monoester was considered to be diffusion-limited, while the distribution of other compounds (diester, glucuronidated or oxidative metabolites) was represented as flow-limited. In both models, the diester was applied as a bolus to the GI lumen. The metabolism of the diester was represented in the GI compartment, liver and plasma. The monoester that arrives to the GI lumen by metabolism of the diester (Clewell et al. 2008) or biliary excretion (Gentry et al. 2011) and the not metabolised diester were absorbed from the GI compartment following 1st order kinetics and transferred to the liver. The oxidation (MEHP, MBP) and glucuronidation (MBP) of the monoester were represented in liver. Clewell et al. (2008) included a hydrolysis of MBP-G to MBP in the GI tract. A biliary excretion of the diester and the monoester in both models, as well as MBP-G (Clewell et al., 2008) and oxidative-MEHP (Gentry et al., 2011) was represented from the liver to GI lumen. The diester and all its metabolites were eliminated from the GI tract to feces. The monoester and oxidative monoesters in both models, as well as MBP-G in Clewell et al. (2008) were also eliminated from plasma to urine.

Later, a PBTK model was established as an exposure prediction tool for DEHP and DnBP in humans (Moreau et al., 2017), based on the model of Gentry et al. (2011), including the four interconnected sub-models for the diester, the hydrolytic monoester, the oxidative metabolites and the glucorinide conjugate. Diester distributed in the gut wall was passed to the liver via the portal blood, while their monoester metabolites MEHP and MBP were readily absorbed in the gut. Transport of monoester into the tissues was modeled using diffusion-limitation. Distribution of oxidative metabolites into the tissues was modeled using flow-limitation, assuming distribution with body water. DEHP is rapidly metabolised to its monoester, mono(2-ethylhexyl) phthalate (MEHP), which is further metabolised by various oxidation reactions to a number of secondary hydrolytic and oxidative metabolites that are conjugated via glucuronidation and other processes before being eliminated. DnBP is metabolised to its monoester, MBP. Oxidative metabolism was described in the liver using a saturable Michaelis-Menten description. A four-compartment model was used to describe different oxidative metabolites in the body. The model was validated for adult male rats using a dataset that is different from the one that was used to parameterise the model (Payan et al., 2001). No parameter values were tweaked to improve model fits to the ‘‘validation’’ data.

The recent model presented by Sharma et al. (2018b) is flow-limited and it comprises different compartments such as gut, liver, blood, fat and gonads. The metabolites of DEHP in liver and gut such as MEHP, 5-OH MEHP, 5oxo-MEHP, 5cx MEPP and phthalic acid were described as a saturable process utilising Michaelis Menten kinetics. The *in vitro* intestinal and hepatic metabolic rates for different metabolites were reported by Choi et al., (2012) in human intestinal and hepatocyte cell line. Based on in-vitro studies of DEHP in the gut and liver, an IVIVE approach was implemented to derive model parameter such as Vmax, describing the maximum rate of metabolism. The estimated parameters V_{max} (in-vitro), and maximum rate of reaction were scaled to the whole body.

7.4 PAHs

Polycyclic Aromatic Hydrocarbons (PAHs) are a group of chemicals that are formed during the incomplete burning of coal, oil, gas, wood, garbage or other organic substances, such as tobacco. PAHs generally occur as complex mixtures and not as single compounds. A few PAHs are used in medicine and to make dyes, plastics and pesticides. Others can be contained in substances such as crude oil, coal, coal tar pitch, creosote, and roofing tar. The primary sources of exposure to PAHs for the general population are via inhalation through tobacco smoke, wood smoke and ambient air, as well as via food ingestion. The majority of people are exposed to PAHs in the workplace. PAHs have also been found in other facilities where petroleum, petroleum products, or coal are used or where wood, cellulose, corn or oil are burned. People living near waste sites containing PAHs may be exposed through contact with contaminated air, water and soil (ATSDR, 1995).

Health effects from chronic or long-term exposure to PAHs may include decreased immune function, cataracts, kidney and liver damage, asthma-like symptoms and lung function abnormalities. Mixtures of PAHs are considered carcinogenic to humans (ATSDR, 1995; World Health Organization, 2010). The toxicokinetic profiles of benzo(a)pyrene (BaP), which has been determined by EPA (2013) as possible human carcinogen, and its metabolite 3-hydroxybenzo(a)pyrene (3-OH-BaP) were investigated by a PBTK model found in literature (Heredia-Ortiz et al., 2014). Two sub-models for BaP and 3-OH-BaP were constructed, while other possible metabolites were represented as compartments in these two sub-models. Eleven compartments of lungs, AT, skin, kidney, liver, GI tract, "rest of the body", arterial blood, venous blood, feces, "other metabolites" were developed for BaP. The same compartments adding bladder

and urine were considered for the metabolite 3-OH-BaP. Oral, dermal exposure and exposure via inhalation was taken into account. It was determined whether the distribution in each organ was limited by tissue perfusion or diffusion (Heredia-Ortiz and Bouchard, 2013). Hepatic metabolism and elimination were described as first-order processes. PBPK model simulations were compared to predictions obtained with a simple compartmental toxicokinetic model. Both models provided similar fits to the observed data. For most workers, a more pronounced difference was observed between simulated and observed time courses when considering an exposure by inhalation. Furthermore, the inhaled dose scenarios simulated to reproduce the urinary profiles were in most cases higher than those recorded from airborne measurements of BaP concentrations in the facilities and time-of-shifts. Cases in which the simulated inhaled BaP concentration levels needed to obtain a better fit to observed profiles were much higher than measured air concentration values further indicate that inhalation was not the main route of exposure. Good agreement of the simulated vs. the observed data was obtained when considering only the dermal exposure route. Simulations thus suggest a mostly dermal exposure of BaP during work.

The PBTK model for BaP exposure via inhalation in rats and humans (Campbell et al., 2016) is an extension of a previously published oral BaP model for rats (Crowell et al., 2011). In Crowell's model, lung, liver, fat and richly and slowly perfused tissues, as well as oral bolus, duodenal and intravenous (IV) infusion exposure routes were modeled. Oral exposures were represented as a two-compartment GI tract, while BaP was metabolised to total metabolites in the lung and liver. Fecal elimination of BaP was also included. BaP distribution from blood to tissues was assumed to be blood-flow limited except for the fat compartment, which was diffusion-limited. The current model was expanded in order to include a description for the 3-OH BaP metabolite. Elimination of free 3-OH BaP from plasma was described as two separate clearances with one representing urinary clearance and the other accounting for a lumped metabolic/fecal clearance. The model-predicted pooled creatinine corrected urinary 3-OH BaP was compared with measured concentrations found in literature (Lafontaine et al., 2006; 2004). The model prediction ranged within a factor between 2 and 3. It has also to be noted, that the particle size distribution induces uncertainty related to the actual uptake of PAHs through inhalation; it has been found that PAHs uptake depends not only on the amount that is adsorbed on airbormne particles, but also on the particle size distribution, which in turn affects the particles retained (and the respective PAHs) across the human respiratory tract (Sarigiannis et al, 2016). However, the model captured successfully the relationship between exposure and urinary excretion of 3-OH BaP for a broad range of BaP exposure levels.

7.5 Brominated flame retardants

Brominated Flame Retardants (BFRs) belong to a large group of substances known as organohalogens that tend to reduce the flammability of products and are used in plastics, electronics, clothes and furniture to prevent fire accidents. Some of the BFRs accumulate via the food chain and the environment and they have been characterised as persistent and toxic as it is suspected to cause endocrine disruption and neurobehavioral effects (Fromme et al. 2016).

Emond et al. (2010) developed a PBPK model for exposure assessment of BDE-47, one of the most toxic flame retardants, in adult female pregnant and male rats. The PBPK model included the main compartments of brain, liver, adipose, kidney, placenta, fetus, blood, while the rest of the organs were represented by one compartment. The placenta and the fetus were only activated for the pregnant female rats. Most of the compartments were represented as perfusion-limited. However, liver, adipose, brain and fetus were represented as diffusion-limited. BDE-47 was metabolised via liver and eliminated through urine and feces.

7.6 Pesticides

Pesticides are chemical compounds used in agriculture to kill pests and in public health to kill vectors of disease, such as mosquitoes (Nicolopoulou-Stamati et al., 2016). By their nature, pesticides are potentially toxic to other organisms, including humans, and need to be disposed properly. Agricultural and public health workers are greatly exposed to hazardous pesticides during their application. Exposure is mainly by dermal route for preparation of sprays and by dermal and inhalation routes during application. Ingestion might occur through consumption of contaminated food during or following work or through oral contact with contaminated hands. Exposure of the general population to pesticides is lower and occurs mainly through consumption of residues of pesticides in food and drinking water (WHO, 2010). Acute health problems that are linked with pesticides are abdominal pain, dizziness, headaches, nausea, vomiting, as well as skin and eye problems (Klaassen, 2007). Associations have been found with different types of cancer and health effects in nervous system, cardiovascular system, gastrointestinal tract, liver, kidneys, reproductive system, endocrine system and blood (Gilden et al., 2010; Sanborn et al., 2007).

There are few PBTK models found in literature, mainly developed for chlorpyrifos (CPF), one of the main pesticides used on crops, animals and buildings. A PBTK model was developed to describe the time course of ADME properties of CPF and its metabolites, CPF-oxon and 3,5,6-trichloropyridinol (TCP) in rat and human (Timchalk et al., 2002). The model assumed that the toxicokinetic response in rats and humans was independent of gender. The absorption of CPF required the use of a two-compartment uptake model. This two-compartment model incorporated 1st order rate equations to describe systemic uptake and transfer between compartments. In addition, absorption of CPF from the diet was incorporated into the model to allow the simulation of chronic dietary administration. TCP was formed by direct CYP450 metabolic conversion of CPF and through A-EST-mediated hydrolysis of CPF-oxon and B-EST binding of CPF-oxon, respectively. The CYP450 activation/detoxification and A-EST detoxification of CPF-oxon were limited to the liver compartment and were all described as Michaelis-Menten processes. The blood kinetics and urinary elimination of TCP were described with a single, one-compartment model utilising a 1st order rate of urinary elimination. The model was evaluated against the experimental data of Yano et al. (2000), that were found to be consistent with the model simulations. However, some quantitative differences revealed that eventually other metabolic pathways might be activated at higher exposure levels.

Another PBTK model (Lu et al., 2010) was developed based on the PBTK model for CPF in rats and humans (Timchalk et al., 2002). Metabolism of CPF was assigned to occur in the blood and liver, with the excreted metabolite, TCP, lumped into a single compartment. The metabolite description was expanded from a volume-of-distribution concept to a physiologic description that can incorporate known differences at different life stages, such as between children and adults. Three exposure scenarios were developed, including a) bolus ingestion (based on levels measured in three meals throughout the sampling day), b) inhalation and c) rate ingestion for non-dietary routes (such as hand-to-mouth activity), while the dermal route of exposure was not considered. The model was evaluated using aggregate exposure data against cumulative urinary excretion data. The model predictions, regarding the major metabolite TCPY in urine, were compared with measured data obtained from children (Nolan et al., 1984; Timchalk et al., 2002). The calculated levels were consistent for some of the children, but in principle it seemed to underestimate TCPY excretion in urine.

7.7 Perfluorinated compounds

Poly- and perfluoroalkyl substances (PFASs) are a class of man-made chemicals that contain a fluorinated alkyl chain and a non-fluorinated group consisting of oxygen, hydrogen, sulfur and/or nitrogen atoms. PFASs have widely been used in consumer and industrial applications, including protective coatings for fabrics and carpets, paper coatings, insecticides, paints, cosmetics and fire-fighting foams (Domingo, 2012, Wang et al. 2014). It has been shown by several studies in humans that certain PFAS may affect the developing fetus and child, including possible behavioral and developmental problems, it may decrease fertility and interfere with the body's natural hormones, increase cholesterol, affect the immune system, and increase cancer risk (ATSDR, 2017).

Perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) are the most widely spread and studied PFASs. Toxicokinetic characteristics of PFOA and PFOS have been studied by Loccisano et al. (2011) in monkeys and humans. The model consisted of nine compartments, including plasma, gut, liver, fat, skin, kidney, "rest of body", filtrate and urine storage. Plasma was represented instead of blood because these compounds do not partition into the red blood cells. The distribution into different tissues was considered as perfusion-limited and no metabolism of the compounds was assumed as it is reported that PFOS and PFOA are well absorbed orally, poorly eliminated and not metabolised (Johnson et al., 1984; Vanden Heuvel et al., 1991). The PFOA model for humans was assessed by comparing plasma and serum data from populations exposed by contaminated water supplies. The concentrations measured in water by the same or other studies were used to simulate the exposure in the model. The two tested reported half-lives let a better fitting of simulated vs. observed data for the data during exposure than during depuration. For both PFOA and PFOS, the assessment process included the comparison with serum data from general population, before and after the phase-out of these chemicals. The results indicated good agreement of simulated vs. experimental data. After validation, the model was used to estimate the half-life, from individual data on PFOA from one study. The estimated individual half-lives were in the range of those estimated by Olsen et al. (2007) and Bartell et al. (2010).

Loccisano et al. (2013) modified a previously developed rat model (Loccisano et al., 2012) in order to be extended to the gestation and lactation life stages and provide estimates of maternal, fetal, and infant exposure to PFOA and PFOS for adult humans. The structural changes made were the addition of mammary tissue, placenta, fetal compartments and a milk compartment for lactation. Only the mother was exposed directly, maternal exposure was by direct intake and through drinking water and infant exposure was through milk. Fetal exposure to PFAA was through placental transfer, which was described as a bidirectional transfer process between free chemical in the placenta and fetal plasma. Placental transfer was described by a simple diffusion process, while transfer from the plasma to the milk compartment was assumed to be flow-limited. Only the free fraction of chemical in plasma was available for uptake into tissues or milk. Clearance of PFAA in the mother was supposed to occur by urinary elimination from the filtrate compartment in both models; clearance in the infant was described with a generic first-order rate constant from the central compartment. To validate the model, multiple human data related to pregnancy or lactation were used. With regard to the lactation model, if a plasma concentration was reported, the exposure was estimated to yield this concentration and then the resulting predicted milk or infant blood concentration was compared to the observed value to evaluate the model structure and parameters. The validity of the model was evaluated by comparing the predicted with the measured values, using graphical methods. Exposure levels were practically estimated using the try and error method.

A new PBTK model was developed by Fabrega et al. (2014) for PFOA and PFOS based on the previously described one (Loccisano et al., 2013). The key process adopted in the model was the

kinetics of resorption by renal transporters in the filtrate compartment, where chemicals were reabsorbed back to plasma through a saturable process. In addition to plasma, gut, liver, fat, kidney, filtrate and the remaining body compartments, the adapted PBTK model included lungs and brain. However, skin was removed as it is not a potential site of absorption/accumulation for PFASs. Human exposure to PFOA and PFOS was evaluated through water consumption and food intake, which was found to be the most important contributive route to the exposure of PFOS and PFOA. Gut was selected as an absorption site, brain as target organ of PFASs neurotoxic effects, liver as an accumulative tissue for organic chemicals, lungs as they may exhibit immaturity after PFOS exposure, fat as a main site of accumulation in lipophilic tissues and kidney for its role in elimination. For model validation, the computational results were compared with data reported in human tissues (Ericson et al., 2007; Pérez et al., 2013). Although the model had been successfully validated by using experimental data in human blood, for other human tissues the results were not very satisfactory.

7.8 Metals

7.8.1 Hexavalent chromium

Chromium is an element that can be found in rocks, animals, plants and soil. It is widely used in manufacturing processes and can be found in many consumer products, such as wood treated with copper dichromate, leather tanned with chromic sulfate and stainless-steel cookware (ATSDR, 2012). High concentrations of chromium VI in environmental media (air, soil and water) can be generally attributed to industrial releases, use and disposal of chromium-based products. However, low concentrations of Cr(VI) have been reported in urban household dust (Stern, 2010), in some foods (Mandiwana et al., 2011) and in drinking water due to Cr-enriched geology (Mills et al., 2011; Oze et al., 2007). Health problems resulting from chronic exposure to chromium are related to the respiratory tract, including airway irritation, airway obstruction, as well as asthma. Condition of very high inhalation exposure to chromium can exert a range of toxicities, including lung, nasal, or sinus cancer (ATSDR, 2011; Langard, 1990; O'Flaherty, 1995).

Several physiologically based pharmacokinetic models have been developed to describe the behavior of Cr (VI) in humans. One of the developed PBTK models (O'Flaherty et al., 2001) was based on existing simpler models for human (O'Flaherty, 1993) and rat (O'Flaherty, 1996). The adaptations included differential absorption of Cr(VI) and Cr(III), rapid reduction of Cr(VI) and Cr(III) in all body tissues and fluids, modest incorporation of chromium into bone and concentration dependent urinary clearance. The model did not include uptake through the skin and a lung compartment. However, it could estimate the upper limit on pulmonary absorption of inhaled chromium. In this model, oral exposure to Cr(VI) and Cr(III) salts via diet and drinking water was assumed. Due to the rapid appearance of Cr(III) and Cr(VI) in the blood, both were considered to be absorbed from the stomach and intestine. Once in the blood, Cr(VI) was assumed to be rapidly reduced by glutathione and hemoglobin to Cr(III). Chromium has been observed to be excreted in the bile and across the wall of the gastrointestinal tract. The rapidity of reduction of Cr(VI) to Cr(III) suggests that there is not urinary excretion of Cr(VI) (Minoia and Cavalleri, 1988). However, a pathway for urinary excretion of Cr(VI) was included in the model. The time course of chromium in plasma, as well as the excretion rate in urine were evaluated using HBM data from a published volunteer study (Paustenbach et al., 1996). In this study, a volunteer received multiple doses (5 within a day) of potassium dichromate ($K_2Cr_2O_7$), amounting for a daily intake of 4.0 mg Cr(VI), for 17 days in the row. Multiple blood and urine samples were collected before, during and after (for another two weeks) the cessation of the experiment. Despite the highly variable exposure scenario, as well as the wide intra-day variability of the urinary excretion rates, the simulated data were able to trace successfully the diurnal variability of both measured blood and urinary data.

Another human PBTK model was adapted from the rodent PBTK model proposed by Kirman et al. (2012) to describe the toxicokinetic processes of Cr(VI) and Cr(III). Gastrointestinal lumen, oral mucosa, stomach, small intestinal tissue, blood, liver, kidney, bone and a combined compartment for remaining tissues were included in the model. For human, the following changes were made: a) multiple bolus exposure events per day were represented, to accommodate the exposure regimens implemented by some human studies; b) two input parameters were added to permit scaling of systemic tissue uptake and release rate constants from mice; c) absorption was modeled in humans as a first order process; d) compartments for duodenum, jejunum, and ileum were lumped into a single compartment for the small intestines and e) the oral cavity compartment was removed from the model since there was no human data available for the oral cavity. Chromium absorption was expected to occur primarily within the small intestine, while Cr(VI) that reached portal plasma was subject to several competing processes: a) reduction to Cr(III); b) uptake into erythrocytes; and c) transit to the liver and systemic tissues. The reduction of Cr(VI) was described as a pH-dependent process. Within the GI tissue, Cr(VI) was subject to further reduction. The majority of chromium in the GI lumen remained unabsorbed and was excreted in feces, while biliary excretion of chromium was considered to be negligible. To validate the model, the data sets of Finley et al. (1997a) were used. The predictions of the model fitted well plasma levels related to 2 different doses, of 5 and 10 mg Cr respectively. However, the model was not able to sufficiently distinguish the lower exposure levels (below 1.0 mg Cr) examined by Finley et al. (1997a). Beyond that, the model described chromium toxicokinetics sufficiently for typical exposure scenarios.

7.8.2 Cadmium

Industrial and agricultural activities are the main sources of cadmium (Cd) release in the environment (Nordberg et al., 2014). Cadmium is a toxic metal, which can mainly enter the human body either orally via food intake (shellfish, liver and kidney meat, cereal products, leafy vegetables) or via inhalation (cigarette smoke). It is considered as one of the metals that poses great threat to human health, as it is associated with a broad spectrum of health conditions, including cardiovascular, kidney and bone diseases (Jarup and Akesson, 2009; Nordberg et al., 2014; Satarug et al., 2010), as well as breast cancer and neurotoxic effects (Nordberg et al., 2014).

Some of the PBTK models developed for human exposure to metals are presented below. The first model for cadmium uptake and retention was proposed by Kjellström and Nordberg (1978), taking into account the exogenous body compartments of lung, intestines and kidney and the endogenous compartments of other tissues. Two cases of cadmium exposure through inhalation as particulate matter were included: smoking and work in a battery factory. After inhalation, cadmium was deposited in the nasopharyngeal, the tracheobronchial, and/or the pulmonary compartments in different proportions, depending on particle size and respiratory characteristics, and then transported by mucociliary clearance to the pharynx. Cadmium distribution in the liver and/or kidney was dependent on the proportion of plasma cadmium bound to metallothionein protein. Cadmium distribution in the body depending on the absorption by alveolar capillary or portal blood was not known and therefore not implemented. Regarding the elimination process, a certain amount of cadmium in blood was assumed to be excreted via intestine to the feces, while an amount of cadmium in liver was assumed to be excreted via bile to the feces. The calculated cadmium concentrations were validated using data from Elinder et al. (1976) and Kjellström et al. (1977). Overall, the model presented difficulties in addressing high levels of exposure that were mainly attributed to specific assumptions regarding urinary excretion.

Another PBTK for Cd was developed (Ruiz et al., 2010a), based on the first model but with some modifications regarding the inter-compartmental transfer of Cd, the growth algorithms for males and females and corresponding organ weights for the estimation of age-specific Cd concentrations. The model simulated lung, liver, kidney, three blood compartments (plasma, erythrocytes and metallothionein) and other tissues and considered two routes of exposure; inhalation and oral. For

inhalation exposure, the model accounted for different deposition patterns for different size particles in different regions of the respiratory tract, while for the oral exposure, Cd may enter the GI tract via food and water or as Cd particles embedded in mucus from the respiratory tract via the mucociliary escalator. The model was validated both against a) simulations to other published model simulations and b) to measured biormarker data (CDC, 2009). The model predicts the latest NHANES data well. However, the range of results showed a better correlation for the males than for females. The model predicted urinary Cd concentration for males (non-smoking) aged 6–59 years, but some predictions were towards the upper limit of the range found in the actual survey. The model over-predicted the actual values for females (non-smoking) aged 6–59 years. This may be due either to potentially outdated intake estimates from NHANES III 1988–1994, or due to the slower elimination of cadmium for females, that was not properly accounted for in model parameterisation.

The model proposed by Kjellström et al. (1978) was also used and modified by Bechaux et al. (2014). In order to take the impact of gender into account, triangular distributions instead of single input values, the ranges of them provided by literature (Ruiz et al., 2010a). Bayesian population model was applied to link external exposure to internal dose provided by the urinary concentrations data. For validation purposes, computationally predicted urinary concentrations were compared with the measured ones. This method was proposed for the interpretation of the National Health and Nutrition Examination Surveys (NHANES) data (Ruiz et al., 2010b). The results showed a significant underestimation of cadmium concentrations in urine predicted by the model. As proposed in the discussion of the work by Ruiz et al. (2010b), due to the long half-life of cadmium in the human body and its accumulation in kidneys, a potential trend in exposure can explain an underestimation of current urinary concentration.

8 Generic PBTK models

Generic PBTK models, are toxicokinetic models that account for the main human anatomy (i.e. all major tissues and body compartments) and physiology (i.e. all major processes related to absorption, distribution, metabolism and elimination), independently of the compound for which they describe its toxicokinetic properties. This well-defined compartmental structure is much closer to real-life physiology and the applicability of the model is ensured by the compound-specific parameterisation. In contrast, compound specific PBTK models focus on the compartments and the processes that are essential to capture the toxicokinetic properties of the specific compound(s). As a result, compound specific PBTK models may differ significantly in the structure and the processes that are included in the conceptual model. The latest years, the interest for generic toxicokinetic models is continuously growing, since they are able to provide rapid screening-level approach to PBTK modeling. In our view, generic PBTK provide a high level of transparency and flexibility as they can predict the ADME properties of a wide range of chemical compounds during the different stages of human life. One of the developed generic PBTK models is the INTEGRA model, which covers a broad range of compounds from different chemical families (Andra et al., 2015; Sarigiannis et al., 2014; Sarigiannis et al., 2016). These include BPA, benzene, toluene, ethylbenzene, xylene, trichloromethane, phthalates, PAHs, Polychlorinated Dibenzo-p-Dioxins (PCDDs), Brominated Diphenyl Ethers (BDEs), pesticides, parabens and perfluorinated compounds.

The generic human PBTK model developed in INTEGRA was designed to cover major ADME processes occurring in the human body at different life stages, to be easily applicable to a broad variety of chemicals after compound specific parameterisation. In practice, it accounted for mother-fetus interaction, capturing all age dependent physiological changes, including the ones of the pregnant mother. All major human organs were included, as well as arterial, venous and portal blood compartments. Xenobiotics and their metabolites were linked through the metabolising tissues.

The model in its generic form included the parent compound and up to three generations of potential metabolites. The mass balance equation for each compartment described all processes with biological significance, such as absorption, metabolism, elimination, and protein binding. In practice, in each tissue three mass balance equations were written, for a) red blood cells, b) plasma and interstitial tissue and c) cells. Specific organs were further divided in sub-compartments: liver was divided in up to 5 compartments so as to better describe the distribution of enzymes and brain was divided in four sub-compartments, namely, main brain, globus palidus, cerebellum and pituitary, so as to better describe the permeability differences among the different brain regions.

The model described mother-fetus interactions by modelling the intra-placental properties that governs the transfer of xenobiotics and their metabolites from the mother to the fetus as it grows. The anthropometric parameters of the models were time dependent in order to provide a lifetime internal dose assessment, as well as to describe the continuously changing physiology of the mother and the developing fetus.

The model included the diffusion flow from uterus to placenta and vice-versa during pregnancy (Beaudouin et al., 2010). Excretion via lactation was described as an output from the mammary tissue compartment through a partitioning process between mammary tissue and milk, and milk withdrawal by suckling, as described for PCBs in rats (Lee et al., 2007) and further adopted for humans (Verner et al., 2008).

The model included also a detailed description of the three main routes of exposure. Inhalation took into account absorption of gases and deposition fractions of particles across the different

human respiratory tract regions based on particles size distribution. Absorption through the oral route was governed by the absorption rates of stomach and intestine. To better describe dermal absorption, skin was modelled as a two layer structure, including stratum corneum that has been described as a “bricks and mortar” structure (Touitou, 2002) and viable epidermis (also accounting for metabolism), where the geometry of all layer microstructure has been explicitly described (Mitragotri et al., 2011). The fact that in each tissue three mass balance equations were written for a) red blood cells, b) plasma and interstitial tissue and c) cells, allowed the application of the model to both flow limited, as well as membrane-limited compounds, by just changing the parameterisation of the membrane permeability product. Although the main metabolic organ was the liver, also other sites of metabolism could be considered (intestine, brain, skin, placenta) based on the presence or not of the enzymes involved in the metabolism of the compound of interest.

Metabolism was described by saturable kinetics. Elimination was described by urine and feces excretion, as well as through lactation for females (when applicable). Binding to red blood cells and plasma proteins were described by the equilibrium of concentration between red blood cells and plasma (accounting also for the hematocrit levels), as well as the fraction unbound in plasma.

For the compound specific parameterisation of the model, data was obtained (a) either from existing experimental values for previous compound-specific PBTK models, or (b) by using advance QSAR models (Sarigiannis et al. 2017; Papadaki et al. 2017) developed in the frame of INTEGRA for tissue:blood partition coefficients and biochemical parameters such as Michaelis Menten constant and Maximal Velocity. This strategy resulted in the parameterisation of totally 136 chemical compounds, for which more than 110 compounds parameterisation was done (or completed) using the above QSAR models.

Jongeneelen and Berge (2011) designed the IndusChemFate generic model primarily for neutral and predominantly ionic organic compounds. The model contained eleven body compartments (lung, heart, brain, skin, adipose, muscles, bone, bone marrow, stomach and intestines (lumped), liver and kidney) and assumed a reference human of 70 kg. Tissue concentrations for each of the chemicals and metabolites could be simulated for either acute, occupational or environmental exposure regimes with its typical duration, routes, concentrations or dose rate. Inhalation in the PBTK model was controlled by the concentration of the compound in the inhaled air, the alveolar ventilation, and the blood/air partition coefficient. For dermal absorption, a modified version of the algorithm developed by ten Berge (2009) was applied.

The physiological model considered the following processes: 1) dermal deposition of a substance on the skin, 2) diffusion to the stratum corneum and 3) absorption to the dermis/blood flow. Oral intake of compounds was considered as a bolus applied to the intestinal lumen (via the stomach) and then absorbed into the intestinal tissue at a first order rate. From the intestines, the compound was released to the blood stream via the liver. Stomach and intestines were lumped in the model.

This model incorporated enterohepatic circulation by defining the ratio of excretion to bile relative to excretion to blood. The chemical in the human body was eliminated in the model by metabolism and direct excretion in air or urine. Metabolism was described by Michaelis–Menten saturable metabolism following the mathematical algorithms as described by Ramsey and Andersen (1984). The parent compound was metabolised by a set of (iso)-enzymes. Usually, one or more metabolites were produced, which may either undergo further metabolism or be excreted. Contrary to many PBPK models, the occurrence of metabolism was not limited to the liver compartment but could be considered in any of the 11 model compartments. However, the default setting was metabolism in the liver only. Compounds could be excreted via urine, either unchanged as parent compound or as a metabolite. The model took into account the renal clearance of substances by means of ultrafiltration in the glomeruli and possible resorption to the blood in the tubuli. When the volatility is high, chemicals are exhaled.

The generalised PBPK model of MENTOR-3P (Georgopoulos and Lioy, 2006) was adopted and simplified as ‘‘flow-limited’’ PBPK formulation in order to capture the dynamics of four As circulating species in body compartments (arsenates, arsenites, and the As metabolites MMA and DMA) (Xue et al., 2010). Dietary and drinking water exposure was considered.

Furthermore, a stochastic PBTK model was developed by Beaudouin et al. (2010) that has been tested on 1,3-butadiene (BD) and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). This model included 22 detailed compartments of the human body. All tissue compartments were assumed to be well-mixed and blood flow-limited. The lungs were separated into two compartments to distinguish the pulmonary functions from the lungs anatomy. Nineteen compartments of the placenta, the amniotic fluid and fetus organs were added to the general PBPK model to describe pregnancy and fetal development. Inhalation and ingestion were integrated in the model. The gastrointestinal tract was subdivided into the stomach and the guts. Each of these was divided into 2 compartments: the lumen and the wall. The exchanges between the lumen and the wall were modeled as a diffusion by a first order reaction. The distribution was assumed to be homogeneous throughout the compartment volume and to be limited by perfusion, i.e., the tissue membranes present no barrier to diffusion. Elimination occured via metabolism, urinary and faecal excretion, exhalation and, in case of lactation, milk production. Liver, lungs, gut and placenta represented the four sites of metabolism.

The MERLIN-Expo tool (Brochot and Quindroit, 2018) was applied to inorganic chemicals (e.g. lead and arsenic), perfluorinated compounds (PFOA, PFOS) and persistent organic pollutants (PCBs, dioxins). The ‘Human’ model implemented in MERLIN-Expo was a PBTK model that subdivided the body in 22 compartments.

The PBTK model accounted for the physiological or biochemical variations that arise throughout the growth and the development of an individual. This model was based on the model developed by Beaudouin et al. (2010) and has been improved to include new features (e.g., binding). Absorption of the contaminants via inhalation was considered. Gas exchanges (inhalation and exhalation of contaminant, oxygenation of blood) in the alveolar space were assumed to be very rapid. The alveolar space was located between the venous blood and the lungs and modeled as an organ. A simple model describes gas exchanges based on a one-directional airflow in the region of gas exchange and a rapid equilibrium between lung air and blood in the alveoli. Absorption by ingestion was also taken into account. The gastrointestinal tract was subdivided into stomach and guts. Each of these was divided into the lumen and the wall, in which the exchanges between the lumen and the wall were modeled as a diffusion by a first order reaction dependent of the concentration of contaminant in the stomach or gut lumen. Alternatively, a direct input could be made in the liver. Distribution refers to the reversible partitioning of a compound into the various tissues of the body from the systemic circulation. Each organ or tissue could receive different doses of the compound and the compound can remain in the organs or tissues for a varying amount of time. The distribution was assumed to be homogeneous throughout the compartment volume and limited by perfusion, i.e., the tissue membranes present no barrier to diffusion. In this PBPK model, metabolism could occur in all compartments except in gut and stomach lumen and in alveolar space. Two equations were proposed to model metabolism either as saturable (Michaelis-Menten equation) or linear process (first order reaction). Excretion could occur in all organs/compartments except in gut and stomach lumen and in alveolar space and was described by a first-order reaction. The biliary excretion and the excretion in feces were considered as the two specific excretion routes in the model. Contaminants excreted by bile entered in the gut lumen and could be reabsorbed.

9 Discussion

A comprehensive review of the available human PBTK models for the 1st set of priority compounds is presented herein. With regard to the specific chemical families and compounds examined, large discrepancies regarding the availability of models were observed. For compounds like BPA and cadmium, there are several available models, while for compounds like brominated flame retardants there is a paucity of human PBTK models. Moreover, it has to be highlighted that there is limited availability of models for the various compounds relevant for the chemical families that eventually include many compounds, e.g., althouth there are many models for BPA, and there is no model for the alternatives BPS and BPF, while similar is the situation for the rest of the substance groups.

Regarding BPA metabolism, all models accounted for a very rapid metabolism, including the first models developed by Shin et al. (2004a) and Teeguarden et al. (2005a). The significant differences between neonates and adults were clearly illustrated and described with metabolic scaling by Edginton and Ritter (2009b). The core finding of their study was that BPA plasma concentrations could be approximately eleven times greater in newborns than in adults exposed to the same weight-normalised dose. In the BPA model developed by Mielke and Gundert-Remy (2009), sulfation was also included as an additional metabolic pathway, assuming that sulfation activity is well expressed in newborns and it is at least as high as in adults, or even higher. Finally, based on the physiologically-based approach for scaling to children (Edginton et al., 2006a) and the more recent findings regarding the ontogeny of enzymes involved in BPA detoxification (Court et al., 2012; Leeder, 2009), in the most recent BPA model by Sarigiannis et al. (2016b) clearance rates were adjusted taking into account the findings of Fisher et al. (2011) and assuming an age-dependent bioavailability difference factor of 2.

Moreover, the model of Sarigiannis et al. (2016b) was used for reconstructing exposure from EU-wide HBM data, while its explicit description of mother-fetus interaction allowed the estimation of the effect of placental deconjugation on fetus internal exposure. Finally, the model presented by Sharma et al. (2018a) evaluated the most recent kinetic data from control human experimental study and extended the adult model to the pregnancy PBTK model with the available BPA biomonitoring cohort studies. The prediction of higher concentration of BPA during the mid-gestational period in the amniotic fluid, placenta, and the fetus liver was in accordance with biomonitoring data, indicating that mid-gestational period might be the critical window of exposure for the fetus.

With regard to metals, three human PBTK models were identified for cadmium and two for hexavalent chromium. With regard to cadmium, most of the models are able to capture the complex interactions of cadmium with biological systems. However, it has to be highlighted that among the different models, the one of Bechaux et al (2014) is able to capture the close relation between cadmium absorption and the expression of the divalent metal transporter 1 (DMT-1), which transports cadmium and iron into the mucosa cell in a competitive manner, by using a different absorption factor for male and female in the general population. Moreover, this situation seems to be exacerbated during pregnancy when enterocytes have an increased DMT-1 density at the apical surface to optimise micronutrients absorption, affecting the overall biologically effective dose. With regard to hexavalent chromium models, the model presented by O'Flaherty et al. (2001) includes differential absorption of Cr(VI) and Cr(III), rapid reduction of Cr(VI) to Cr(III) in all body fluids and tissues, modest incorporation of chromium into bone, and concentration-dependent urinary clearance consistent with parallel renal processes that conserve chromium efficiently at ambient exposure levels, while the model of Kirman et al. (Kirman et al., 2013) highlighted the notable physiological differences between rodents and humans potentially important for Cr(VI) reduction.

Polyaromatic hydrocarbons (PAHs) comprise a very large chemical family of more than 46 chemicals that are often found in complex mixture form. For substances of this complex mixture, only two PBTK models were identified; both were related to the reference compound among the various congeners, namely benzo[a]pyrene. The model proposed by Heredia-Ortiz et al., (2014) explicitly described the kinetics of B[a]P transformation into a major metabolite (3-Hydroxybenzo(a)pyrene) identified in urine, while the model of Campbell et al. (2016) included additional routes of exposure, being able to address internal dosimetry of more complex exposure scenarios.

Regarding PFCs, two models have been recently developed addressing the issue of non-elimination and limited urinary excretion of PFOS and PFOA addressing extrapolation from monkey to humans (Loccisano et al., 2011) and the *in uterus* and lactation exposure (Loccisano et al., 2013). The model developed by Fabrega et al. (2014) described more explicitly the kinetics of resorption by renal transporters in the filtrate compartment, where chemicals were resorbed from urine back to plasma through a saturable process, while for validation purposes, human data on PFOA and PFOS in human tissues were used. This strategy for estimating tissue:blood partitioning resulted in more accurate model predictions highlighting the advantages of using (*ex-vivo*) human data over (*in vivo*) animal data, especially for persistent compounds.

With regard to phthalates, a PBTK model has been developed by Moreau et al. (2017) for di-2-ethylhexyl phthalate (DEHP) and dibutyl phthalate (DnBP) as case compounds. This modelling effort aimed at providing exposure estimates starting from the NHANES biomonitoring data and compared these estimates with high-throughput HT Stochastic Human Exposure and Dose Simulation model (SHEDS-HT) and the ExpoCast heuristic model and non-HT approaches based on chemical specific exposure estimations in the environment in conjunction with human exposure factors. The second model on phthalates by Sharma et al. (2018b) addressed internal dosimetry of DEHP, while for the parameterisation of the model a bottom-up approach was applied, where all the parameters were derived from a combination of *in silico* (QSAR), *in vitro* (metabolism) and literature data.

For brominated flame retardants, no human PBTK model has been identified, so the PBTK model for developmental exposure to BDE-47 in rats (Emond et al., 2010) has been reviewed, as a basis for a future extrapolation to humans, while for aniline and structurally related compounds a PBTK model developed for rat has been extrapolated to humans (Nguyen et al., 2015).

For the mixture of pesticides two models have been found, addressing chlorpyrifos in rats and its extrapolation to humans (Timchalk et al., 2002) and its specific metabolite 3,5,6-trichloro-2-pyridinol (TCPY) in young children (Lu et al., 2010).

Finally, five generic PBTK models have been identified, either as stand-alone internal dosimetry models like the IndusChemFate (Jongeneelen and Berge, 2011) and the stochastic PBTK model that was developed by Beaudouin et al. (2010), or incorporated in integrated external-internal exposure computational platforms such as INTEGRA (Sarigiannis et al., 2014), MENTOR 3P (Xue et al., 2010) and Merlin-Expo (Ciffroy et al., 2016).

It has to be noted that there is a noticeable paucity for available models for the majority of the substances for all substance groups. Availability or paucity of models is governed by (a) the complexity of the chemico-biological interactions and how well these are understood and described / modelled for a given compound and (b) how difficult it is to obtain reliable data for the model parameterisation. However, in many cases, the effort for developing compound specific PBTK models and obtaining data is driven by societal and regulatory needs. The availability of PBTK models for BPA is a good example in this sense; the increased public and regulatory concern in the last eight years about BPA and its potential toxicity during early life exposure resulted in

considerable efforts towards the development of the respective PBTK models. Moreover, there are noticeable differences among the developed models, that partially reflect the scientific questions that evolved during the BPA controversy. This explains the comprehensive approach (multi-route exposure, in uterus exposure and lactation) adopted by the Sarigiannis et al. (2016b) model.

How complex should a PBTK model be? Should the complexity of the model be adapted to the specific research question to be addressed? Regarding model structure, it is generally considered that too complex a structure can be deleterious for the accuracy of the model. Effectively each parameter value presents a given level of variability and the use of a high number of parameters (in relation to a complex model structure) increases the uncertainty in the model. However, in order to promote the acceptance of PBTK models in the regulatory arena it is critical to move towards generic PBTK models.

Generic PBTK incorporate differences related to inter-individual variability by changing the respective anatomic and physiologic parameters. Efforts to properly parameterise the interactions of the xenobiotics with the given biological systems is a more biology-based approach than trying to progressively approximate the human physiology by introducing ad-hoc compartments aiming to mathematically converge simulation with toxicokinetic data. Thus, the key issue towards PBTK models development and acceptance is parameterisation. For the models presented herein, various parameterisation strategies have been followed including (a) calculations based on *in vivo* experimental data, (b) calculation from *in vitro* experimental data, (c) utilisation of values from existing models, (d) fitting of parameters on the basis of experimental data and (e) use of algorithms, namely QSARS and combinations thereof.

Although there is no golden strategy for the derivation of PBTK model parameterisation, given the shift of interest in PBTK models for human risk assessment, model parameterisation strategies relying on human data (*in vivo*, *ex vivo* or *in vitro*) seem to be continuously gaining ground. Towards this aim, the use of targeted HBM campaigns as the ones foreseen in the HBM4EU project, are expected to greatly facilitate the parameterisation process for data poor chemicals, such as bisphenol S and F. On the other hand, computational methods such as QSARs have already been proven to be effective for the parameterisation of toxicokinetic properties (Peyret and Krishnan, 2011). More advanced algorithms that employ machine learning techniques (Ventura et al., 2013) have been shown to be very efficient covering a large chemical space in terms of predicting both metabolic parameters (Sarigiannis et al., 2017) and tissue:blood partition coefficients (Papadaki et al., 2017; Sarigiannis et al., 2017). In addition, existing parameterisation of specific compounds (e.g. BPA) could provide the mechanistic basis of the chemico-biological interactions estimates, based on similarities of the chemical structure. This could greatly facilitate the development of more reliable computationally predicted PBTK parameters of other compounds of the same chemical family, by including the known parameters in the training dataset of the QSAR algorithm.

Finally, a key issue that has to be addressed by future models are mixture interactions. The importance of these interactions is of particular importance for addressing the cumulative exposure regarding the multitude of xenobiotics to which humans are exposed daily (Sarigiannis and Hansen, 2012); this is even more important under occupational exposure. It has been found that for the almost ubiquitous in the ambient and indoor air BTEX mixture, the internal dose of the toxic metabolites in the target tissues is modified by 50% for exposure levels close to the occupational regulatory limit (threshold limit value, TLV) (Sarigiannis and Gotti, 2008). Similar effects are expected in hot spots where people are exposed to compounds metabolised by the same P450 isophorms, such as PAHs. Moreover, more complex interactions among completely different chemical families have been reported, such as pesticides (atrazine) and heavy metals (arsenic).

With regard to future needs of PBTK modelling, it has to be noted that the advent of the exposome and multi-omics analytical and bioinformatics platforms (Sarigiannis, 2017), as well as the shift of toxicological research to non-animal testing as aptly shown by the large efforts in high throughput screening (Hartung et al., 2013), have changed the requirements of PBTK modelling; models are now requested to associate environmentally relevant exposures to molecular responses and to describe exposure-response relationships across new testing (*in vitro*) systems (Judson et al., 2010; Judson et al., 2011), rather than to calculate tissue doses of *in vivo* testing. This further supports the need for the development of generic human PBTK models and the need for coordinated strategies for the acquisition of data that will further facilitate successful model parameterisation.

10 Conclusions

Physiology based toxicokinetic models provide unique opportunities in modern risk assessment, providing the missing link of external exposure to internal dosimetry, assimilation of biomonitoring data, *in vitro* testing and molecular epidemiology.

For the first set of prioritised compounds dealt with in the HBM4EU project, the review of the available PBTK models highlights significant conceptual differences between older models compared to the ones developed in the recent years. In the past PBTK models focused on capturing specific chemico-biological interactions that dominate the process of metabolism and elimination; the most recent models, instead, aim at addressing internal dosimetry and the prediction of measured biomarkers under more complex exposure scenarios. However, due to the lack of coordinated strategies for deriving useful biomonitoring data for toxicokinetic properties, significant problems in model parameterisation still remain; these are further increased by the lack of human toxicokinetic data from human volunteers due to ethics issues, as well as to the extent they are really representative of the interindividual variability.

All of the above results in a relative paucity in reliable models for compounds of key regulatory and societal interest, such as bisphenol-F and bisphenol-S, much heralded substitutes for the regulatorily constrained bisphenol-A. QSARs for toxicokinetic properties is an interesting approach to PBTK model parameterisation for data poor chemicals. Overall QSARs should be expanded to model additional chemico-biological interactions, such as intestinal absorption and renal clearance; this could support the development of more complex generic PBTK models, where application to newly derived chemicals should be a problem of parameterisation rather than one of conceptual model development.

Finally, another gap identified is the development of a consistent and computationally efficient framework for mixture interaction among compounds that could eventually interact in terms of metabolism. This is something that could also be addressed by generic PBTK models; however this requires the use of saturable kinetics with regard to the metabolism description.

Concluding all the above and having in mind that that PBTK models aim to serve more precise exposure and risk assessment, it is highly recommended that:

- in terms of conceptual models, efforts are shifted toward the development of generic multi-compartmental and multi-route models,
- development of well-designed and targeted biomonitoring strategies that would efficiently support the accurate parameterisation (in tandem with QSAR-based model estimation, *in-vivo* and *in-vitro* data) for newly developed and data poor compounds.

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12 References

Abraham, K., Mielke, H., Huisinga, W., Gundert-Remy, U., 2005. Elevated internal exposure of children in simulated acute inhalation of volatile organic compounds: effects of concentration and duration. Arch Toxicol 79, 63-73.

Agoram, B., Woltosz, W.S., Bolger, M.B., 2001. Predicting the impact of physiological and biochemical processes on oral drug bioavailability. Adv Drug Deliv Rev 50 Suppl 1, S41-67.

Andra, S.S., Charisiadis, P., Karakitsios, S., Sarigiannis, D.A., Makris, K.C., 2015. Passive exposures of children to volatile trihalomethanes during domestic cleaning activities of their parents. Environmental research 136, 187-195.

ATSDR, 1995. Public Health Statement for Polycyclic Aromatic Hydrocarbons (PAHs).

ATSDR, 2002. Aniline. Division of Toxicology ToxFAQs.

ATSDR, 2011. Chromium Toxicity: What Are the Physiologic Effects of Chromium Exposure? Case Studies in Environmental Medicine (CSEM).

ATSDR, 2012. Public Health Statement: Chromium. Division of Toxicology and Human Health Sciences

ATSDR, 2017, Health Effects of PFAS, https://www.atsdr.cdc.gov/pfc/health_effects_pfcs.html,

Beaudouin, R., Micallef, S., Brochot, C., 2010. A stochastic whole-body physiologically based pharmacokinetic model to assess the impact of inter-individual variability on tissue dosimetry over the human lifespan. Regulatory Toxicology and Pharmacology 57, 103-116.

Bechaux, C., Bodin, L., Clemencon, S., Crepet, A., 2014. PBPK and population modelling to interpret urine cadmium concentrations of the French population. Toxicol Appl Pharmacol 279, 364-372.

Bois, F.Y., Jamei, M., Clewell, H.J., 2010. PBPK modelling of inter-individual variability in the pharmacokinetics of environmental chemicals. Toxicology 278, 256-267.

Brochot, C., Quindroit, P., 2018. Modelling the Fate of Chemicals in Humans Using a Lifetime Physiologically Based Pharmacokinetic (PBPK) Model in MERLIN-Expo, in: P. Ciffroy, A. Tediosi, E. Capri (Eds.), Modelling the Fate of Chemicals in the Environment and the Human Body. Springer International Publishing, Cham, pp. 215-257.

Campbell, J., Franzen, A., Van Landingham, C., Lumpkin, M., Crowell, S., Meredith, C., Loccisano, A., Gentry, R., Clewell, H., 2016. Predicting lung dosimetry of inhaled particleborne benzo[a]pyrene using physiologically based pharmacokinetic modeling. Inhal Toxicol 28, 520-535.

Choi, K., Joo, H., Campbell, J.L., Jr., Clewell, R.A., Andersen, M.E., Clewell, H.J., 3rd, 2012. In vitro metabolism of di(2-ethylhexyl) phthalate (DEHP) by various tissues and cytochrome P450s of human and rat. Toxicology in vitro : an international journal published in association with BIBRA 26, 315-322.

Ciffroy, P., Alfonso, B., Altenpohl, A., Banjac, Z., Bierkens, J., Brochot, C., Critto, A., De Wilde, T., Fait, G., Fierens, T., Garratt, J., Giubilato, E., Grange, E., Johansson, E., Radomyski, A., Reschwann, K., Suciu, N., Tanaka, T., Tediosi, A., Van Holderbeke, M., Verdonck, F., 2016. Modelling the exposure to chemicals for risk assessment: a comprehensive library of multimedia and PBPK models for integration, prediction, uncertainty and sensitivity analysis – the MERLIN-Expo tool. Science of The Total Environment 568, 770-784.

Clewell, R.A., Clewell, H.J., 3rd, 2008. Development and specification of physiologically based pharmacokinetic models for use in risk assessment. Regulatory toxicology and pharmacology : RTP 50, 129-143.

Clewell, R.A., Kremer, J.J., Williams, C.C., Campbell, J.L., Andersen, M.E., Borghoff, S.J., 2008. Tissue exposures to free and glucuronidated monobutylyphthalate in the pregnant and fetal rat following exposure to di-n-butylphthalate: Evaluation with a PBPK model. Toxicological Sciences 103, 241-259.

Court, M.H., Zhang, X., Ding, X., Yee, K.K., Hesse, L.M., Finel, M., 2012. Quantitative distribution of mRNAs encoding the 19 human UDP-glucuronosyltransferase enzymes in 26 adult and 3 fetal tissues. Xenobiotica 42, 266-277.

Crowell, S.R., Amin, S.G., Anderson, K.A., Krishnegowda, G., Sharma, A.K., Soelberg, J.J., Williams, D.E., Corley, R.A., 2011. Preliminary physiologically based pharmacokinetic models for benzo[a]pyrene and dibenzo[def,p]chrysene in rodents. Toxicol Appl Pharmacol 257, 365-376.

Csanady, G.A., Oberste-Frielinghaus, H.R., Semder, B., Baur, C., Schneider, K.T., Filser, J.G., 2002. Distribution and unspecific protein binding of the xenoestrogens bisphenol A and daidzein. Arch Toxicol 76, 299-305.

Domingo, J.L., 2012. Health risks of dietary exposure to perfluorinated compounds. Environ Int 40, 187-195.

Edginton, A.N., Ritter, L., 2009. Predicting plasma concentrations of bisphenol A in children younger than 2 years of age after typical feeding schedules, using a physiologically based toxicokinetic model. Environmental Health Perspectives 117, 645-652.

ECHA, Inclusion of substances of very high concern in the Candidate List for eventual inclusion in Annex XIV. 03.01.2018, TEM-0013.08., Helsinki, 2018.

Edginton, A.N., Schmitt, W., Voith, B., Willmann, S., 2006. A mechanistic approach for the scaling of clearance in children. Clin Pharmacokinet 45, 683-704.

EFSA, 2015. Scientific Opinion on the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs: Executive summary.

Eissing, T., Kuepfer, L., Becker, C., Block, M., Coboeken, K., Gaub, T., Goerlitz, L., Jaeger, J., Loosen, R., Ludewig, B., Meyer, M., Niederalt, C., Sevestre, M., Siegmund, H.U., Solodenko, J., Thelen, K., Telle, U., Weiss, W., Wendl, T., Willmann, S., Lippert, J., 2011. A computational systems biology software platform for multiscale modeling and simulation: Integrating whole-body physiology, disease biology, and molecular reaction networks. Frontiers in Physiology FEB.

Emond, C., Raymer, J.H., Studabaker, W.B., Garner, C.E., Birnbaum, L.S., 2010. A physiologically based pharmacokinetic model for developmental exposure to BDE-47 in rats. Toxicology and Applied Pharmacology 242, 290-298.

Fabrega, F., Kumar, V., Schuhmacher, M., Domingo, J.L., Nadal, M., 2014. PBPK modeling for PFOS and PFOA: validation with human experimental data. Toxicol Lett 230, 244-251.

FDA, 2014. Bisphenol A (BPA): Use in Food Contact Application.

Fromme, H., Becher, G., Hilger, B., Völkel, W., 2016. Brominated flame retardants – Exposure and risk assessment for the general population. International Journal of Hygiene and Environmental Health. 219, 1-23.

Fisher, J.W., Twaddle, N.C., Vanlandingham, M., Doerge, D.R., 2011. Pharmacokinetic modeling: prediction and evaluation of route dependent dosimetry of bisphenol A in monkeys with extrapolation to humans. Toxicol Appl Pharmacol 257, 122-136.

Ganzleben, C., Antignac, J.P., Barouki, R., Castano, A., Fiddicke, U., Klanova, J., Lebret, E., Olea, N., Sarigiannis, D., Schoeters, G.R., Sepai, O., Tolonen, H., Kolossa-Gehring, M., 2017. Human biomonitoring as a tool to support chemicals regulation in the European Union. Int J Hyg Environ Health 220, 94-97.

Gentry, P. R., H. J. Clewell, R. Clewell, J. Campbell, C. Van Landingham & A. M. Shipp (2011) Challenges in the application of quantitative approaches in risk assessment: a case study with di-(2-ethylhexyl)phthalate. *Critical Reviews in Toxicology,* 41**,** 1-72.

Georgopoulos, P.G., Lioy, P.J., 2006. From a theoretical framework of human exposure and dose assessment to computational system implementation: the Modeling ENvironment for TOtal Risk Studies (MENTOR). Journal of toxicology and environmental health. Part B, Critical reviews 9, 457-483.

Georgopoulos, P.G., Sasso, A.F., Isukapalli, S.S., Lioy, P.J., Vallero, D.A., Okino, M., Reiter, L., 2008a. Reconstructing population exposures to environmental chemicals from biomarkers: challenges and opportunities. Journal of Exposure Science and Environmental Epidemiology 19, 149-171.

Georgopoulos, P.G., Wang, S.W., Yang, Y.C., Xue, J., Zartarian, V.G., McCurdy, T., Ozkaynak, H., 2008b. Biologically based modeling of multimedia, multipathway, multiroute population exposures to arsenic. Journal of Exposure Science and Environmental Epidemiology 18, 462-476.

Gilden, R.C., Huffling, K., Sattler, B., 2010. Pesticides and health risks. Journal of obstetric, gynecologic, and neonatal nursing : JOGNN 39, 103-110.

Harrison, J.H., Jr., Jollow, D.J., 1987. Contribution of aniline metabolites to aniline-induced methemoglobinemia. Mol Pharmacol 32, 423-431.

Hartung, T., Luechtefeld, T., Maertens, A., Kleensang, A., 2013. Integrated testing strategies for safety assessments. Altex 30, 3-18.

Heredia-Ortiz, R., Bouchard, M., 2013. Understanding the linked kinetics of benzo(a)pyrene and 3-hydroxybenzo(a)pyrene biomarker of exposure using physiologically-based pharmacokinetic modelling in rats. Journal of Pharmacokinetics and Pharmacodynamics 40, 669-682.

Heredia-Ortiz, R., Maitre, A., Barbeau, D., Lafontaine, M., Bouchard, M., 2014. Use of Physiologically-Based Pharmacokinetic Modeling to Simulate the Profiles of 3-Hydroxybenzo(a) pyrene in Workers Exposed to Polycyclic Aromatic Hydrocarbons. Plos One 9, e102570.

Heudorf, U., Mersch-Sundermann, V., Angerer, J., 2007. Phthalates: Toxicology and exposure. International Journal of Hygiene and Environmental Health 210, 623-634.

Jarup, L., Akesson, A., 2009. Current status of cadmium as an environmental health problem. Toxicol Appl Pharmacol 238, 201-208.

Johnson, J.D., Gibson, S.J., Ober, R.E., 1984. Cholestyramine-enhanced fecal elimination of carbon-14 in rats after administration of ammonium [14C]perfluorooctanoate or potassium [14C]perfluorooctanesulfonate. Fundam Appl Toxicol 4, 972-976.

Jongeneelen, F.J., Berge, W.F.T., 2011. A generic, cross-chemical predictive PBTK model with multiple entry routes running as application in MS Excel; design of the model and comparison of predictions with experimental results. Annals of Occupational Hygiene 55, 841-864.

Jongeneelen, F.J., Ten Berge, W.F., 2011. A Generic, Cross-Chemical Predictive PBTK Model with Multiple Entry Routes Running as Application in MS Excel; Design of the Model and Comparison of Predictions with Experimental Results. Annals of Occupational Hygiene 55, 841-864.

Judson, R.S., Houck, K.A., Kavlock, R.J., Knudsen, T.B., Martin, M.T., Mortensen, H.M., Reif, D.M., Rotroff, D.M., Shah, I., Richard, A.M., Dix, D.J., 2010. In vitro screening of environmental chemicals for targeted testing prioritization: The toxcast project. Environmental Health Perspectives 118, 485-492.

Judson, R.S., Kavlock, R.J., Setzer, R.W., Cohen Hubal, E.A., Martin, M.T., Knudsen, T.B., Houck, K.A., Thomas, R.S., Wetmore, B.A., Dix, D.J., 2011. Estimating toxicity-related biological pathway altering doses for high-throughput chemical risk assessment. Chemical Research in Toxicology 24, 451-462.

Kamrin, M.A., 2009. Phthalate risks, phthalate regulation, and public health: a review. Journal of toxicology and environmental health. Part B, Critical reviews 12, 157-174.

Kearney, T.E., Manoguerra, A.S., Dunford, J.V., 1984. Chemically induced methemoglobinemia from aniline poisoning. Western Journal of Medicine 140, 282-286.

Keith, L.H., 1997. Environmental Endocrine Disruptors: A Handbook of Property Data. Wiley.

Kirman, C.R., Aylward, L.L., Suh, M., Harris, M.A., Thompson, C.M., Haws, L.C., Proctor, D.M., Lin, S.S., Parker, W., Hays, S.M., 2013. Physiologically based pharmacokinetic model for humans orally exposed to chromium. Chemico-Biological Interactions 204, 13-27.

Kirman, C.R., Hays, S.M., Aylward, L.L., Suh, M., Harris, M.A., Thompson, C.M., Haws, L.C., Proctor, D.M., 2012. Physiologically based pharmacokinetic model for rats and mice orally exposed to chromium. Chem Biol Interact 200, 45-64.

Kjellström, T., Nordberg, G.F., 1978. A kinetic model of cadmium metabolism in the human being. Environmental Research 16, 248-269.

Klaassen, C.D., 2007. Casarett & Doull's Toxicology: The Basic Science of Poisons, Seventh Edition. McGraw-Hill Education.

Krauss, M., Schaller, S., Borchers, S., Findeisen, R., Lippert, J., Kuepfer, L., 2012. Integrating Cellular Metabolism into a Multiscale Whole-Body Model. PLoS Computational Biology 8.

Kurebayashi, H., Harada, R., Stewart, R.K., Numata, H., Ohno, Y., 2002. Disposition of a low dose of bisphenol a in male and female cynomolgus monkeys. Toxicol Sci 68, 32-42.

Kurebayashi, H., Okudaira, K., Ohno, Y., 2010. Species difference of metabolic clearance of bisphenol A using cryopreserved hepatocytes from rats, monkeys and humans. Toxicology Letters 198, 210-215.

Langard, S., 1990. One hundred years of chromium and cancer: a review of epidemiological evidence and selected case reports. Am J Ind Med 17, 189-215.

Lee, C.H., Kim, S.H., Kwon, D.H., Jang, K.H., Chung, Y.H., Moon, J.D., 2013. Two Cases of Methemoglobinemia Induced by the Exposure to Nitrobenzene and Aniline. Annals of Occupational and Environmental Medicine 25, 31-31.

Lee, S.K., Ou, Y.C., Andersen, M.E., Yang, R.S.H., 2007. A physiologically based pharmacokinetic model for lactational transfer of PCB 153 with or without PCB 126 in mice. Archives of Toxicology 81, 101-111.

Leeder, J.S., 2009. Developmental pharmacogenetics: A general paradigm for application to neonatal pharmacology and toxicology. Clinical Pharmacology and Therapeutics 86, 678-682.

Loccisano, A.E., Campbell, J.L., Andersen, M.E., Clewell, H.J., 2011. Evaluation and prediction of pharmacokinetics of PFOA and PFOS in the monkey and human using a PBPK model. Regulatory Toxicology and Pharmacology 59, 157-175.

Loccisano, A.E., Campbell, J.L., Jr., Butenhoff, J.L., Andersen, M.E., Clewell, H.J., 3rd, 2012. Evaluation of placental and lactational pharmacokinetics of PFOA and PFOS in the pregnant, lactating, fetal and neonatal rat using a physiologically based pharmacokinetic model. Reprod Toxicol 33, 468-490.

Loccisano, A.E., Longnecker, M.P., Campbell, J.L., Andersen, M.E., Clewell, H.J., 2013. Development of pbpk models for pfoa and pfos for human pregnancy and lactation life stages. Journal of Toxicology and Environmental Health - Part A: Current Issues 76, 25-57.

Loizou, G., Spendiff, M., Barton, H.A., Bessems, J., Bois, F.Y., d'Yvoire, M.B., Buist, H., Clewell, H.J., Meek, B., Gundert-Remy, U., Goerlitz, G., Schmitt, W., 2008. Development of good modelling practice for physiologically based pharmacokinetic models for use in risk assessment: The first steps. Regulatory Toxicology and Pharmacology 50, 400-411.

Lu, C., Holbrook, C.M., Andres, L.M., 2010. The implications of using a physiologically based pharmacokinetic (PBPK) model for pesticide risk assessment. Environ Health Perspect 118, 125-130.

Mandiwana, K.L., Panichev, N., Panicheva, S., 2011. Determination of chromium(VI) in black, green and herbal teas. Food Chemistry 129, 1839-1843.

Meeker, J.D., Sathyanarayana, S., Swan, S.H., 2009. Phthalates and other additives in plastics: human exposure and associated health outcomes. Philosophical transactions of the Royal Society of London. Series B, Biological sciences 364, 2097-2113.

Mielke, H., Gundert-Remy, U., 2009. Bisphenol A levels in blood depend on age and exposure. Toxicology Letters 190, 32-40.

Mills, C.T., Morrison, J.M., Goldhaber, M.B., Ellefsen, K.J., 2011. Chromium(VI) generation in vadose zone soils and alluvial sediments of the southwestern Sacramento Valley, California: a potential source of geogenic Cr(VI) to groundwater. Applied Geochemistry 26, 1488-1501.

Minoia, C., Cavalleri, A., 1988. Chromium in urine, serum and red blood cells in the biological monitoring of workers exposed to different chromium valency states. Sci Total Environ 71, 323-327.

Mitragotri, S., Anissimov, Y.G., Bunge, A.L., Frasch, H.F., Guy, R.H., Hadgraft, J., Kasting, G.B., Lane, M.E., Roberts, M.S., 2011. Mathematical models of skin permeability: An overview. International Journal of Pharmaceutics 418, 115-129.

Moreau, M., Leonard, J., Phillips, K.A., Campbell, J., Pendse, S.N., Nicolas, C., Phillips, M., Yoon, M., Tan, Y.M., Smith, S., Pudukodu, H., Isaacs, K., Clewell, H., 2017. Using exposure prediction tools to link exposure and dosimetry for risk-based decisions: A case study with phthalates. Chemosphere 184, 1194-1201.

National Research Council, 2008. Phthalates and Cumulative Risk Assessment: The Tasks Ahead. The National Academies Press, Washington, DC.

Nguyen, H.Q., Stamatis, S.D., Kirsch, L.E., 2015. A Novel Method for Assessing Drug Degradation Product Safety Using Physiologically-Based Pharmacokinetic Models and Stochastic Risk Assessment. Journal of Pharmaceutical Sciences 104, 3101-3119.

Nicolopoulou-Stamati, P., Maipas, S., Kotampasi, C., Stamatis, P., Hens, L., 2016. Chemical Pesticides and Human Health: The Urgent Need for a New Concept in Agriculture. Frontiers in Public Health 4, 148.

Nordberg, G.F., Fowler, B.A., Nordberg, M., 2014. Handbook on the Toxicology of Metals. Elsevier Science.

O'Flaherty, E.J., 1993. Physiologically based models for bone-seeking elements. IV. Kinetics of lead disposition in humans. Toxicol Appl Pharmacol 118, 16-29.

O'Flaherty, E.J., 1996. A physiologically based model of chromium kinetics in the rat. Toxicol Appl Pharmacol 138, 54-64.

O'Flaherty, E.J., Kerger, B.D., Hays, S.M., Paustenbach, D.J., 2001. A physiologically based model for the ingestion of chromium(III) and chromium(VI) by humans. Toxicological sciences : an official journal of the Society of Toxicology 60, 196-213.

O'Flaherty, E.J., 1995. Chromium Toxicokinetics, in: R.A. Goyer, M.G. Cherian (Eds.), Toxicology of Metals: Biochemical Aspects. Springer Berlin Heidelberg, Berlin, Heidelberg, pp. 215-228.

Oze, C., Bird, D.K., Fendorf, S., 2007. Genesis of hexavalent chromium from natural sources in soil and groundwater. Proc Natl Acad Sci U S A 104, 6544-6549.

Papadaki, K.C., Karakitsios, S.P., Sarigiannis, D.A., 2017. Modeling of adipose/blood partition coefficient for environmental chemicals. Food and Chemical Toxicology 110, 274-285.

Peyret, T., Krishnan, K., 2011. QSARs for PBPK modelling of environmental contaminants. SAR and QSAR in Environmental Research 22, 129-169.

Price, K., Krishnan, K., 2011. 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 22, 107-128.

Ramsey, J.C., Andersen, M.E., 1984. A physiologically based description of the inhalation pharmacokinetics of styrene in rats and humans. Toxicology and Applied Pharmacology 73, 159-175.

Ruiz, P., Fowler, B.A., Osterloh, J.D., Fisher, J., Mumtaz, M., 2010. Physiologically based pharmacokinetic (PBPK) tool kit for environmental pollutants--metals. SAR QSAR Environ Res 21, 603-618.

Sanborn, M., Kerr, K.J., Sanin, L.H., Cole, D.C., Bassil, K.L., Vakil, C., 2007. Non-cancer health effects of pesticides: systematic review and implications for family doctors. Canadian family physician Medecin de famille canadien 53, 1712-1720.

Sarigiannis, D., Gotti, A., Karakitsios, S., 2011. A Computational Framework for Aggregate and Cumulative Exposure Assessment. Epidemiology 22, S96-S97.

Sarigiannis, D., Karakitsios, S., 2011. Perinatal Exposure to Bisphenol A: The Route of Administration Makes the Dose. Epidemiology 22, S172.

Sarigiannis, D., Karakitsios, S., Gotti, A., Loizou, G., Cherrie, J., Smolders, R., De Brouwere, K., Galea, K., Jones, K., Handakas, E., Papadaki, K., Sleeuwenhoek, A., 2014. Integra: From global scale contamination to tissue dose, Proceedings - 7th International Congress on Environmental Modelling and Software: Bold Visions for Environmental Modeling, iEMSs 2014, pp. 1001-1008.

Sarigiannis, D.A., 2017. Assessing the impact of hazardous waste on children's health: The exposome paradigm. Environ Res 158, 531-541.

Sarigiannis, D.A., Gotti, A., 2008. Biology-based dose-response models for health risk assessment of chemical mixtures. Fresenius Environmental Bulletin 17, 1439-1451.

Sarigiannis, D.A., Hansen, U., 2012. Considering the cumulative risk of mixtures of chemicals - A challenge for policy makers. Environmental Health: A Global Access Science Source 11.

Sarigiannis, D.A., Karakitsios, S.P., 2012. A dynamic physiology based pharmacokinetic model for assessing lifelong internal dose, AIChE 2012, Pittsburgh, PA.

Sarigiannis, D.A., Karakitsios, S.P., Handakas, E., Simou, K., Solomou, E., Gotti, A., 2016. Integrated exposure and risk characterization of bisphenol-A in Europe. Food and Chemical Toxicology 98, 134-147.

Sarigiannis, D.A., Papadaki, K., Kontoroupis, P., Karakitsios, S.P., 2017. Development of QSARs for parameterizing Physiology Based ToxicoKinetic models. Food and Chemical Toxicology 106, 114-124.

Sarigiannis, D.A., Karakitsios, S.P., Zikopoulos, D., Nikolaki, S., Kermenidou, M., 2015. Lung cancer risk from PAHs emitted from biomass combustion. Environmental Research. 137, 147-156.

Sasso, A.F., Isukapalli, S.S., Georgopoulos, P.G., 2010. A generalized physiologically-based toxicokinetic modeling system for chemical mixtures containing metals. Theoretical Biology and Medical Modelling 7.

Satarug, S., Garrett, S.H., Sens, M.A., Sens, D.A., 2010. Cadmium, environmental exposure, and health outcomes. Environ Health Perspect 118, 182-190.

Sharma, R.P., Schuhmacher, M., Kumar, V., 2018a. The development of a pregnancy PBPK Model for Bisphenol A and its evaluation with the available biomonitoring data. Science of Total Environment *in press*.

Sharma, R.P., Schuhmacher, M., Kumar, V., 2018b. Physiology based Pharmacokinetic (PBPK) modeling for DEHP metabolites integrating its in vitro metabolism: a bottom up modeling approach. Toxicology Letters *Submitted*.

Shin, B.S., Kim, C.H., Jun, Y.S., Kim, D.H., Lee, B.M., Yoon, C.H., Park, E.H., Lee, B.M., Yoon, C.H., Park, E.H., Lee, K.C., Han, S.Y., Park, K.L., Kim, H.S., Yoo, S.D., 2004. Physiologically based pharmacokinetics of bisphenol A. Journal of Toxicology and Environmental Health - Part A 67, 1971-1985.

Stern, A.H., 2010. A quantitative assessment of the carcinogenicity of hexavalent chromium by the oral route and its relevance to human exposure. Environ Res 110, 798-807.

Swan, S.H., 2008. Environmental phthalate exposure in relation to reproductive outcomes and other health endpoints in humans. Environmental research 108, 177-184.

Tan, Y.M., Liao, K., Conolly, R., Blount, B., Mason, A., Clewell, H., 2006. Use of a physiologically based pharmacokinetic model to identify exposures consistent with human biomonitoring data for chloroform. Journal of Toxicology and Environmental Health - Part A: Current Issues 69, 1727-1756.

Teeguarden, J.G., Waechter, J.M., Clewell, H.J., Covington, T.R., Barton, H.A., 2005. Evaluation of oral and intravenous route pharmacokinetics, plasma protein binding, and uterine tissue dose metrics of bisphenol A: A physiologically based pharmacokinetic approach. Toxicological Sciences 85, 823-838.

ten Berge, W., 2009. A simple dermal absorption model: derivation and application. Chemosphere 75, 1440-1445.

Thayer, K.A., Doerge, D.R., Hunt, D., Schurman, S.H., Twaddle, N.C., Churchwell, M.I., Garantziotis, S., Kissling, G.E., Easterling, M.R., Bucher, J.R., Birnbaum, L.S., 2015. Pharmacokinetics of Bisphenol A in Humans Following a Single Oral Administration. Environment international 83, 107-115.

Timchalk, C., Nolan, R.J., Mendrala, A.L., Dittenber, D.A., Brzak, K.A., Mattsson, J.L., 2002. A Physiologically based pharmacokinetic and pharmacodynamic (PBPK/PD) model for the

organophosphate insecticide chlorpyrifos in rats and humans. Toxicological sciences : an official journal of the Society of Toxicology 66, 34-53.

Touitou, E., 2002. Drug delivery across the skin. Expert Opinion on Biological Therapy 2, 723-733.

USEPA, 2013. Provisional Guidance for Quantitative Risk Assessment of Polycyclic Aromatic Hydrocarbons.

Valcke, M., Krishnan, K., 2011. Evaluation of the impact of the exposure route on the human kinetic adjustment factor. Regulatory Toxicology and Pharmacology 59, 258-269.

Vanden Heuvel, J.P., Kuslikis, B.I., Van Rafelghem, M.J., Peterson, R.E., 1991. Tissue distribution, metabolism, and elimination of perfluorooctanoic acid in male and female rats. Journal of biochemical toxicology 6, 83-92.

Ventura, C., Latino, D.A.R.S., Martins, F., 2013. Comparison of Multiple Linear Regressions and Neural Networks based QSAR models for the design of new antitubercular compounds. European journal of medicinal chemistry 70, 831-845.

Verner, M.A., Charbonneau, M., Lopez-Carrillo, L., Haddad, S., 2008. Physiologically based pharmacokinetic modeling of persistent organic pollutants for lifetime exposure assessment: A new tool in breast cancer epidemiologic studies. Environmental Health Perspectives 116, 886-892.

Wagner, J.G., 1973. Properties of Michaelis-Menten equation and its integrated form which are useful in pharmacokinetics. Journal of Pharmacokinetics and Biopharmaceutics 1, 103-121.

WHO, 2010. Exposure to highly hazardous pesticides: A major public health concern, Geneva, Switzerland.

Willhite, C.C., Ball, G.L., McLellan, C.J., 2008. Derivation of a bisphenol A oral reference dose (RfD) and drinking-water equivalent concentration. Journal of toxicology and environmental health. Part B, Critical reviews 11, 69-146.

Willmann, S., Lippert, J., Sevestre, M., Solodenko, J., Fois, F., Schmitt, W., 2003. PK-Sim®: A physiologically based pharmacokinetic 'whole-body' model. Drug Discovery Today: BIOSILICO 1, 121-124.

Willmann, S., Schmitt, W., Keldenich, J., Lippert, J., Dressman, J.B., 2004. A physiological model for the estimation of the fraction dose absorbed in humans. Journal of Medicinal Chemistry 47, 4022-4031.

World Health Organization, 2010. WHO Guidelines for Indoor Air Quality: Selected Pollutants. WHO.

Xue, J., Zartarian, V., Wang, S.W., Liu, S.V., Georgopoulos, P., 2010. Probabilistic modeling of dietary arsenic exposure and dose and evaluation with 2003-2004 NHANES data. Environmental Health Perspectives 118, 345-350.

Yang, X., Doerge, D.R., Teeguarden, J.G., Fisher, J.W., 2015. Development of a physiologically based pharmacokinetic model for assessment of human exposure to bisphenol A. Toxicol Appl Pharmacol 289, 442-456.

Yang, Y., Xu, X., Georgopoulos, P.G., 2010. A Bayesian population PBPK model for multiroute chloroform exposure. Journal of Exposure Science and Environmental Epidemiology 20, 326-341.

Yu, L.X., Amidon, G.L., 1999. A compartmental absorption and transit model for estimating oral drug absorption. International journal of pharmaceutics 186, 119-125.

13 ANNEX 1: PBTK Models Review

Table of Contents

INTRODUCTION

The present version of this document contains a synthesis on current PBTK models developed by different authors to represent the toxicokinetics of the first set of priority compounds determined in the HBM4EU project: phthalates/DINCH, bisphenols, PAHs, PFAS, BFRs, cadmium, chromium (VI), and pesticides (in the frame of mixtures). In addition, the available generic PBTK models, as well as their applicability domain are presented herein. Overall, this work aims to contribute to the *"review on PBPK models"* (deliverable 12.1 in the annex 1 of the project). Another document has been developed and complement this review on the aspects related to the parameterisation of the models. The title of the cited document is *"PBTK model refinement: parameterisation"* and aims to contribute to the PBTK model refinement (deliverable 12.3 in the annex 1 of the project).

We have decided to consider in priority human PBTK models when they were available. Animal models have been described as well. One of the interests of the animal models is that they present generally a high level of detail in the representation of the toxicokinetic processes and give to us a good understanding of these processes and their influence on the model results. Moreover, for the animal models, there are often more available data that let fitting some parameters of the model and other sets of data that can ideally let the model validation, thus providing a good basis for extrapolation to humans. Some of the models described herein were initially developed either for the rat or for the monkey, while two models realised an extrapolation between the non-pregnant and the pregnant physiological stages. Most of the studied animal models were extrapolated to the human.

The following pages contain a description and discussion of the studied models.

PAHs

1. Use of Physiologically-Based Pharmacokinetic Modeling to Simulate the Profiles of 3-Hydroxybenzo(a)pyrene in Workers Exposed to Polycyclic Aromatic Hydrocarbons (Heredia-Ortiz et al., 2014)

1.1. Chemical compound(s):

Benzo(a)pyrene (BaP) and the metabolites: 3-OH-BaP, “other metabolites”.

1.2. Species and stages:

Developed in the rat (Heredia-Ortiz and Bouchard, 2013), extrapolated to the human

1.3. Model structure, main assumptions and processes:

1.3.1. Structure

2 sub-models: BaP and 3-OHBaP. “Other metabolites” were represented as compartments in these two sub-models.

11 compartments for the BaP (lungs, AT, skin, kidney, liver, GI tract, "rest of the body", arterial blood, venous blood, faeces, "other metabolites").

13 compartments for the 3-OH-BaP (the same as for BaP + bladder + urine).

1.3.2. Oral exposure

Oral bolus, direct entry into the liver after application of an absorption coefficient and the portal vein flow. The oral route was not activated for the simulation of an occupational exposure.

1.3.3. Inhalation exposure

In the inhaled exposure equation, a diffusion component (permeability constant) was included. It seems they represent venous and inhalation entries, arterial and exhalation exits, in the same way as other authors also did (Hissink et al., 2009; Jongeneelen and Ten Berge, 2011). Some abbreviations were not explained (ex. QP, PB).

1.3.4. Dermal exposure

The variation of the amount of the molecule in the skin was determined by Eq 1, in which A_{skin} is the amount of the molecule in the skin, $Coeff_{permeab\ skin}$ the skin permeability coefficient (cm h^{-1}), S^2_{skin} the skin surface of exposure (cm^2), C_{dose} the concentration of the molecule in the “dose” compartment, C_{skin} the concentration of the molecule in the skin, P_{DV} is a constant related to the absorption (not explained this abbreviation). The part of the equation written in grey corresponds to the exchanges of the molecule between the skin and the blood determined by the arterial blood flow and the partition coefficient, as indicated in Eq 5.

Eq 1

$$\frac{dA_{skin}}{dt} = Q_{skin} \times \left(C_{art} - \frac{C_{skin}}{PC_{skin:blood}}\right) + Coeff_{permeab\ skin} \times S^2_{skin} \times \left(C_{dose} - \frac{C_{skin}}{P_{DV}}\right)$$

1.3.5. Distribution

“For each organ, it was determined whether the transfer was limited by tissue perfusion or diffusion (permeability), hence if a tissue: blood equilibrium was reached instantaneously or if transfer to the tissue was limited by diffusion (permeability) of the molecule through the cell membranes” (Heredia-Ortiz and Bouchard, 2013). They used the toxicokinetics data of BaP and 3-OH-BaP

measured in the different tissues of rats at several time points following a single IV dose of BaP (Marie et al., 2010). A perfusion limited transfer to each tissue was firstly considered by Heredia-Ortiz et Bouchard (2013) and the time for the maximum concentration in each tissue compared to the experimental data of Marie et al. (2010). The lung for BaP and 3-OH-BaP, the adipose tissue and the kidney for 3-OH-BaP were then modified to diffusion-limited kinetics in order to represent the delay in the maximum concentration and start of depuration in these tissues after a single IV dose of BaP.

1.3.6. Metabolism

The equation of hepatic metabolism did not present the structure of the Michaelis-Menten (M-M) equation (Eq 2, (Wagner, 1973) for saturable metabolism, in which v represents the velocity of the reaction, Vmax the maximum velocity, Km the M-M constant and C the concentration of the molecule in the origin compartment. Instead, these authors applied the structure of Eq 3, similar in appearance to Eq 2, but describing a first order instead of second order process. Effectively, in Eq 3, the velocity of the reaction can be reduced to a clearance times a concentration. This equation includes the partition coefficient of the molecule between the liver and the blood (PCliver: blood, unitless) in the denominator.

Eq 2 $$v = \frac{V_{max} \times C}{K_m + C}$$

Eq 3 $$v = \frac{V_{max} \times C_{liver}}{K_m \times PC_{liver:\,blood}}$$

1.3.7. Elimination

- From the liver to the GI tract: 1st order elimination depending on the biliary rate and the concentration of the molecule in the liver.
- From the GI tract to the feces: 1st order elimination depending on the fecal elimination rate and the concentration of the molecule in the GI tract.
- From the kidney to the bladder: representation of this elimination way for the metabolite (3-OH-BaP). Some abbreviations were not explained. It included a permeability coefficient.

1.3.8. Biliary excretion

For the metabolite (3-OH-BaP), representation of the reabsorption from the GI tract (=constant x amount in the GI compartment).

1.3.9. Binding

"From model simulation of the time course of BaP and 3-OHBaP in blood and tissues in dynamic equilibrium with blood, a bi-exponential elimination behavior was observed… There is good evidence of binding of BaP to lipoproteins and the influence of plasma lipoproteins and albumin as carriers of BaP in rats" (Heredia-Ortiz and Bouchard, 2013). However, the authors explained that the binding was not represented in the model because of a lack of data in the literature letting a correct representation of this mechanism.

1.4. Parameterisation:

Cf. document *"PBTK model refinement: parameterisation".*

1.5. Extrapolation rat to human

- Physiological parameters: the rat values were replaced by the human values from Davies and *Morris (1993)* and *Brown et al. (1997)*.
- Tissue: blood partition coefficients and tissue permeability coefficients were considered as species invariant.

- The bile flow rate and the glomerular filtration rate were calculated from rat to human by considering the values reported by Davies and Morris (1993). The skin permeability coefficient was calculated from rat to human by applying the scaling algorithm proposed by Morimoto et al. (1992). The extrapolation of metabolic constants was made by applying a scaling constant which value was obtained by fitting this parameter on the basis of the urine data of one worker.

1.6. Sensitivity analysis

Stochastic variation of all the parameters simultaneously. Study of the difference between the tested values and the initially optimised ones on the concentration of 3-OH-BaP in the urine. Comparison at different time points.

1.7. Assessment, validation

Inhalation and dermal exposure scenarios were estimated to fit the data of concentration of these molecules in the urine of occupationally exposed workers. Good fitting of the model when considering only the dermal exposure route. The results were presented graphically. The error in the estimation was not explicitly quantified. In all the cases, as the authors pointed out, the sample points could be reproduced by several plausible exposure scenarios; the resulting urinary biomarker profiles alone did not allow confirming the main route of exposure.

1.8. Questions:

- Several abbreviations in the equations presented in the appendix were not explained.

1.9. Discussion:

- The determination of the parameter values was realised by group of parameters. Each one of these groups of parameters was fitted to experimental data obtained by a given exposure route. The selection made (groups of parameters, experimental study for each group) seems appropriate. However, the partition coefficient value obtained for the lungs seems inadequate. Effectively, while the PC of the other tissues varied between 1.9 (skin) and 65.9 (adipose tissue), the fitted PC for the lungs had a value of 2670. Probably other mechanisms not represented in the model, in addition to the partitioning, contributed to this value.
- The extrapolation of metabolic constants was made by applying a scaling constant which value was obtained by fitting it to the urine data of one worker. The data obtained in just one individual seem insufficient to estimate one key parameter in the extrapolation of the model from rat to human.
- The sensitivity analysis realised over different time points is especially interesting in the case of a representation of different physiological stages.

2. Predicting lung dosimetry of inhaled particleborne benzo(a)pyrene using physiologically based pharmacokinetic modeling (Campbell et al., 2016)

2.1. Chemical compound(s):

Benzo(a)pyrene

2.2. Species and stages:

Humans

2.3. Model structure, main assumptions and processes:

2.3.1. Structure

The inhalation model for BaP in rats and humans is an extension of a previously published oral BaP model for rats (Crowell et al., 2011). In Crowell's model, BaP concentrations were estimated for the lung, liver, fat and richly and slowly perfused tissues. Oral bolus, duodenal and intravenous (IV) infusion exposure routes were modeled. Oral exposures were represented as a two-compartment GI tract, and metabolism of BaP to total metabolites was modeled in the lung and liver. Fecal elimination of BaP was also included. BaP transfer from blood to tissues was assumed to be blood-flow limited except for the fat compartment, which was diffusion-limited. The current model expanded the description from Crowell et al. (2011) to include a description for the 3-OH BaP metabolite in order to simulate the limited human data available.

2.3.2. Inhalation and oral exposure

The model was parameterised regarding inhalation exposure and timing, alveolar ventilation and fractional deposition of inhaled particles in the upper and lower respiratory tract. In order to account for the presence of BaP in the human diet, a parameter for daily dietary intake was introduced to the model.

2.3.3. Distribution

Dissociation of deposited BaP from carrier particles was implemented by introducing a first order rate constant by which BaP would be transferred to the lung tissues

2.3.4. Metabolism

Dissociated BaP was assumed to enter the total lung tissue volume, where it would be subject to saturable oxidative metabolism. Deposited particle-associated BaP in the lung can be cleared via two processes in this model. The first is to be released into the lung-lining fluid and taken up by the lung. The second is to remain adhered to the particles deposited in the lung and be cleared via the mucociliary escalator (rapid clearance) or engulfed by macrophages (slow clearance). In vitro to in vivo extrapolation (IVIVE) was used to incorporate metabolism of BaP in the liver and lung. Metabolism of BaP was assessed in pooled rat and female human liver microsomes.

2.3.5. Elimination

Elimination of free 3-OH BaP from plasma is described as two separate clearances with one representing urinary clearance and the other accounting for a lumped metabolic/fecal clearance to reduce the number of parameters to be estimated. Urinary elimination of free 3-OH BaP (CLURN3C) was described as a clearance process from the venous blood compartment and set to approximate the glomerular filtration rate (GFR) of the free fraction of 3-OH in plasma

2.3.6. Binding

Binding was not mentioned.

2.4. Parameterisation:

Cf. document “PBTK model refinement: parameterisation”.

2.5. Extrapolation rat to human

Human data was found from literature or were scaled from rat data.

2.6. Sensitivity analysis

Sensitivity analysis was performed using the parameter estimation tool found in the AcslX software package (ver. 3.1.4.2) (Orlando, FL). The parameters of interest were varied by ±1% of their nominal values, and normalised sensitivity coefficients (the ratio changes in varied parameter to response variable, normalised to the nominal value of the varied parameter and the response variable) were calculated. The response variable was the lung tissue free BaP concentration taken at the end of the inhalation exposure interval for rats (30 min) or the end of a single cigarette exposure for human (5.1 min).

2.7. Assessment, validation

No studies were identified in the published literature in which lung or blood levels of BaP were reported in humans following inhalation of measured levels of BaP. Lafontaine et al. (2004) provided the only data for urinary metabolites levels associated with individual breathing zone measurements of BaP.

2.8. Questions:

Were there other modifications except for the one presented for lung compartment (rest of the structure compartments, equations and parameters used)?

2.9. Discussion:

- The capability of inhaled BaP lung tissue dosimetry was added to the previous oral BaP model.
- Metabolic and tissue diffusion parameters are needed in order the inhalation model to be further refined to discriminate between deposition, dissociation and absorption of BaP into tracheobronchial and alveolar compartments.
- Region-specific respiratory tract dosimetry of inhaled BaP and metabolites would be useful for future PBPK refinement.

Perfluorinated compounds

3. Evaluation and prediction of pharmacokinetics of PFOA and PFOS in the monkey and human using a PBPK model (Loccisano et al., 2011)

3.1. Chemical compound(s):

Perfluorooctanoate (PFOA) and perfluorooctane sulfonate (PFOS).

3.2. Species and stages:

Development of the model for monkeys, extrapolation to humans.

3.3. Model structure, main assumptions and processes:

3.3.1. Structure

Nine compartments: plasma, gut, liver, fat, skin, kidney, "rest of body", filtrate, urine storage. The plasma was represented instead of the blood, under the consideration that these compounds don't partition into the red blood cells.

3.3.2. Oral exposure

- Bolus to the gut.
- Transfer from the gut to the liver by the portal vein (Eq 4, black). A_{gut} is the amount of the molecule in the gut (mg), Q_{gut} the portal plasma flow from the gut to the liver (L h^{-1}), and Free the free fraction of the molecule in the plasma.

Eq 4

$$\frac{dA_{gut}}{dt} = Bolus + Q_{gut} \times C_{art\ gut} \times Free - Q_{gut} \times C_{gut} \times \frac{Free}{PC_{gut:plasma}}$$

3.3.3. Distribution

Considered as perfusion-limited. In this model Eq 5 was multiplied by the free fraction of the molecule in the plasma in order to represent the high binding of these molecules to the plasma proteins (cf. 3.3.7),.

3.3.4. Metabolism

No metabolism was represented. *“In summary, animal studies have shown that these compounds (PFOA and PFOS) are well absorbed orally, poorly eliminated, and not metabolized…”* (Loccisano et al., 2011)*(Sharma et al., 2018a)*

3.3.5. Elimination

- First order clearance from plasma to the filtrate compartment. This clearance was calculated as the product of the arterial concentration of the molecule, the free fraction of the molecule in the plasma and the clearance rate from the plasma to the filtrate compartment.
- First order transfer of the molecule from the filtrate to the “urine storage” compartment (same clearance rate used from the plasma to the filtrate compartment).
- Elimination of the molecule in the urine from the “urine storage compartment. This elimination presented a delay for PFOS.

3.3.6. Renal resorption

Loccisano et al. (2011) hypothesised that the long plasma half-lives of PFOA were due to renal resorption. Thus, they represented a renal resorption in the filtrate compartment. It was represented as a saturable flow (Eq 2) from the filtrate to the kidney compartment. This hypothesis was considered for the monkey and for the human.

3.3.7. Binding

"PFOA and PFOS have been shown to be >97% bound to plasma proteins such as albumin in the rat, monkey and human…; a constant free fraction of each chemical (<0.03) was used" (Loccisano et al., 2011). A term representing the free fraction of the molecule in the plasma was included in the distribution equations (3.3.3).

3.4. Parameterisation:

Cf. document *"PBTK model refinement: parameterisation".*

3.5. Extrapolation from monkey to human

- Modification of the physiological parameters.
- As a consequence of the units in which it was expressed, the cardiac output (L h^{-1} $kg^{-0.75}$) was scaled as a function of the BW.
- The same $PC_{tissue:\ plasma}$ estimated for the monkey model from rodent data were used for the human. The authors indicated *"Fiserova-Bergerova (1975) examined partition coefficients for two compounds (forane and methylene chloride) in several species (man, monkey, dog, and rat). Tissue: blood partition coefficients were very similar for the tissues examined across species"*.
- The Michaelis-Menten affinity constant K_t (mg L^{-1}) was considered the same in humans as in monkeys. The parameter of maximum resorption in the filtrate compartment (V_{max}, mg h^{-1} $kg^{-0.75}$) was estimated in order to give the reported half-life in humans. Two different half-lives (2.3 and 3.8 years) were reported in the literature and used in the model.
- The urinary elimination rate constant (K_{urinec}, $kg^{0.25}$ h^{-1}) was scaled as a function of the BW. K_{urinec} was thereafter estimated by fitting of this parameter on the basis of urine and serum PFOA and PFOS concentrations in humans, after chronic oral exposure in the water supply.
- The same free concentration of the molecules in the blood was considered in both species.

3.6. Sensitivity analysis

- One parameter each time: 1% of variation of its value and calculation of the sensitivity analysis normalised results. Evaluation of the influence on the predicted plasma area under the curve.
- The sensitivity analysis was realised at two different experimental dose levels for each molecule.
- The results showed no differences between the doses tested for PFOA, while the results for PFOS were different depending on the dose.

3.7. Assessment, validation

The error in the estimates was not quantified. The results were presented graphically.

- PFOA, monkey: assessment by comparison with plasma and urine concentration data in the monkey after a single IV exposure: good agreement.
- PFOA, monkey: assessment by comparison with plasma and urine concentration data in the monkey after repeated oral exposure: good shape of the simulated curves vs. the experimental ones. During exposure, the simulated concentrations in plasma were slightly overestimated and the concentrations in urine were underestimated.
- PFOS, monkey: assessment by comparison with plasma and urine concentration data in the monkey after a single IV exposure: the fitting was poor, especially at the end of the depuration curves, where the simulated concentrations were overestimated.

- PFOS, monkey: assessment by comparison with serum concentration data in the monkey after a repeated oral exposure at different doses: the fitting was poor during exposure for the high doses. During exposure for the higher dose, the simulated concentrations reached a plateau while a continuous increase was observed experimentally. The depuration curve was adequate for the high dose and overestimated for the mid dose. The authors commented that an adjustment of the parameters driving the renal resorption let an improvement of these estimations.
- PFOA human: assessment by comparison with plasma and serum data from populations exposed by the contaminated water supplies. The concentrations measured in water by the same or other studies were used to simulate the exposure in the model. In most of the cases, only one sampling point was available and it was considered that the measured plasma concentration corresponded to the steady state. Other studies reported also the concentrations in the serum before (exposure) and after (depuration) the installation of a water filtration system. The two tested reported half-lives let a better fitting of simulated vs. observed data for the exposure than for the depuration data.
- PFOA and PFOS, human: assessment by comparison with serum data of the general population before and after the phase-out of these chemicals. Good fitting of simulated vs. experimental data. The level of exposure was estimated.
- After validation, the half-life was estimated with the model, from individual data on PFOA in one study. These estimated individual half-lives were in the range of those estimated by Olsen et al. (2007) and Bartell et al. (2010).

3.8. Questions:

- The estimation of some $PC_{tissue:\ plasma}$ is not clear from the cited references. It is the case for the $PC_{skin:\ plasma}$ as the cited reference Kudo et al. (2007) does not include data for this tissue. For the same reason, it's not clear how the authors have estimated the $PC_{tissue:\ blood}$ for PFOS for the "rest of body" compartment from the data of DePierre et al. (2009).
- The reference cited for the estimation of the $PC_{tissue:\ blood}$ for PFOS (DePierre, 2009, personal communication) is not detailed enough as to find it. This source of data has not been found, but (Bogdanska et al., 2011) contains data that most probably correspond to the same experiment.
- Why the urinary elimination rate constant is expressed in $kg^{0.25}\ h^{-1}$?
- The human data let probably a validation and not only an assessment of the model. However, it's difficult to confirm it as the source of the human data used to fit K_{urinec} during the extrapolation from monkey to human was not stated. Thus, we do not know if the data used for the assessment were previously used for the parameterisation or not.

3.9. Discussion:

- PC estimation data and dose effect: the experimental toxicokinetics data from two publications, one in rats (Kudo et al., 2007) and one in mice (DePierre, 2009 – Bogdanska et al., 2011), were used to estimate the $PC_{tissue:\ plasma}$ for PFOA and PFOS (Cf. document *"PBTK model refinement: parameterisation".*). Differences in the toxicokinetics depending on the exposure levels were observed by Kudo et al. (2007) and by Bogdanska et al. (2011). The dose effect observed by Kudo et al. (2007) was complex: the increase in the concentration in tissues with the increase in the dose was not the same for each tissue. When we estimate the $PC_{tissue:\ serum}$ from the data of Kudo et al. (2007) corresponding to the high level of exposure, the $PC_{liver:\ serum}$ and the $PC_{kidney:\ serum}$ were respectively 0.62 and 0.28 times lower than those estimated from the low level of exposure data. At the same time, the authors observed that the ratio of the amount of PFOA excreted into the bile to the amount of PFOA in the liver was 3.7 times higher at the high dose compared to the low dose.

These results suggest probably an activation of the hepatic metabolism and a higher elimination of the molecule in the bile at high doses. These results are coherent with those of Bogdanska et al. (2011) in which, for most of the tissues, the $PC_{tissue:\ blood}$ was higher after receiving the high than the low dose. During the 5-days exposure period, the tissue: blood ratio did not reach the equilibrium for the animals exposed to the low dose while the equilibrium was attained from the first day in the animals exposed to the high dose (fig. 1 in Bogdanska et al., 2011). These results suggest the metabolism was more important at higher doses, the elimination of the molecule from the organism compensated the entry of the molecule by exposure and the steady state was attained. Thus, there would be activation processes of the hepatic metabolism over a given exposure level.

- Interesting: even if these rates were not used in the model, Kudo et al. (2007) estimated the biliary and renal clearance rates of PFOA during the in vivo experiment in rats. The equations for these calculations consisted on the quotient of the cumulative amount of the molecule respectively in bile and in the urine by the area under the curve of the molecule (probably in blood). For PFOA, “The biliary excretion rate increased in a dose-dependent manner, although the differences among the doses were not statistically significant” (Kudo et al., 2007). The renal clearance was not significantly different among doses.
- Realistic representation of the blood flows in the liver, that included an entry by the arterial flow to the liver, an entry by the venous portal flow from the gut to the liver and the sum of both flows to calculate the venous flow from the liver to the systemic circulation.
- The sensitivity analysis (S.A.) was realised at two different experimental dose levels for each molecule. The results of the S.A. showed no differences between the doses tested for PFOA, what indicates that the saturable mechanisms in the model (renal absorption) were either non saturated or saturated for both doses. The S.A. results for the PFOS were different depending on the dose, what shows that the renal absorption was saturated at the high dose, while it was not saturated at the low dose.
- The assessment of the model for PFOS in the monkey showed a poor fitting during exposure for the high doses. Interesting: during exposure for the higher dose, the simulated concentrations raised too early and reached a plateau while a continuous increase in the concentrations at a slower rate was observed experimentally. In view of these results, the correction of the equation representing a saturable renal resorption by a simple 1st order kinetics equation would let to correct this problem, that was observed only for the higher dose. This is supported by the high sensitivity of the model to the parameters related to the renal reabsorption. Its modification would have a high influence on the serum concentrations.

4. Development of PBPK Models for PFOA and PFOS for Human Pregnancy and Lactation Life Stages (Loccisano et al., 2013)

4.1. Chemical compound(s):

PFOS and PFOA

4.2. Species and stages:

Human pregnancy and lactation life stages

4.3. Model structure, main assumptions and processes:

4.3.1. Structure

The rat model, previously developed and described by Loccisano et al. (2012) was extended to the gestation and lactation life stages in order to provide estimates of maternal, fetal, and infant exposure to PFOA and PFOS for adult humans. The structural changes made to the adult human model were the addition of mammary tissue, placenta, and fetal compartments, and a milk compartment for lactation.

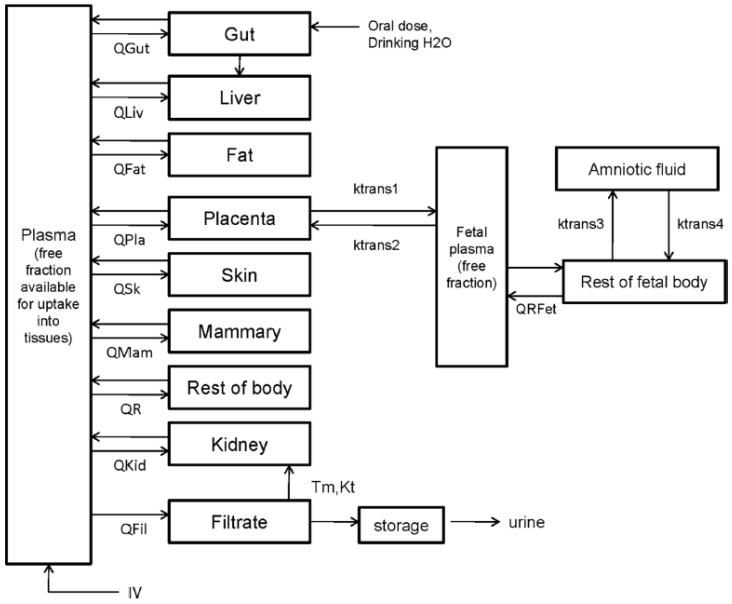

Figure 1: PBPK model structure for simulating PFOA and PFOS exposure during pregnancy in humans (maternal, left; fetal, right). Fetal plasma circulation is separate from the maternal circulation.

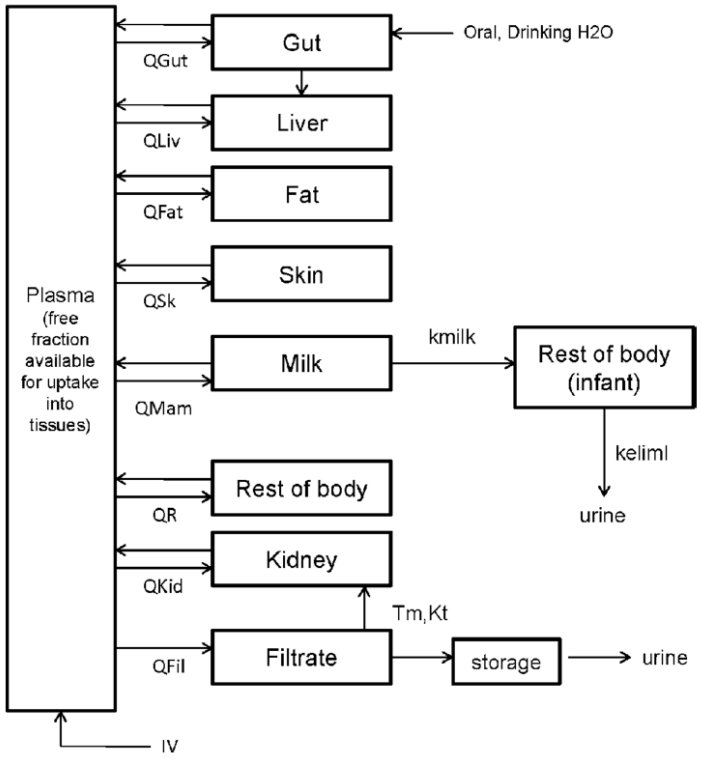

Figure 2: PBPK model structure for simulating PFOA/PFOS exposure during lactation in humans (maternal, left; infant, right). Chemical in plasma was assumed to be in direct contact with the milk compartment. Limited data was available for concentrations of PFAAs in the infant; thus, the infant was treated as a single compartment.

4.3.2. Oral exposure

Only the mother is exposed directly. Maternal exposure is by direct intake or through drinking water. Fetal exposure to PFAA is through placental transfer, which is described as a bidirectional transfer process (from mother to fetus and fetus to mother) between free chemical in the placenta and fetal plasma. The infant exposure is through milk.

4.3.3. Distribution

Blood flows are represented to and from the tissues; only the free fraction of chemical in plasma is available for uptake into tissues. Because contributions to various exposure sources are unknown, the IV route is used as a generic input to plasma. Chemical is transferred to the fetus through the placenta. Placental transfer is described by a simple diffusion process. Transfer from the plasma to the milk compartment was assumed to be flow-limited. Only the free fraction of chemical in plasma was available for uptake into tissues or milk.

4.3.4. Metabolism

PFAA are well-absorbed and are not metabolised appreciably, so most of the compound reaches systemic circulation.

4.3.5. Elimination

Clearance of PFAA in the mother occurs by urinary elimination from the filtrate compartment in both models; clearance in the infant is described with a generic first-order rate constant from the central compartment.

4.3.6. Renal resorption

Renal resorption in the model is described by a transporter maximum (Tm) and an affinity constant (Kt). Although renal function is altered during pregnancy (Dunlop 1979; 1981), no data were

available on the changes in renal resorption of PFAA during this life stage. Thus, the same values used for Tm and Kt in the adult human model were used for the mother in the gestation and lactation models.

4.3.7. Binding

PFOA and PFOS are highly bound to plasma proteins in the human (>97% bound). Although the overall concentration of serum proteins decreases during gestation due to increased plasma volume, there are no data available on PFAA binding to plasma proteins during pregnancy nor are there available data to provide evidence that the free fraction of PFAAs change during pregnancy. Thus, explicit binding of PFAAs to plasma proteins is not simulated, but a constant free fraction of chemical in plasma is accounted for, as the free fraction will determine how much chemical is available for uptake into tissues.

4.4. Parameterisation:

Cf. document “PBTK model refinement: parameterisation”.

4.5. Extrapolation rat to human

Most of the parameters were estimated for rats and mice and were used in human model. Only the parameters for placental transfer were scaled to fetal body weight$^{0.75}$.

4.6. Sensitivity analysis

A normalised sensitivity analysis was performed on the gestation and lactation models for both chemicals in order to examine the influences of each model parameter on the model output. The influence of each model parameter on maternal plasma, fetal plasma, and infant concentrations were examined by calculating the area under the curve (AUC) for maternal, fetal, or infant plasma PFAA concentration that resulted from increasing each parameter by 1%. Each parameter was increased separately.

4.7. Assessment, validation

The human data where more than one concentration during pregnancy or lactation was available was used for model evaluation. For the lactation model, if a plasma concentration was reported, the exposure was estimated to yield this concentration and then the resulting predicted milk or infant blood concentration was compared to the observed value to evaluate the model structure and parameters. The goodness of the model fit to the latter data points was considered to reflect the validity of the model structure and parameterisation approach. Agreement of model predictions with reported data was examined graphically. Exposure estimation was an iterative process. For exposure estimations, agreement between predicted and observed concentrations was considered satisfactory if the predicted value was within 1% of the observed value. If the difference was more than that, exposure was reestimated.

4.8. Questions:

No species extrapolation for the input parameters of PBPK model. Does this influence the results?

4.9. Discussion:

- Validation data based on paired samples with greater temporal separation or expected variation, such as women who did or did not breast feed, would support a more informative validation.

- Only a limited number of measurements were available with which to estimate the PFOA milk/plasma partition coefficient. Additional biomonitoring data on matched serum and milk concentrations may improve the lactation model predictions.
- Additional data on renal resorption of PFAA in the mother, fetus, and infant (and thus how long the chemicals will be retained in the body) should improve the ability of the models to recapitulate human studies.
- More detailed kinetic studies in pregnant and lactating women and infants.

5. PBPK modeling for PFOS and PFOA: Validation with human experimental data (Fabrega et al., 2014)

5.1. Chemical compound(s):

PFOS and PFOA

5.2. Species and stages:

Humans

5.3. Model structure, main assumptions and processes:

5.3.1. Structure

A new PBPK model for PFOA and PFOS was developed based on a previously reported model (Loccisano et al., 2013). A recent publication from the same group has extended this study to PBPK/PD coupled mechanistic pathway model (miRNA-BDNF) for the PFOS induced neurotoxicity (Sharma et al., 2017). The key process adopted in the model is the kinetics of resorption by renal transporters in the filtrate compartment, where chemicals are reabsorbed back to plasma through a saturable process. In addition to plasma, gut, liver, fat, kidney, filtrate, and the remaining body compartments, the adapted PBPK model included lungs and brain. However, since it is not a potential site of absorption/accumulation for PFASs, skin was removed.

5.3.2. Oral exposure

Human exposure to PFOA and PFOS was evaluated through two different pathways: water consumption and food intake. Water ingestion was calculated as the product of the concentration in human drinking water in Catalonia. . Similarly, dietary exposure was estimated based on the mean PFAS concentration in 40 food items, which are representative of the Catalan diet, and the respective daily consumption by the general population. Food intake was found to be the most important contributive route to the exposure of PFOS and PFOA, with percentages of 97% and 98% of the total intake, respectively.

5.3.3. Distribution

Gut was selected as an absorption site**.** Brain was selected as target organ of PFASs neurotoxic effects, liver as an accumulative tissue for organic chemicals, lungs because they may exhibit immaturity after PFOS exposure, and fat as a main site of accumulation in lipophilic tissues.

5.3.4. Metabolism

5.3.5. Elimination

Kidney and filtrate were selected for its role in elimination and urinary elimination from the filtrate compartment was considered.

5.3.6. Renal resorption

The key process adopted in the model is the kinetics of resorption by renal transporters in the filtrate compartment, where chemicals are resorbed from urine back to plasma through a saturable process. This resorption mechanism could be responsible for the high persistence of PFOA and PFOS in human blood, compared to the reported low persistence found in other animal species (e.g., rat, monkey).

5.3.7. Binding

In plasma, more than 90% of PFOA and PFOS is bound to albumin, while <10% is free to move to other tissues.

5.4. Parameterisation:

Cf. document “PBTK model refinement: parameterisation”.

5.5. Extrapolation rat to human

Extrapolation was not used, only some data directly from human autopsy tissues.

5.6. Sensitivity analysis

Sensitivity analysis was not performed in this publication, but in another publication of same group, sensitivity and uncertainty analysis was performed (Fabrega et al., 2016).

5.7. Assessment, validation

For validation purposes, data on PFOA and PFOS in human tissues from people living in the area of study (Tarragona County) were used. The levels of 13 PFASs, including PFOA and PFOS, were reported in blood samples of 48 residents in that same area. In addition to the model validation, a study on the best partition coefficients was conducted. Hence, the model was tested by using, as input data, partition coefficients from studies conducted with either rats or humans. Data sets were compared to detect any improvement in the performance of both original and adapted PBPK models.

5.8. Questions:

No species extrapolation for some of the input parameters of PBPK model. How does this influence the results?

5.9. Discussion:

- The results highlight the importance to obtain partitioning data from humans in order to estimate more accurately the body burdens of PFASs in particular, and chemical contaminants in general.
- The improvement in the current model predictions confirms that the application of human data is always more desirable than data coming from animals.
- More data regarding the levels of PFASs in human tissues are needed.
- Despite only blood is commonly used for PBPK modeling validation, the comparability with other human compartments would ensure the reliability of the model with respect to target tissues.
- The inclusion of the mammary gland within the PBPK model should be also considered in future studies, as it is known as the most sensitive target organ for PFOA toxicity in animals.
- The assessment of suitability of PBPK modeling for the evaluation of mixtures of PFASs could be also considered.

Bisphenols

6. Evaluation of Oral and Intravenous Route Pharmacokinetics, Plasma Protein Binding, and Uterine Tissue Dose Metrics of Bisphenol A: A Physiologically Based Pharmacokinetic Approach (Teeguarden et al., 2005a)

6.1. Chemical compound(s):

Bisphenol A (BPA) and its glucuronide metabolite BPAG.

6.2. Species and stages:

Model developed for the adult rat and extrapolated to the human.

6.3. Model structure, main assumptions and processes:

6.3.1. Structure

Two sub-models: BPA and BPAG. Five compartments for BPA: gastrointestinal (GI) lumen, liver, blood, uterus*, body (=1-remaining tissues-bone). Two compartments for BPAG: "volume of distribution"=plasma, GI lumen.

**"A uterine tissue compartment was included to allow the correlation of simulated estrogen receptor (ER) binding of BPA with increases in uterine wet weight (UWW) in rats"* (Teeguarden et al., 2005a).

6.3.2. Oral exposure

- Bolus to the GI lumen.
- First order absorption from the GI lumen to the liver.

6.3.3. IV exposure

A direct entry of the molecule in the blood compartment was represented to test the IV data in rats.

6.3.4. Distribution

Represented as perfusion-limited in all the compartments (Eq 5).

No blood flow distribution represented to the GI lumen. This tissue was represented only as a compartment of absorption of BPA and of elimination and reabsorption of BPAG in the bile.

The blood flow to the body was calculated as the difference between the cardiac output and the blood flows to the liver and to the uterus.

6.3.5. Metabolism

Hepatic metabolism from BPA to BPAG considered as second order kinetics (Eq 2). In the same way as Hissink et al. (2009), Teeguarden et al. (2005) applied in this equation the concentration of the molecule in the venous blood leaving the liver. The choice of the concentration in the venous blood from liver, the arterial concentration or the concentration in liver tissue was discussed previously.

The metabolised BPA was transferred to the BPAG sub-model, after correction by the molecular weight of both molecules. A fraction of the formed BPAG was transferred to the GI lumen and the rest was transferred to the "volume of distribution" (plasma) compartment (cf. 6.3.6).

6.3.6. Fecal elimination

- A fraction of the BPAG formed by hepatic metabolism of BPA was transferred to the GI lumen. This fraction corresponded to the percentage of BPAG eliminated via the bile ("bile").

- First order elimination of BPAG from the GI lumen to the feces.

6.3.7. Urinary elimination

- The BPAG formed by hepatic metabolism that was not transferred to the GI lumen, thus the fraction (1 - "bile"), was transferred to the "volume of distribution" compartment.
- First order elimination of BPAG from the "volume of distribution" compartment to the urine.

6.3.8. Enterohepatic resorption

A fraction of the BPAG eliminated to the GI lumen (cf. 6.3.6) was hydrolysed to BPA and reabsorbed from the GI lumen to the liver at a first order rate. The passage from one sub-model (BPAG) to the other one (BPA) implied a correction by the molecular weight of both molecules.

6.3.9. Binding

"Bisphenol A binds to plasma proteins in rodents, monkeys, and humans. The bound form represents ~90–95% and the free form ~5–10% of the total (Csanady et al., 2002; Kurebayashi et al., 2002; Mayersohn, 2003). Humans and monkeys appear to have modestly lower free fractions (5%) (Csanady et al., 2002) than rats (~5–10%) (Mayersohn, 2003)" (Teeguarden et al., 2005a). The plasma binding of BPA was determined experimentally *in vitro* using plasma from rats. A regression equation was obtained from the experimental data, that described the relation between the proportion of bound and free BPA. No significant sex differences were observed.

Teeguarden et al. (2005) indicated: *"The resulting partition coefficients (from Csanady et al., 2002) account for the net affect of processes controlling apparent partitioning (e.g., binding to plasma proteins)"*. That's the reason by which the binding to plasma proteins was not represented in most of the components of the model. This binding was represented only for the uterine compartment, for which no value of the PC was available and the $PC_{muscle:\ blood}$ was used. The representation of the binding was considered as necessary to model properly the uterine tissue receptor binding. The binding to the uterine estrogen receptor was calculated by the Michaelis-Menten equation (2^{nd} order kinetics).

6.4. Parameterisation:

Cf. document *"PBTK model refinement: parameterisation".*

6.5. Extrapolation rat to human

- Modification of the physiological parameters.
- Modification of some parameters related to the toxicokinetics of the molecule in the body (cf. document *"PBTK model refinement: parameterisation".*).

6.6. Sensitivity analysis

One parameter each time (1% of difference in its value), study of the influence on the BPA and BPAG concentrations in blood. Normalised results. The sensitivity analysis was realised at different time points.
In general, the rat and human models were sensitive to the same parameters (it seems coherent, as no modifications in the structure of the model were realised to extrapolate the model from rats to humans).
The results showed a variation of the sensitivity to the different parameters as a function of the time.

6.7. Assessment, validation

The error in the estimations was not explicitly quantified by the authors. The results were commented from graphic representations.

- Rat:

- Assessment on BPA plasma concentration data from rats after IV administration of the molecule (Upmeier et al., 2000). These data had been used to calibrate the volume of distribution and Vmax of the BPA. Good agreement of the simulated vs. the observed data.
- Assessment on BPA blood concentration data from rats after oral exposure to the molecule at a dose of 100 mg kg^{-1} (Pottenger et al., 2000). A few data were available for the males. More data were available for females. These data had been used to calibrate several parameters in the model. Generally good agreement simulated vs. observed data.
- Assessment on BPAG blood concentration data from female and male rats after oral exposure to BPA at a dose of 100 mg kg^{-1} (Pottenger et al., 2000). Underestimation of the pic concentrations in the female, not observed in the male. Better agreement of the simulated vs. the observed data at later time points in the female than in the male, for which an underestimation of the simulated data was evident at this stage. The data from this experience and treatment had served to calibrate several parameters in the model.
- Assessment on cumulative BPAG excreted in urine and in feces in female and male rats after oral dosing to 100 mg kg^{-1}. Good agreement of the simulated vs. the observed data at the latest time points. No agreement at the beginning of the curves, when the observed data were delayed compared to the simulated data. The data from this experience and treatment had served to calibrate several parameters in the model.
- Validation on BPA blood concentration data from female rats after oral exposure to the molecule at a dose of 10 mg kg^{-1} (Pottenger et al., 2000). The simulated results underestimated the observed concentrations at steady state.

- Human:
  - Assessment on time course data of the concentration of BPAG in plasma in men and women after oral exposure to BPA. Agreement of the simulated vs. the observed data at the beginning of the depuration (<12 h post-exposure) in men. Scarce data available for women. Underestimation by the model of the concentrations at later points of the time course, for men and women.
  - Assessment on cumulative BPAG excreted in urine and in feces in men and women after oral exposure. Good agreement of the simulated vs. the observed data.

6.8. Questions:

- The system of equations for the uterus seems unsolvable (equations 16 and 17 in the publication may represent a cyclic system of equations).
- Not clear the toxicokinetic study that served as a basis for the calibration of several parameters (i.e. V_{max}, rates of BPAG elimination, percentage of BPAG eliminated via the bile) in the human model.

6.9. Discussion

- About the $PC_{tissue:\ blood}$ values (cf. document *"PBTK model refinement: parameterization"*.), Teeguarden et al. (2005) indicated: *"The resulting partition coefficients (from Csanady et al., 2002) account for the net affect of processes controlling apparent partitioning (e.g., binding to plasma proteins)"*. That's the reason by which the binding to plasma proteins was not represented in general in the model. Teeguarden et al. (2005) could use the $PC_{liver:\ blood}$ for the liver. For the uterus and the body compartments there were no measured values and the authors applied the $PC_{muscle:\ blood}$. In relation with the specificity of the uterine tissue in the model, Teeguarden et al. (2005) indicated: *"The dose metrics for estrogen receptor occupancy by an ER agonist are likely a more accurate measure for predicting uterine*

responses than are the blood concentrations of the agonist"; *"To properly apply the muscle partition coefficient to the uterus, we must separate the receptor binding and partitioning processes in the model".*

- *"…(1) the concentration of BPA in the blood was divided by 0.83 (rat blood: plasma partition coefficient (Mayersohn, 2003) to calculate the BPA concentration in the plasma…(5) BPAG was assumed not to distribute to red blood cells, so the blood concentrations of BPAG were estimated as the plasma concentration x (1.0-hematocrit). The rat hematocrit was assumed to be 0.45 (Waynford and Flecknell 1992)" (Teeguarden et al., 2005a)*. It does not seem coherent to use different calculations to extrapolate the concentrations from blood to plasma and vice versa depending on the molecular species, especially in this case in which both ways of calculation don't give the same results. The recalculations from blood to plasma (and vice versa) by considering the hematocrit value could be applied for both molecules.
- Comprehensible and clear passage from one sub-model to another by expressing the concentrations of each molecule in nmol g^{-1} instead of ng g^{-1}.
- The values of the parameters related to the saturable metabolism of BPA in the liver (V_{max}, mg h^{-1} $kg^{-0.75}$) and the first-order constant for the enterohepatic reabsorption of the BPAG in the GI tract were extremely different when the model was used to simulate either the IV or the oral routes of exposure in the rat. As the authors discussed: *"The rate constant for enterohepatic recirculation used to fit the i.v. data was much lower than for the oral route data. Although experimental variability cannot be ruled out, it seems unlikely that route differences would be as high as a factor of 7. Instead, it is likely that, like the larger oral route V_{max} for glucuronidation, the difference is attributable to oversimplification of hepatointestinal handling of BPA and BPAG"*. About the V_{max}, the differences in the values of this parameter could be explained by activation or saturation processes. The values of this parameter were 1000 and 5000 respectively in females and males after an oral exposure to 100 mg kg^{-1}, while its value was only 250 after an IV exposure to 10 mg kg^{-1}. Considering the differences in the route of exposure, the value of the rate of uptake in the gastrointestinal tract can influence the estimated values of the V_{max}. The value of this parameter could also be reconsidered, as it was estimated by fitting to experimental data and not on the basis of bibliographic information. Moreover, this rate of uptake was detected during the sensitivity analysis as a parameter with an important influence on the results of the model. This parameter can also have accounted for the differences in the values of the enterohepatic reabsorption of the BPAG in the GI tract. However, while the differences in the V_{max} can be partly explained by saturation or activation processes of the saturable hepatic metabolism, it is difficult to justify the marked differences in the enterohepatic reabsorption constant as this process was represented as first order kinetics.

7. Physiologically Based Pharmacokinetics of Bisphenol A (Shin et al., 2004b)

7.1. Chemical compound(s):

Bisphenol A

7.2. Species and stages:

Rats and 70kg human

7.3. Model structure, main assumptions and processes:

7.3.1. Structure

PBPK model included venous and arterial blood and tissues, such as vein, artery, lung, liver, spleen, kidneys, heart, testes, muscle, brain, adipose tissue, stomach and small intestine. Differential mass balance equations were written for individual tissues; a) for non-eliminating organs (spleen, kidneys, heart, testes, brain, muscle, adipose tissue, stomach and small intestine), b) for an eliminating organ (liver), c) for lungs, d) for blood (vein and artery), e) for lumen and f) for small intestine after oral administration.

7.3.2. Oral exposure

Multiple iv injections to rats and single iv injection (5mg dose) and multiple oral administrations to steady state (100mg doses every 24h) to a 70kg human. An intestinal lumen input was added to the intestinal compartment and an absorption rate constant of 0.0006min^{-1} was used for simulating multiple oral doses.

7.3.3. Distribution

7.3.4. Metabolism

7.3.5. Elimination

7.3.6. Binding

7.4. Parameterisation:

Cf. document “PBTK model refinement: parameterisation”.

7.5. Extrapolation rat to human

The input parameters regarding human PBPK model were found using scaling methods from rat data. The same was also used for predicting time courses of BPA in blood and various other human organs.

7.6. Sensitivity analysis

No sensitivity analysis is presented.

7.7. Assessment, validation

- The hepatic clearance was assumed to be equal to the hepatic blood flow rate, as the urinary excretion and bile flow rates of bisphenol A are minimal.

- Bisphenol A was distributed in the small intestine most extensively, which may be a result of biliary excretion of bisphenol A glucuronide and subsequent hydrolysis followed by absorption of the hydrolysed free bisphenol A across the intestinal membrane.
- Values for CL, V_{ss}, and $t_{1/2}$ predicted for 70-kg human were similar to those predicted by simple allometric scaling.
- Bisphenol A was predicted to be extensively distributed to various body tissues, with tissue levels exceeding serum levels except for muscle and adipose tissue.
- The results for human blood levels were found to be comparable to the corresponding literature ones.

7.8. Questions:

More details would be required for the distribution, metabolism, elimination and binding processes.

7.9. Discussion:

The input parameters regarding human PBPK model were found using scaling methods from rat data. The same was also used for predicting time courses of BPA in blood and various other human organs. So, uncertainty might be present in the estimated values.

- The present PBPK model assumed a certain oral absorption rate constant that was obtained in rats after oral administration. “With this oral dose in rats, a flip-flop occurred between the absorption and elimination rate constants due to a slow gastrointestinal absorption. In case of human exposure to bisphenol A via various routes, the exposure rate may be different from that assumed in the present model. Alternatively, whether a similar flip-flop of the absorption and elimination rate constants occurs at lower exposure rates remains uncertain”: Therefore, caution is needed in interpreting the simulated human data.

8. Development of a physiologically based pharmacokinetic model for assessment of human exposure to bisphenol A (Yang et al., 2015)

8.1. Chemical compound(s):

Bisphenol A

8.2. Species and stages:

Adult rhesus monkeys and adult humans

8.3. Model structure, main assumptions and processes:

8.3.1. Structure

An eight-compartment PBPK model for BPA (serum, liver, fat, gonads, richly perfused tissues, slowly perfused tissues, brain, and skin) and two single-compartment (volume of distribution, V_{body}) sub-models for BPAG and BPAS were constructed. In accordance with the original model (Fisher et al., 2011), the selection of compartments was based on kinetic considerations (e.g. liver) and the model's potential use for internal dose metrics estimation (e.g. brain and gonads). A skin compartment was added for the future assessment of dermal exposure.

8.3.2. Oral exposure

After oral administration, gastric emptying of BPA into the small intestine was described using a first order gastric emptying constant (GEC, L/h/kg−0.25). BPA emptied from the stomach lumen into the small intestine lumen was assumed to be immediately available within enterocytes by passive diffusion, where BPA is either rapidly absorbed into the portal blood supply or subject to glucuronidation in the GI tract, as described in the original monkey BPA PBPK model (Fisher et al., 2011). The oral uptake of BPA from enterocytes into the portal blood supply and the liver was described as a first order process (K1C, L/h/kg−0.25).

8.3.3. Distribution

Uptake of BPAG produced in the small intestine to the liver via the portal vein was described using a first order term (KGIinC, L/h/kg−0.25).

8.3.4. Metabolism

The phase II metabolites, BPA glucuronide (BPAG) and BPA sulfate (BPAS), were simply described as a single non-physiological compartment given that these conjugates display no known estrogenic activity. Based upon in vitro metabolism studies of BPA in the liver, an IVIVE approach was employed to derive model parameters representing hepatic glucuronidation and sulfation of BPA, which were described using Michaelis–Menten equations. The rate of BPAG formation equals to the rate of BPA glucuronidation in the liver and the small intestine. The formation of BPAS was assumed to occur in the liver (Kurebayashi et al., 2010), but not in the small intestine due to the lack of direct empirical evidence.

8.3.5. Elimination

Ten percent of BPAG derived from the small intestine and the liver was assumed to be secreted into the gut through the bile ducts, and undergo enterohepatic recirculation (EHR), whereas the remaining 90% of BPAG formed was taken up into the volume of the distribution (systemic circulation) in the BPAG sub-model. Such an assumption is critical to describe the lingering of serum d_6-BPAG levels, as well as serum d_6-BPA levels, at later time points. With no information to assume otherwise, BPA sulfation was assumed to occur only in the liver and the resulting BPAS

was taken up completely into the systemic circulation. No biliary excretion of BPAS was assumed to occur.

8.3.6. Binding

No binding information

8.4. Parameterisation:

Cf. document “PBTK model refinement: parameterisation”.

8.5. Extrapolation monkeys to human

The input parameters of the model for human were those used in the original model, obtained in adult rats.

8.6. Sensitivity analysis

A local sensitivity analysis was implemented to assess the impact of model parameter perturbations on the model output, i.e. model predicted serum BPA concentrations, as a function of time. A single oral dose of 100 µg/kg of d_6-BPA was simulated for adult humans. The normalised sensitivity coefficient (NSC) was calculated according to Clewell (1994). A positive NSC suggests a direct correlation between the model output and the corresponding parameter, while a negative NSC indicates the model output is inversely associated with the specific parameter. Parameters with maximum absolute NSC values over a 24 h period exceeding 0.1 were considered to be sensitive. A NSC value of 1 indicates that the changes in the model parameter and the model output display a 1 to 1 relationship. Those parameters with maximum absolute NSC values greater than 1 were considered to have a high impact on model output.

8.7. Assessment, validation

The mean relative deviation (MRD) and the average fold error (AFE) were calculated to provide a measurement of prediction precision and bias with equal value to under- and over-predictions and to assess model performance. The data sets used for model calibration were taken from a recent clinical study, in which six adult men and eight adult women were given a single oral dose of 100 µg/kg d_6-BPA via a vanilla wafer cookie after overnight fasting (referred to as cookie data). The use of stable isotope labeled BPA circumvented potential contamination from the laboratory environment and BPA-containing materials encountered during sampling and analysis. After dosing, blood samples (total 29 time points) were collected over a period of 72 h and serum was separated. In addition, all urine specimens voided during the course of blood collections were also collected, for which the time and the volume of each micturition were recorded. Urinary excretion data, along with the serum concentration profiles collected from the first round of dosing, in three subjects, 1 male and 2 females, were used for model evaluation. In addition, other three pharmacokinetic studies with BPA in adult humans were used for model evaluation.

8.8. Questions:

The only modification of the original model was the addition of the skin compartment? How about the rat input data, which were used as inputs? Isn’t there any difference regarding data for humans? Was calibration only done with pharmacokinetic data regarding serum concentration and urinary excretion only for kinetic datasets providing empirical evidence for the determination of BPA model parameters? How about the other parameters of PBPK model?

8.9. Discussion:

- Very detailed and comprehensive work. Description in detail for every process covered by the model. Validation of the model with experimental data.
- Assumptions for processes that we don't know they exist, i.e. biliary excretion of BPAG, may decrease the power of the model.

9. Predicting plasma concentrations of bisphenol A in children younger than 2 years of age after typical feeding schedules, using a Physiologically Based Toxicokinetic Model (Edginton and Ritter, 2009a)

9.1. Chemical compound(s):

Bisphenol A

9.2. Species and stages:

Children younger than 2 years old (developing a model for an average 30-year-old male of 73kg and 176cm and making the necessary modifications)

9.3. Model structure, main assumptions and processes:

9.3.1. Structure

A nested coupled PBTK structure was used consisting of a BPA submodel coupled to a BPA-Glu submodel. The model included 15 organs as well as arterial, venous, and portal blood compartments. The organs were connected via blood flows, and the circulation system is closed via the lung.

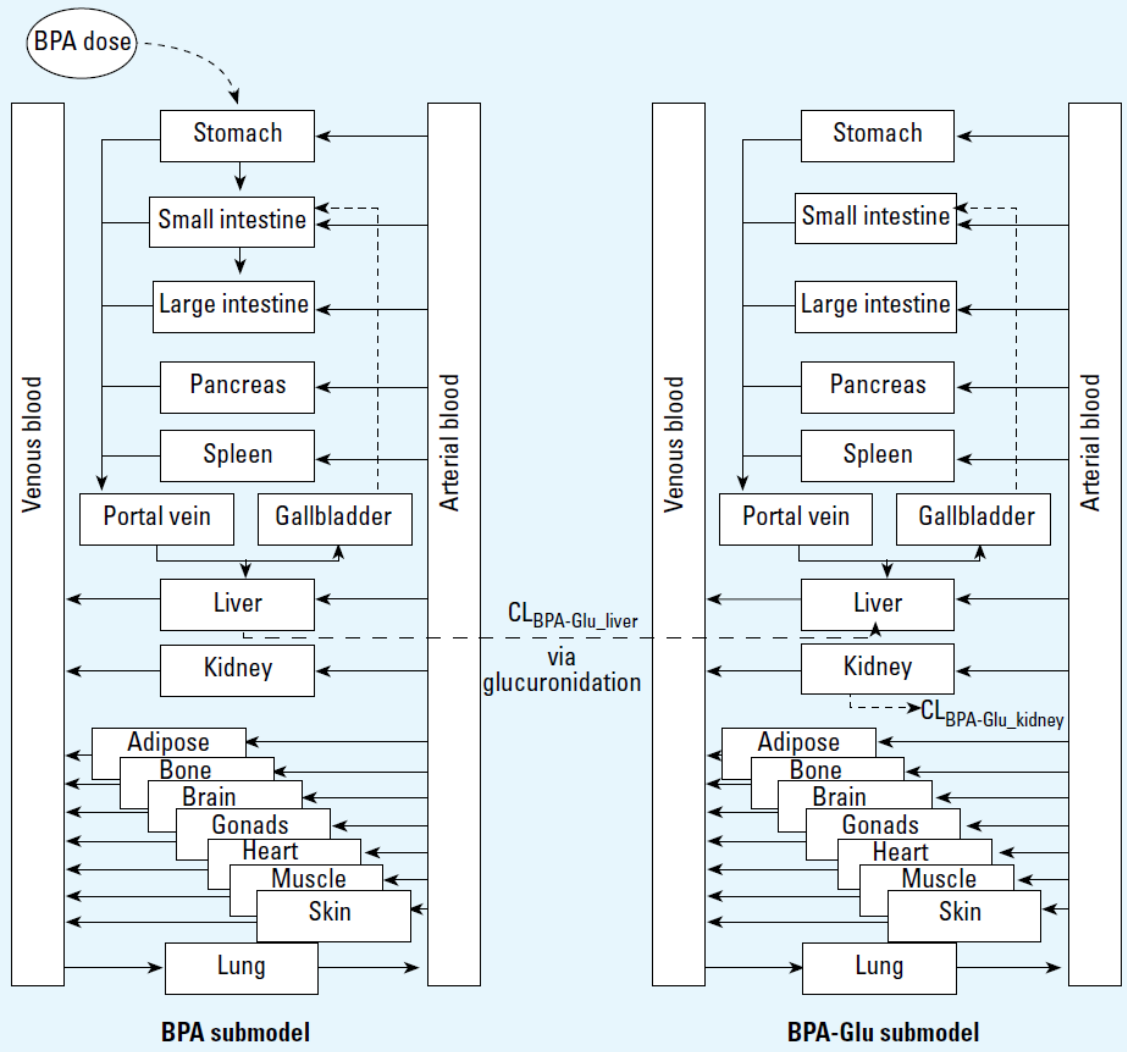

Figure 3: BPA and BPA-glu model structure

9.3.2. Oral exposure

The oral absorption model is that of Willmann et al. (Willmann et al., 2003b; Willmann et al., 2004b), and this model provided BPA input to the portal vein. Scaling the gastrointestinal parameters of gastrointestinal geometry, gastric emptying time, intestinal permeability, gastric and intestinal pH, small intestinal transit time, and intestinal surface area to children between 0 and 2 years of age was considered.

9.3.3. Distribution

The distribution of BPA through the human tissues was described using issue/blood partitioning.

9.3.4. Metabolism

100% of the elimination of BPA was attributable to metabolism to its glucuronidated metabolite, BPA-Glu. UGT2B7 the enzyme was considered responsible for BPA glucuronidation. The intrinsic clearance of BPA to BPA‑Glu from adults to children was scaled. UGT2B7 activity in term neonates is only 5% that of adults, increases to 30% by 3 months of age, and reaches adult levels by 1 year of age.

9.3.5. Elimination

100% of the elimination of BPA was attributable to metabolism to its glucuronidated metabolite, BPA-Glu. Urinary excretion is 100% responsible for BPA-Glu clearance in humans. Allometric relationships formed the basis for scaling the age-dependence of $CL_{BPA\text{-}glu}$.

9.3.6. Binding

The enzyme UGT2B7 was considered responsible for BPA glucuronidation and hepatic clearance, where newborns had only 5% of the enzymatic activity of the adult liver.

9.4. Parameterisation:

Cf. document “PBTK model refinement: parameterization”.

9.5. Extrapolation rat to human

The algorithms for the calculation of tissue/blood partitioning (Rodgers et al., 2005; Rodgers and Rowland, 2006) were modified with respect to a) the interplay between neutral lipids and extracellular water and b) the interplay between the volume fraction neutral lipids and extracellular water in order to be applied to children.

9.6. Sensitivity analysis

The average steady-state plasma concentration was the outcome of sensitivity analysis. Its simplest form was used where an input parameter value is changed by 1% and the relative change in outcome is calculated when all other input parameters are fixed. Sensitivity analysis was used to assess the variation of both BPA and BPA-Glu organ/tissue volumes, organ blood flows, hematocrit, fu, organ/plasma partition coefficients, red blood cell partition coefficient, red blood cell permeability, organ Permeability x surface area (PS), organ-specific PSrbc, intrinsic hepatic clearance of BPA, and intrinsic kidney clearance of BPA-Glu on average steady-state plasma concentration of both BPA and BPA-Glu.

9.7. Assessment, validation

A whole-body PBTK model previously used for scaling drug pharmacokinetics from adults to children (Edginton et al., 2006b) was implemented. This model has been shown to be physiologically consistent in adults and in children down to newborns. Some examples of this consistency include the following: sum of blood flows = cardiac output; sum of splanchnic organs =

portal vein flow; total body water, lipid, and protein is age dependent and consistent with the literature; and addition of blood pool volumes and vascular volume for each organ = total blood content.

9.8. Questions:

9.9. Discussion:

- The clearance scaling method is built on average in vitro activity levels and is not conservative in predicting plasma concentrations in the most developmentally delayed pediatric liver.
- Only local sensitivity analysis was performed, so any significant parameter correlations would not be revealed using this method.
- The need to determine adult BPA clearance with certainty is revealed, given the relative importance of this parameter on the outcome of the model.
- More studies needed on urinary concentrations of BPA regarding children in order direct validation of PBPK model in young children to be performed. Once acceptance and/or modification of the model is completed, we can extrapolate among ages, doses, and disease states as well as estimate tissue loads with greater confidence.
- Age-dependent differences may be substantial but cannot be absolutely quantified because of a need for both clearer understanding of the in-situ hepatic intrinsic BPA clearance in the adult and urinary concentrations in children < 6 years of age to define daily BPA intake.
- It is apparent from this modeling study that newborns with less than average glucuronidation capacity may not be adequately considered based on a factor of 10 to account for human variability in BPA toxicokinetics.

10. Integrated exposure and risk characterisation of bisphenol-A in Europe (Sarigiannis et al., 2016b)

10.1. Chemical compound(s):

Bisphenol A

10.2. Species and stages:

Humans

10.3. Model structure, main assumptions and processes:

10.3.1. Structure

A generic PBTK model that captures satisfactorily life stage changes and physiological and metabolic efficiency change over an individual's lifetime (from conception till 80 years of age) was developed in INTEGRA and was used in this study. All major human organs are included, as well as arterial, venous, and portal blood compartments.

10.3.2. Oral and other routes of exposure

The model includes also a detailed description for the three main routes of exposure; oral, inhalation and dermal. Inhalation takes into account absorption of gases and deposition fractions of particles across the different human respiratory tract regions based on particles size distribution. Absorption through the oral route is governed by the absorption rates of stomach and intestine. To better describe dermal absorption, skin has been modeled as a two layer structure, including stratum corneum that has been described as a “bricks and mortar” structure and viable epidermis. Exposure is explicitly described for each pathway and route of exposure, taking into account all the age and gender exposure modifiers, such as activity based inhalation rate, dietary patterns and intake rates per food item, amount of soil and dust ingested or hand-to-mouth behavior. For estimating the total amount of BPA that the infant is orally exposed, the sum of free BPA and BPAglu needs to be taken into account, since all conjugated BPA is cleaved in the gastrointestinal tract.

10.3.3. Distribution

In each tissue three mass balance equations are written, for (a) red blood cells, (b) plasma and interstitial tissue and (c) cells, allowing the application of the model to both flow limited, as well as membrane-limited compounds. Specific organs were further divided in sub-compartments: liver is divided in up to 5 compartments so as to better describe the distribution of enzymes, and brain is divided in four sub-compartments, namely, main brain, globus palidus, cerebellum and pituitary, so as to better describe the permeability differences among the different brain regions.

10.3.4. Metabolism

Xenobiotics and their metabolites are linked through the metabolising tissues. This is mainly the liver, but also other sites of metabolism might be considered (intestine, brain, skin, placenta) based on the presence or not of the enzymes involved in the metabolism of the compound of interest. The main detoxification pathway of BPA is phase II glucuronidation (and sulfation at early developmental stages). Thus, in this model, the parent compound (BPA) and one metabolite (BPA-Glu and BPA-Sulf for fetus and early infancy) was taken into account. Glucuronidation and sulfation capacities throughout the several developmental stages are critical parameters of the BPA toxicokinetic model.

10.3.5. Elimination

Through lactation, besides free BPA, BPA-glu is also excreted. The elimination of BPA-glu for humans was carried out only via urine.

10.3.6. Binding

BPA is strongly bound to red blood cells and plasma proteins.

10.4. Parameterisation:

Cf. document “PBTK model refinement: parameterisation”.

10.5. Sensitivity analysis

Global sensitivity analysis was performed on the model.

10.6. Assessment, validation

The conservative nature of the bottom-up intake calculation is verified by estimating intake from real-life HBM data. The use of internal dosimetry coupled to the exposure reconstruction algorithm allowed the calculation of external and subsequently internal dose starting from the available HBM data.

10.7. Questions:

10.8. Discussion:

- The values of the upper part of the intake distributions (95%, max) are the result of the highest food residues identified in some studies from the literature review. These values do not significantly affect the mean of the food residue distribution, yet they result in significant deviation from the mean in the overall distribution. In practice, it is very unlikely that someone consumes only canned food and beverages.
- Health risks might be underestimated for specific population groups (e.g. neonates and infants) if the assessment does not take into account variability in internal exposure due to genetic, physiological and developmental factors.

11. The development of a pregnancy PBPK Model for Bisphenol A and its evaluation with the available biomonitoring data (Sharma et al., 2018a)

11.1. Chemical compound(s):

Bisphenol A

11.2. Species and stages:

Adult human, pregnant mother and fetus

11.3. Model structure, main assumptions and processes:

11.3.1. Structure

The basic structure of the P-PBPK model has been adapted from an adult model, which included plasma, liver, kidneys, fat, brain, skin and a rest of the body compartment for the remaining tissues. The placenta and the fetus compartments were added into the model. The fetus compartment is further extended to fetus sub-model considering liver, kidney, brain, amniotic fluid and plasma as fetus sub-compartments. The dynamic physiological parameters for the pregnant mother that changes during the gestational period such as plasma volume, hematocrit percentage, the fetus and the placental growth were accounted for the development of P-PBPK model. The physiological and metabolic parameters were applied for the fetus model as dynamic parameters of gestational period and chemical-specific parameters such as partition coefficient were kept similar to the adult human model in the case of both Mother and fetus organs. The placental-fetal unit assumes a bidirectional transfer process describing BPA and BPA-G transfer between mother placenta to fetus plasma and vice versa. The transfer rate was assumed as a simple diffusion process. The elimination of BPA in the mother was assumed to be similar to adult human, which occurs via its rapid metabolism in the liver and intestine, subsequently excreted via urine. However, the clearance of BPA and its conjugates in the fetus was described with first order transfer rate from fetus plasma to mother plasma via the placenta.

11.3.2. Oral and other routes of exposure

Both oral and dermal routes of exposure was considered for this model. BPA and BPAG uptake from the gut to the system was described by first order reaction, considering gastric emptying delay for BPA arrival to the gut. The oral absorption rate of the BPA was optimised against the Thayer et al. (2015) data. The data on uptake of BPAG from the intestine to the liver was taken from the previous study of Yang et al. (2015). Reported permeability coefficient data for the adult model provided by Mielke et al. (2011) was used to develop the P-PBPK model.

11.3.3. Distribution

The partition coefficient (PC) for liver, fat, brain, and skin were taken from the study done by Fisher et al., (2011). The placental and kidney partition coefficient for BPA were taken from Csanády et al. (2002). BPAG was distributed to maternal placenta using placenta partition coefficient taken from the previous mice study (Kawamoto et al., 2007). For other fetus compartments, partition coefficients were kept similar to as mother's organs partition coefficients

11.3.4. Metabolism

Metabolism in pregnancy was introduced via scaling of the in-vitro Vmax for glucuronidation and sulfation, considering the pre-pregnancy body weight. The BPA metabolism data for the fetus was scaled using human in-vitro data and fetus microsomal protein content, and, growing fetus liver

and body weight. Two metabolic kinetic parameters namely Vmax (maximum rate of reaction) and Km (affinity of the substrate for the enzyme), for mother and fetus, is taken from in-vitro studies and has been scaled to in-vivo. The current hepatic in-vitro cell line data were used for deriving maximum reaction velocity (Coughlin et al., 2012b). Similar to adult's scaling, the metabolism in the fetus liver was directly scaled from the in vitro hepatocyte data, considering the developmental changes in the fetus such as fetus liver volume and its microsomal content. Though there is a lack of glucuronidase data specific to the fetus deconjugation, presuming deconjugation process as an important toxicokinetic process, in the present P-PBPK model it was taken into account for the fetus compartment. The assumption has made that deconjugation of the BPAG to BPA was based on first-order rate transfer constant. The half-life of the chemicals is used to establish the rate of deconjugation estimated to be 0.35 hr-1 (k = 0.693/t1/2). The same value is used in the case of both placental and fetus deconjugation. To maintain the cyclic deconjugation and conjugation reaction into the model, the available free BPA undergoes simultaneously for glucuronidation into the liver following distribution to the liver compartment to mimic the real biological phenomena.

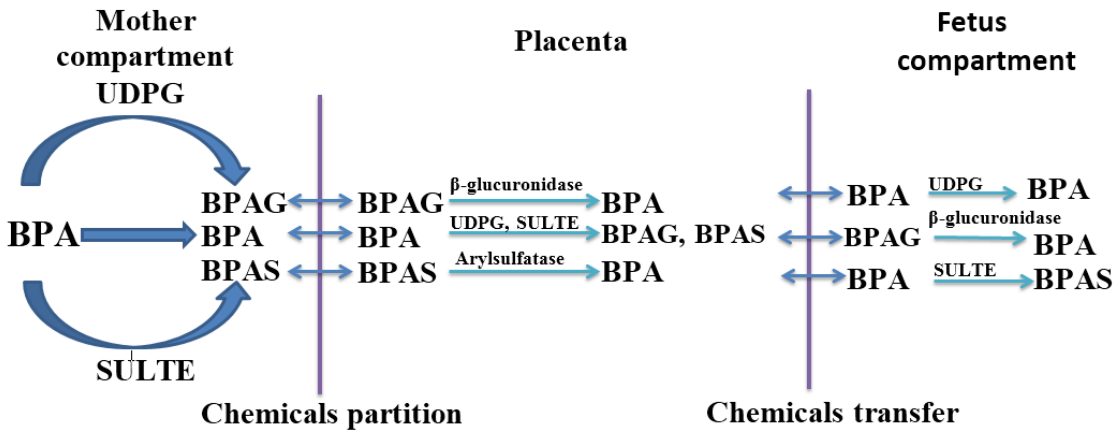

Figure 4: BPA Metabolic kinetics in the pregnant woman

11.3.5. Elimination

The elimination of BPA in the mother was assumed to be similar to adult human, which occurs via its rapid metabolism in the liver and intestine, subsequently excreted via urine. However, the clearance of BPA and its conjugates in the fetus was described with first order transfer rate from fetus plasma to mother plasma via the placenta.

11.3.6. Binding

BPA is strongly bound to red blood cells and plasma proteins.

11.4. Parameterisation:

Cf. document "PBTK model refinement: parameterisation".

11.5. Sensitivity analysis

No sensitivity analysis

11.6. Assessment, validation

Validation of the developed adult PBPK model was performed by comparing the model predictions with plasma data obtained from the human study by Thayer et al., (2015) in which volunteers were orally administered 100 µg/kg BW dose of deuterated BPA. These predictions were performed by taking into account only female volunteers, and their individual BMI and body weight. The exposure dose was normalised according to body weight and the fat content of individual volunteers was

calculated based on body weight and BMI of the respective subject. Out of 14 subjects (male and female), only 7 female subjects were considered from Thayer's study and simulated time-plasma BPA data profile were validated against their observed data. The observed concentration in different cohorts during pregnancy was used for P-PBPK model evaluation. For instance, maternal blood concentration during pregnancy or at the delivery time was used for exposure estimation. Five biomonitoring cohort data on fetus plasma, liver, mother placenta and amniotic fluid are used for model calibration and evaluation purpose.

11.7. Questions:

11.8. Discussion:

- Detail metabolic toxicokinetics in mother and fetus was reviewed and included in the proposed model. Glucuronidation and deglucuronidation in both mother and fetus liver and placenta are found to be an important mechanism that alters BPA toxicokinetic profile.
- For the development of the model, a two-stage approach was employed: first the development and validation of the adult PBPK model against the kinetic data from control human experimental study and second extension of the adult model to the P-PBPK model and further evaluation with the available BPA biomonitoring cohort studies. The prediction of higher concentration of BPA during the mid-gestational period in the amniotic fluid, placenta, and the fetus liver are in accordance with biomonitoring data, indicating mid-gestational period might be the critical window of exposure for the fetus.
- This study considered two extreme dose scenarios (min-max) for the simulation and in turn plotting of simulated data under the box plot to capture all the data set that allows comparing with biomonitoring data.
- There are several data gaps identified, which need to be addressed to improve the model. For example, kinetics of BPA glucuronidation/sulfation and deglucoronidation/desulfation at the fetus level, and placental BPA conjugation and deconjugation, and metabolic variation due to functional polymorphism among the different population, are some of the major concern.
- In order to address the issue of temporal variation of short life chemical, there is a need to have very control case studies dealing with the timing of exposure (food intake) and schedule of sampling.

Cadmium

12. A Kinetic Model of Cadmium Metabolism in the Human Being (Kjellström and Nordberg, 1978)

12.1. Chemical compound(s):

Cadmium

12.2. Species and stages:

Humans

12.3. Model structure, main assumptions and processes:

12.3.1. Structure

The model included the exogenous compartments of lung and intestines, liver, kidney and the endogenous compartment of other tissues.

12.3.2. Oral exposure

The first part of the model followed the generally accepted principles: Cadmium compounds are inhaled as particulate matter. They are deposited in the nasopharyngeal, the tracheobronchial, and/or the pulmonary (=alveolar) compartment in different proportions, depending on particle size and respiratory characteristics. Particles with a mass median aerodynamic diameter (MMAD) of 5 um were estimated to be deposited mainly in the nasopharyngeal compartment (75%) and less in the alveolar (20%) and tracheobronchial compartments (5%). Smaller particles (MMAD = 0.05 um) are, on the other hand, deposited mainly in the alveolar compartment (55%) with 10% in the trachea bronchial compartment and nothing in the nasopharyngeal compartment. The remaining proportions of 5 and 35% are exhaled. The particles deposited in the nasopharyngeal and tracheobronchial compartments are transported with mucociliary clearance to the pharynx. They may then be swallowed. spat out, or, in the case of nasal deposition, may be blown out in a handkerchief. The model was applied to two cases of cadmium exposure through inhalation: smoking and work in a battery factory. Cadmium in cigarette smoke was assumed to be in the form of cadmium oxide fumes with a very small MMAD, whereas the cadmium oxide dust in the factory had a larger MMAD but was still mainly less than 5 um.

12.3.3. Distribution

Upon administration of varying doses of cadmium to experimental animals and humans, the larger the dose, the larger proportion of the dose will be found in the liver. A certain proportion of plasma cadmium may be bound to metallothionein. When such is the case, a very quick transfer of cadmium to the kidney will occur. Whether there is a difference in cadmium distribution in the body depending on the absorption by alveolar capillary or portal blood is not known. In the model, no difference was assumed. Mechanisms effectuating a dose dependence of distribution between liver and kidney have been introduced. Fractions of the total amount available to blood thus go into different blood compartments. After long-term low-level exposure, about one third of body burden is in the kidneys**.**

12.3.4. Metabolism

From a one-compartment metabolic model, the half-time of cadmium in human liver had been estimated to be about 7 years.

12.3.5. Elimination

The major cadmium excretion routes are via feces and urine. The non-absorbed part of ingested cadmium will occur in feces as well as the “true” fecal excretion. The excretion in urine was only dependent on body burden, but the excretion rate was a function of the dose. At the lowest daily dose, the urinary excretion was about 0.007% of body burden. Other excretion routes are not likely to contribute significantly to total excretion. For the modeling procedure, it was assumed that a certain proportion of cadmium in blood (Bl) was excreted via the intestinal walls to the feces. Furthermore, a proportion of cadmium in liver was assumed to be excreted via bile to the feces. The half-time in kidney has been estimated to be about twice as long as in the liver. It was assumed that the “other tissue” compartment would have a relatively long half-time and we would fit the coefficients of the model so that about half of body burden would be in this compartment in older age groups (>40 years).

12.3.6. Binding

In human beings and horses exposed only to background concentrations of cadmium in the environment, a larger proportion of body cadmium was found in the kidneys bound to metallothionein. Two forms of metallothionein have been isolated, which may behave differently regarding their relative accumulation and urinary excretion. Cadmium in blood cells is in large part bound to a protein with the same size as metallothionein and is not readily exchangeable with plasma cadmium.

12.4. Parameterisation:

Cf. document “PBTK model refinement: parameterisation”.

12.5. Extrapolation to human

The inputs were found by empirical considerations.

12.6. Sensitivity analysis

To see the stability of the estimates from the model, a series of calculations with different coefficient values than the optimum set was performed. The coefficients were, one at a time, decreased or increased 10%.

12.7. Assessment, validation

The results were validated using empirical and literature data on cadmium concentrations in Japanese and Swedish people.

12.8. Questions:

What happens in the endogenous compartments of the model? The processes that occur in kidney and liver are described, but not in the other tissues.

12.9. Discussion:

- The first attempt to tie together accumulation in major compartments such as liver and kidney with concentrations in blood and urine.
- “The formulation of the present model involved a series of assumptions, some of which were not firmly based on empirical data”. More research needed to improve the model, for example kinetics of cadmium metabolism.
- Improvement of the model to cover all exposure situations (not applicable for extremely high exposures).
- Reliable input parameters and interindividual variations in exposure should be considered.

13. PBPK and population modelling to interpret urine cadmium concentrations of the French population (Bechaux et al., 2014)

13.1. Chemical compound(s):

Cadmium

13.2. Species and stages:

Humans

13.3. Model structure, main assumptions and processes:

13.3.1. Structure

The model proposed by Kjellström et al. (1978) was used, which considers two intake routes: inhalation and oral, amount and flow between 8 compartments: lung, intestine, 3 blood compartments (plasma, erythrocytes and metallothionein), liver, kidney and other tissues and two excretion routes: feces and urine. A Bayesian population model was applied to link external exposure to internal dose provided by the urinary concentrations data.

13.3.2. Oral exposure

See section 12.3.2

13.3.3. Distribution

See section 12.3.3

13.3.4. Metabolism

See section 12.3.4

13.3.5. Elimination

See section 12.3.5

13.3.6. Binding

See section 12.3.6

13.4. Parameterisation:

Cf. document “PBTK model refinement: parameterisation”.

13.5. Extrapolation to human

The inputs were found by empirical considerations.

13.6. Sensitivity analysis

Sensitivity analysis was not presented.

13.7. Assessment, validation

A Bayesian population model was applied to link external exposure of French population from the internal dose provided by the urinary concentrations. A function λ was introduced, which was characterised by a vector of parameters β and corrects the dietary intakes according to the date the occurred. Two different models were tested; one simple with 3 parameters and one more complicated with 4 parameters. From the two developed models, the model selection was performed by calculating the Root Mean Square Error of Prediction (RMSEP) of each model as follow: the data set is randomly divided into 3 subsets respecting the proportion of individuals in

each age class. Then the model was fitted from two-thirds of the data set and the RMSEP was calculated on the remaining third. This procedure was repeated three times and the mean of the RMSEP for both models was compared. The model was validated using the concentrations of cadmium measured for 1900 adults between 18 and 75 years in 2006-2007 (ENNS study) (Castetbon et al., 2009) and past exposures in 1992, 1998 and 2000.

13.8. Questions:

More detailed description of the PBPK model proposed by Kjellström et al. (1978).

13.9. Discussion:

- Inter-individual variability regarding the impact of gender was taken into account in PBPK modeling by using triangular distributions instead of single input values.
- Age-dependent variability was only considered by modifying the body weight and the renal function with the age.
- Changes in exposure were also considered through Bayesian method and a scaling function λ that corrected the dietary intakes according to the date they occurred.
- Contamination (smoking) and food consumption data were used for the implementation of the model.
- The model for estimating the urinary concentration in cadmium in 2030 considers stable dietary exposure and no trend in exposure from tobacco smoke. It would be better to consider both dietary exposure and exposure from smoking.
- Other sources of exposure (e.g. house dust) could also be considered.

14. Physiologically based pharmacokinetic (PBPK) tool kit for environmental pollutants - metals (Ruiz et al., 2010a)

14.1. Chemical compound(s):

Cadmium

14.2. Species and stages:

Humans

14.3. Model structure, main assumptions and processes:

14.3.1. Structure

The developed model was based on the model proposed by Kjellström (1978), but with some modifications regarding the intercompartmental transfer of Cd and the growth algorithms for males and females and corresponding organ weights which are used to calculate age-specific Cd concentrations. The model describes aggregated lung, liver, kidney, blood, and other tissues.

14.3.2. Inhalation and oral exposure

The model simulated two routes of exposure; inhalation and oral, either individually or simultaneously. For inhalation exposures, the model accounts for different deposition patterns for different size particles in nasopharyngeal, tracheobronchial, and alveolar regions of the respiratory tract, and for the oral route of exposure, Cd may enter the GI tract via food or water contaminated with Cd, or as Cd particles embedded in mucus from the respiratory tract via the mucociliary/tracheobronchial escalator. Oral exposure can result from diet, soil, or water.

14.3.3. Distribution

Intake by oral and inhalation routes are transferred to an uptake pool that distributes to three blood compartments. Cd can accumulate in the kidneys and is excreted through the urine; Cd can also accumulate in the liver, likely via biliary secretion, and is excreted through the feces.

14.3.4. Metabolism

See section 12.3.4

14.3.5. Elimination

Elimination of Cd through urine and feces.

14.3.6. Binding

See section 12.3.6

14.4. Parameterisation:

Cf. document “PBTK model refinement: parameterisation”.

14.5. Extrapolation to human

The inputs were found by empirical considerations.

14.6. Sensitivity analysis

Good modelling practice requires an evaluation of the confidence in the model; the robustness of the models was studied using sensitivity analysis. This analysis shows the strength and relevance of the inputs in determining the variation in the output. Sensitivity analysis of the re-coded models was performed using the sensitivity ratio (SR) approach (Morgan et al., 1992). A positive SR indicates that an increase in the input value results in an increase in the concentration value. A

negative SR indicates the opposite effect. High values for the SR (positive or negative) indicate high sensitivity of the model to that variable. A range sensitivity analysis was performed; variables were varied over a range of a factor of +/-2 from nominal. Individual model variables were varied over the same relative range and the resulting changes in the model outputs were recorded.

14.7. Assessment, validation

The performance of the model was evaluated by calculating a value for percent median absolute performance error (MAPE %) based on estimates of performance error (PE) (El-Masri and Kenyon, 2008). The accuracy of the prediction was measured by root median-square performance error. The model was validated by comparing simulations to other published model simulations and to human data sets. Specifically, the Cd model was validated using biomonitoring data on US urinary excretion levels from the Fourth National Report on Human Exposure to Environmental Chemicals.

14.8. Questions:

More details regarding the modifications made in the developed model (gender and age dependent) for Cd.

14.9. Discussion:

- Age related kidney degeneration, decrease in exposure to Cd as a function of lifestyle and time and the influence of essential nutrients, such as iron, cadmium and zinc, as well as uncertainties in pharmacokinetic parameters should be thoroughly considered.
- All routes, time periods and circumstances of exposure should have been validated.

Chromium (VI)

15. A Physiologically Based Model for the Ingestion of Chromium (III) and Chromium (VI) by humans (O'Flaherty et al., 2001)

15.1. Chemical compound(s):

Chromium (III), Chromium (VI)

15.2. Species and stages:

Humans

15.3. Model structure, main assumptions and processes:

15.3.1. Structure

The developed model was based on the existing physiologically based model of human body and bone growth (O'Flaherty, 1993) and an existing PBPK model of chromium kinetics in rats (O'Flaherty, 1996). The adaptations included differential absorption of Cr(VI) and Cr(III), rapid reduction of Cr(VI) and Cr(III) in all body tissues and fluids, modest incorporation of chromium into bone and concentration dependent urinary clearance. The model did not include a physiologic lung compartment but it can be used to estimate the upper limit on pulmonary absorption of inhaled chromium. The model did not consider uptake through the skin.

15.3.2. Oral exposure

Humans were orally exposed to chromium(VI) and chromium(III) salts present in the diet and in drinking water.

15.3.3. Distribution

Appearance of both Cr(III) and Cr(VI) in the blood is so rapid that it is apparent both must be absorbed from the stomach. Both are absorbed from the intestine. Accordingly, the first-order rate constant for passage beyond the gastrointestinal absorption region is set at 14/day.

15.3.4. Metabolism

Clearance of ultra-filterable chromium increases with increasing body burden suggests the possible operation of a capacity-limited renal reabsorption process.

15.3.5. Elimination

Chromium has been observed to be excreted in the bile and across the wall of the gastrointestinal tract after intravenous administration of either Cr(VI) and Cr(III). There is no evidence to suggest that extra urinary excretion is significant under more natural exposure conditions. Although a pathway for urinary excretion of Cr(VI) is included in the present model, it is essentially inoperative due to the rapidity of reduction of Cr(VI) to Cr(III).

15.3.6. Binding

Once in the blood, Cr(VI), rapidly taken up into the red cell as the chromate anion by the non-specific anion carrier pathway, is rapidly reduced by glutathione and hemoglobin.

15.4. Parameterisation:

Cf. document “PBTK model refinement: parameterisation”.

15.5. Extrapolation to human

15.6. Sensitivity analysis

Sensitivity analysis was not presented.

15.7. Assessment, validation

The model was calibrated against blood and urine chromium concentration data from a group of controlled studies in which adult human volunteers drank solutions generally containing up to 10mg/day of soluble inorganic salts of either Cr(III) or Cr(VI) (Finley et al., 1997b; Kerger et al., 1996; Paustenbach et al., 1999).

15.8. Questions:

Would the addition of lung compartment change the results obtained from the PBPK model?

15.9. Discussion:

- Insufficient data exists regarding the description of the lung compartment.
- Inspection of the model structure, parameterisation and predicted behaviors revealed that it would not be easily modified to reflect the key processes identified for assessing Cr toxicokinetics in GI compartments.

16. Physiologically based pharmacokinetic model for humans orally exposed to chromium (Kirman et al., 2013)

16.1. Chemical compound(s):

Chromium (III), Chromium (VI)

16.2. Species and stages:

Humans

16.3. Model structure, main assumptions and processes:

16.3.1. Structure

The human PBPK model was adapted from the rodent PBPK model proposed by Kirman et al. (2012) to describe the key toxicokinetic processes. Compartments were included for gastrointestinal lumen, oral mucosa, stomach, small intestinal tissue, blood, liver, kidney, bone and a combined compartment for remaining tissues. The following changes were made to adapt the model code for fitting human data sets: (1) code was added to allow for multiple bolus exposure events per day to accommodate the exposure regimens implemented by some human studies; (2) two model parameters were added to permit scaling of systemic tissue uptake and release rate constants from mice to help ensure consistency in the liver/kidney Cr concentration ratios; (3) because the human data were generally collected at doses much lower than those assessed in rodents, absorption was modeled in humans as a first order process (i.e., a single model parameter equivalent to Vmax/km); (4) compartments for duodenum, jejunum, and ileum were lumped into a single compartment for the small intestines in the human model since section-specific data were not available in humans to estimate Cr uptake; and (5) the oral cavity compartment was removed from the model since there are no human data available for the oral cavity.

16.3.2. Oral exposure

Humans are mainly exposed to Cr(VI) through drinking water. The toxicokinetics of Cr(VI) in the upper gastrointestinal tract of humans are important for assessing internal tissue dose in risk assessment. Fasted human stomach fluid was collected and ex vivo Cr(VI) reduction studies were conducted and used to characterise reduction of Cr(VI) in human stomach fluid as a mixed second-order, pH-dependent process.

16.3.3. Distribution

The distribution of Cr(III) from plasma to tissues is largely determined by its binding to transport proteins, which may help to explain how plasma chromium levels remain relatively low despite much higher concentrations in mammalian tissues. Cr(VI) reaching the stomach becomes mixed with saliva, gastric fluid, food, and water, and while in the lumen of the stomach and small intestines, is subject to three competing processes: (1) transit through the GI lumen sections; (2) reduction to Cr(III); and (3) uptake/absorption into GI tissue. Chromium absorption is expected to occur primarily within the small intestine. Based on rodent studies [16], the rate of uptake of chromium from the GI lumen is greatest in the duodenum, and lower in jejunum and ileum. Cr(VI) that reaches portal plasma is subject to several competing processes: (1) reduction to Cr(III); (2) uptake into erythrocytes; and (3) transit to the liver and systemic tissues

16.3.4. Metabolism

Time-course data for chromium in plasma following Cr(VI) exposure provide useful information on the systemic clearance of Cr(III) from plasma, since systemic levels largely reflect Cr(VI) that has been reduced to Cr(III) in the GI tract and portal system.

16.3.5. Elimination

The reduction of Cr(VI) has been described as a pH-dependent process. With respect to pH, a longitudinal gradient is present within the lumen of the stomach and small intestines with stomach << duodenum < jejunum < ileum. Within the GI tissue, Cr(VI) is subject to further reduction, while both forms of chromium may be absorbed into portal plasma, or returned to the GI lumen with sloughed cells. The majority of chromium in the GI lumen remains unabsorbed and is excreted in feces. Biliary excretion of chromium is expected to be negligible.

16.3.6. Binding

Transferrin, a protein that is important for delivery of iron to tissues, possesses two binding sites, one of which has a high affinity for Cr(III) (i.e., Cr(III) will displace iron at neutral pH), and therefore is expected to play a role in the delivery of Cr(III) from the GI tract to tissues. A low-molecular weight protein that is capable of tightly binding Cr(III) has been detected in a number of mammalian tissues and may play a role in transport from tissues to kidney and its ultimate excretion in urine.

16.4. Parameterisation:

Cf. document “PBTK model refinement: parameterisation”.

16.5. Extrapolation rat to human

The majority of model parameters were obtained by adjusting their values to obtain model predictions that fit available human data sets based upon visual and statistical optimisation.

16.6. Sensitivity analysis

A sensitivity analysis was conducted for the human model by increasing individual model parameter values one at a time by 5% over their default values for a defined exposure simulation (exposure to 0.05 mg/kg spread over 5 equal bolus exposure events per day) and noting the percent change in value predicted by the model for several internal dose measures.

16.7. Assessment, validation

For the purposes of model validation, model predictions were compared to a literature data set (Finley et al., 1997b) held back from model parameterisation.

16.8. Questions:

16.9. Discussion:

- Important differences between rodents and humans are explained.
- Fitting data for individuals provide greater insight on individual variability.
- Additional data for Cr(VI) reduction would help to inform key assumptions made for the development of the PBPK model.

Phthalates

17. Using exposure prediction tools to link exposure and dosimetry for risk based decisions: A case study with phthalates (Moreau et al., 2017)

17.1. Chemical compound(s):

DEHP and DnBP

17.2. Species and stages:

Humans

17.3. Model structure, main assumptions and processes:

17.3.1. Structure

The most recent phthalate model, developed by Clewell et al. (2008) for DBP has been modified to be applicable to DEHP and has been extended to human.

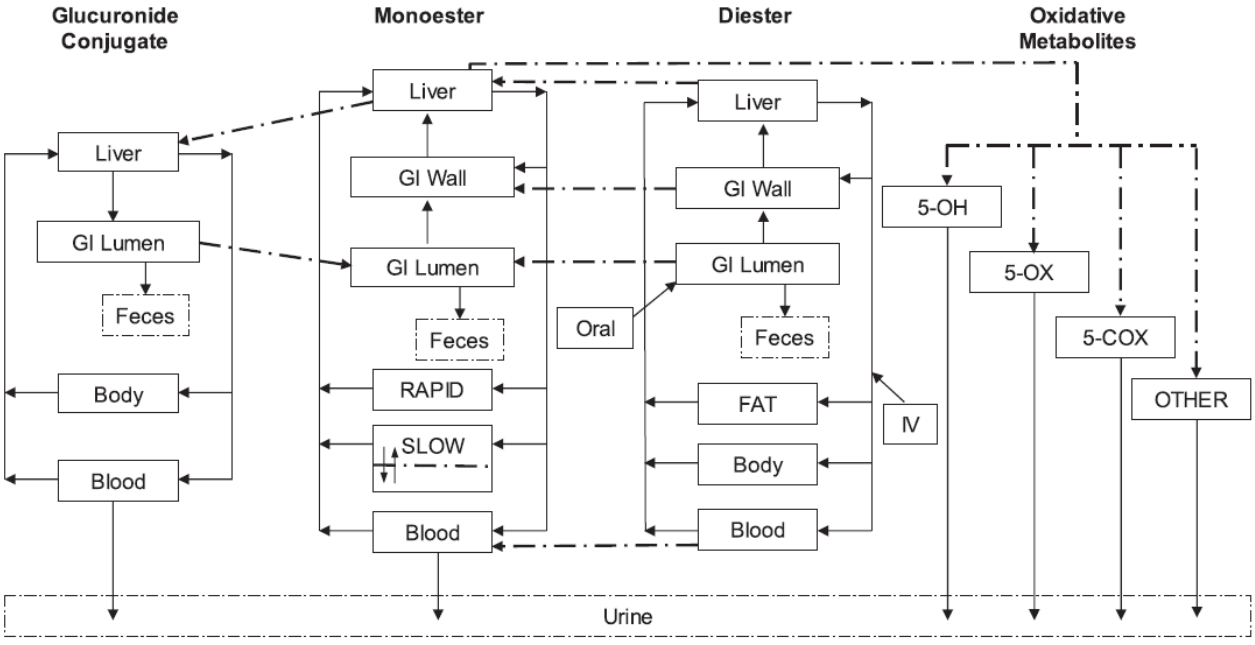

Figure 5: PBPK model for DEHP, DnBP and their metabolites structure

The current model includes four interconnected sub-models for the diester, the hydrolytic monoester, the oxidative metabolites and the glucuronide conjugate. The three oxidative metabolites of MEHP (i.e., 5OXO-MEHP, 5OH-MEHP and 5CX-MEPP) were incorporated as a fraction of the total MEHP oxidative metabolism with a volume of distribution approximating body water distribution. The model was manually optimised to simulate kinetic time-course data in human plasma (DEHP and total MEHP) and urine (MEHP, 5OXOMEHP, 5OH-MEHP and 5CX-MEPP) after oral consumption, based on controlled dosing studies in humans.

17.3.2. Oral exposure

The primary route of human exposure to DEHP and DnBP in the general population is through oral consumption, which is mainly due to the transfer of substances from food packaging onto food products as well as dust and soil ingestion. Oral absorption is described as a first order process.

17.3.3. Distribution

Diester that is taken up into the gut wall is passed to the liver via the portal blood. Unlike the diester, their monoester metabolites MEHP and MBP are readily absorbed in the gut. Transport of monoester into the tissues is modeled using diffusion-limitation. Metabolites of MEHP and MBP formed by P450 metabolism in the liver are released into the body via the venous blood. Distribution of oxidative metabolites into the tissues is modeled using flow-limitation, assuming distribution with body water.

17.3.4. Metabolism

DEHP is rapidly metabolised to its monoester, mono(2-ethylhexyl) phthalate (MEHP), which is further metabolised by various oxidation reactions to a number of secondary hydrolytic and oxidative metabolites that are conjugated via glucuronidation and other processes before being eliminated. The three oxidative metabolites of interest here are mono(2-ethyl-5-hydroxyhexyl) phthalate (5OH-MEHP), mono(2-ethyl-5-oxo-hexyl) phthalate (5OXO-MEHP) and mono(2-ethyl-5-carboxy-pentyl) phthalate (5CX-MEPP). DnBP is metabolised to its monoester, mono-butylphthalate (MnBP). Oxidative metabolism is described in the liver using a saturable Michaelis-Menten description. The oxidised monoesters are then excreted into the bile or released into systemic circulation. Biliary metabolites are released into the upper intestine (GC1), where they may be reabsorbed (described as a first order rate) or passed in the feces (described as a first order clearance rate). A three-compartment model is used to describe the oxidative metabolites in the blood, liver and other tissues.

17.3.5. Elimination

Some diester may enter circulation intact via oral absorption or be passed into the lower intestine (GC2), where it is excreted in the feces. Movement through the intestine and fecal excretion are described as clearance rates. Diester that is taken up into the gut wall is passed to the liver via the portal blood where it is hydrolysed, released into systemic circulation or excreted into the bile. Biliary diester is excreted into the upper intestine. Movement of free monoesters through the GI and fecal excretion are clearance rates. The free monoesters may be excreted into the bile (recirculated to small intestine) or released into systemic circulation. Urinary excretion of oxidative metabolites is modeled using a first order clearance rate from the plasma compartment.

17.3.6. Binding

Enzymes responsible for the hydrolysis of the diesters are present in the intestinal mucosa, blood and liver.

17.4. Parameterisation:

Cf. document “PBTK model refinement: parameterisation”.

17.5. Extrapolation rodents to human

The rodent model was extended to human with known values for the required physiological and kinetic parameters or scaling of the rodent values to estimate human equivalent ones.

17.6. Sensitivity analysis

Sensitivity analysis was not conducted.

17.7. Assessment, validation

The results of human exposure levels to phthalates obtained from reverse dosimetry PBPK model were compared with the results obtained from two other computational models, the HT Stochastic

Human Exposure and Dose Simulation model (SHED-HT) and the ExpoCast empirical heuristic model, and reported literature data.

17.8. Questions:

Does the estimation of input parameters using Monte Carlo simulations give reliable results?

17.9. Discussion:

- The short half-lives of phthalates may result in uncertainties in estimated exposure from reverse dosimetry given that biomonitoring data only provides a measure of concentration at the time of sample collection.
- Exposure to phthalates can also vary among individuals as well as among populations, depending on the types and levels of exposure sources such as specific food categories and consumer products.
- In the current study, metabolites were used for reverse dosimetry to estimate the exposure to their respective parent chemicals, which may have resulted in additional uncertainties in the predicted exposure for those parents.
- Inter-individual variability in pharmacokinetics, most importantly for metabolism parameters, was simulated by varying those metabolism parameters when conducting Monte Carlo simulations. Computational methods needed to estimate input parameters for different compounds.

18. Physiology based Pharmacokinetic (PBPK) modeling for DEHP metabolites integrating its in vitro metabolism: a bottom up modeling approach (Sharma et al., 2018b)

18.1. Chemical compound(s):

DEHP and DnBP

18.2. Species and stages:

Adult humans

18.3. Model structure, main assumptions and processes:

18.3.1. Structure

The model is basically flow limited model and it structure is provided in Figure 6. It comprises different compartments such as gut, liver, blood, fat and gonads. The gonads compartment was included in the model, keeping in mind using of model for DEHP reproductive toxicity at the later stage. The DEHP main metabolite MEHP was distributed to the given compartments, while other metabolites were confined to the blood compartment presuming their volume of distribution is equivalent to plasma volume. Following oral administration of DEHP, it gets readily metabolised into MEHP (M1) and MEHP further metabolise into 5-OH MEHP (M2), 5-cx MEPP (M3) and phthalic acid (M5). 5-OH MEHP is further metabolising into 5-oxo MEHP (M4). The model was coded as a set of ordinary differential equations, written in the GNU MCSim modeling language and solved by numerical integration with the GNU MCSim using R platfrom

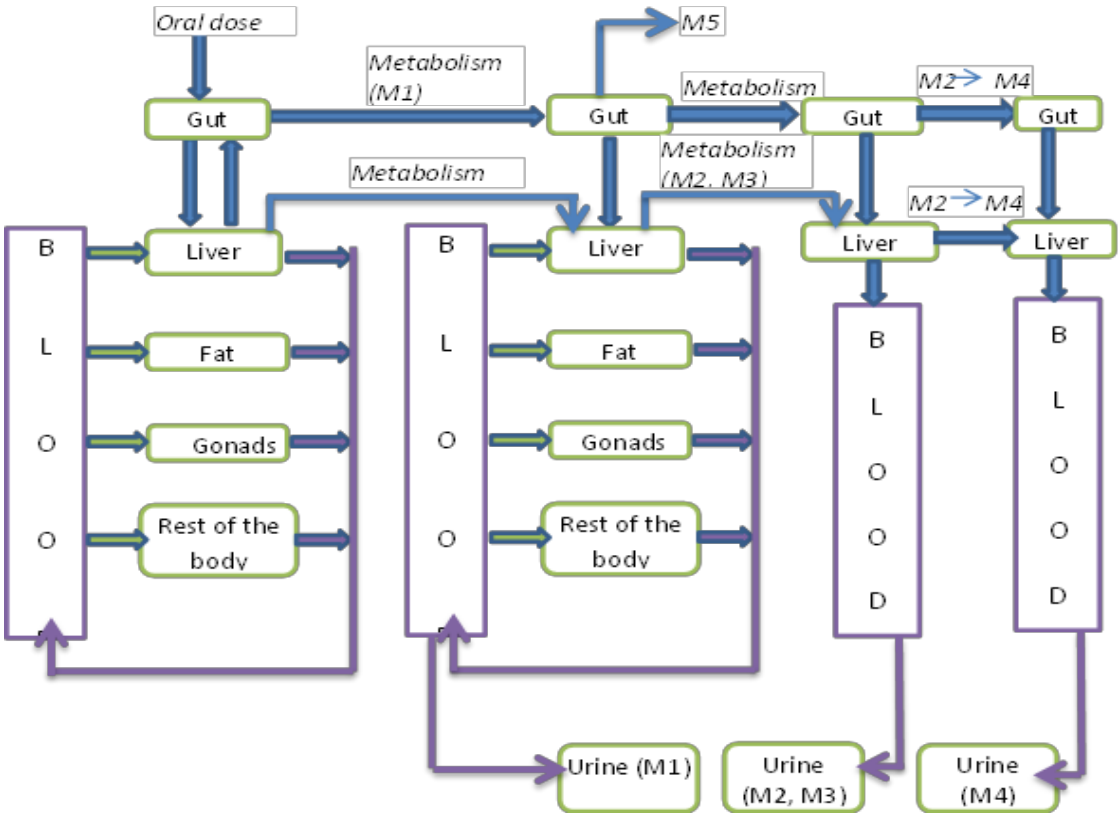

Figure 6: PBPK model for DEHP, its metabolites structure

18.3.2. Oral exposure

Primary route of oral exposure was considered for this model development. The absorption of DEHP from the gut to blood is described by partitioning of chemical between gut and plasma. The uptake of MEHP metabolite formed in gut to liver was described by first order rate.

18.3.3. Distribution

The DEHP and MEHP are distributed to the different compartments considering their partition coefficients estimated in different studies. The partition coefficients for DEHP were estimated using the algorithm based on tissue composition method (Poulin and Krishnan, 1995b; Poulin and Krishnan, 1996; Poulin and Theil, 2000). A log ko/w of 7.6 was used for the estimation of tissue: plasma partition coefficient. The distribution of MEHP was done using partition coefficient values measured experimentally via vial-equilibration method by Keys et al. (2000b). Due to the lack of data on distribution for other metabolites and to simplify the model, other metabolites (3 metabolites) are transferred to the blood compartment, assuming their volume of distribution equivalent to the plasma volume. The transfer of the metabolites formed in the liver to the blood was described by first order uptake rate and these parameters were calibrated against the Koch et al. (2005) data.

18.3.4. Metabolism

The metabolites of DEHP in liver and gut such as MEHP, 5-OH MEHP, 5oxo-MEHP, 5cx MEPP and Phthalic acid is described as a saturable process utilising Michaelis Menten equation. The equation involves two important parameters namely V_{max} (maximum velocity of metabolic reaction) and K_m (affinity concentration at which half maximal reactions occurs). The in vitro intestinal and hepatic metabolic rates for different metabolites were reported by Choi et al., (2012) in human intestinal and hepatocyte cell line. Based on in-vitro studies of DEHP in the gut and liver, an IVIVE approach was implemented to derive model parameter such as Vmax, describing the maximum rate of metabolism. The estimated parameters (V_{max} in-vitro), maximum rate of reaction were scaled to the whole body.

18.3.5. Elimination

Rate of excretion of DEHP and its metabolites in urine was assumed to be directly proportional to the rate of clearance from the plasma. The model presumed that DEHP clearance is solely depend on metabolism as it is completely metabolised to MEHP. The excretion rate for the MEHP and other metabolites were described using first order rate equation using elimination rate constants. They were obtained by using the relationship of elimination rate constant and chemical's plasma half-life i.e. ratio of ln2 (0.693)/t1/2 (half-life).

18.3.6. Binding

Unbound fraction in plasma for MEHP is used from reported study in Adachi et al., (2015).

18.4. Parameterisation:

Cf. document "PBTK model refinement: parameterisation".

18.5. Sensitivity analysis

Sensitivity analysis was performed using FME package of R.

18.6. Assessment, validation

In this study, multiple parameters such as partition coefficient, biochemical (metabolism), absorption and elimination and target variables such as DEHP metabolites concentration, were considered to conduct sensitivity analysis and uncertainty analysis. The bottom up approach was applied in order to develop the PBPK model for DEHP metabolites, where all the parameters were

derived from in-silico (QSAR), in-vitro (metabolism) and from published literature. PBPK model has accounted the parameter statistical distribution followed Monte Carlo simulation reflecting uncertainty in the model. Following a single oral dose of 48,500 µg of DEHP, the observed concentration of metabolites in blood and urine were used to calibrate the model. The simulated model for four metabolites (MEHP, MEHP-OH, 2 carboxy-MEPP and 5-oxo-MEHP) blood concentrations are not only in closely agreement with observed data points but also captured the trend of time course profile. The structure of the model and the model parameters remained unchanged from their calibrated values, and the predicted percentage mole elimination data for four metabolites in urine were compared with the data reported in Anderson et al., (2011) for the evaluation of model credibility. The observed cumulative amount of all metabolites is well predicted by the PBPK model as it is within the range of simulation.

18.7. Questions:

18.8. Discussion:

- The results show that current developed model can predicts the plasma and urine concentration of DEHP metabolites for different scenario of exposures.
- The model accounted four metabolites and the generation of metabolites is mechanistically described using integrated physiological parameters and Michaelis-Menten parameters such as Vmax and Km derived from human hepatic cell line.
- Sensitive analysis was done for all the parameters and metabolic parameter found to be more sensitive than other parameters.
- Monte Carlo sampling techniques were used accounting probabilistic information about pharmacokinetics parameters that estimated the DEHP metabolites concentration in plasma and urine at three percentile considering uncertainty in model.

Pesticides

19. A Physiologically Based Pharmacokinetic and Pharmacodynamic (PBPK/PD) Model for the Organophosphate Insecticide Chlorpyrifos in Rats and Humans (Timchalk et al., 2002)

19.1. Chemical compound(s):

Chlorpyrifos

19.2. Species and stages:

Rats and Humans

19.3. Model structure, main assumptions and processes:

19.3.1. Structure

The current PBPK model was developed to describe the time course of absorption, distribution, metabolism and excretion of CPF, CPF-oxon and TCP and the inhibition of target esterases by CPF-oxon in the rat and human. The model assumes that the pharmacokinetic and pharmacodynamic response in rats and humans is independent of gender, which is consistent with the observed response in human males and females reported in this study.

19.3.2. Exposure

CPF oral administration in corn oil vehicle and chronic dietary administration, dermal uptake of CPF (more than 90% of the systemically absorbed dose in humans).

19.3.3. Distribution

The absorption of CPF required the use of a two-compartment uptake model. This two-compartment model incorporated 1st order rate equations to describe systemic uptake and transfer between compartments. In addition, absorption of CPF from the diet was incorporated into the model to allow for the simulation of chronic dietary administration.

19.3.4. Metabolism

The CYP450-mediated activation and detoxification of CPF to CPF-oxon and TCP, respectively, was limited to the liver compartment. The model was linked to the CPF-oxon model that contained equations to describe the A-EST hydrolysis of CPF-oxon to TCP in both the liver and blood compartments. The CYP450 activation/detoxification and A-EST detoxification of CPF-oxon were all described as Michaelis-Menten processes.

19.3.5. Elimination

TCP was formed by the direct CYP450 metabolic conversion pf CPF and through A-EST-mediated hydrolysis of CPF-oxon and B-EST binding of CPF-oxon, respectively. The blood kinetics and urinary elimination of TCP were described with a single, one-compartment model utilising a 1st order rate of urinary elimination.

19.3.6. Binding

Interactions of the oxon with enzyme B-EST (AChE, BuChE and CaE) were modeled as 2nd order processes occurring in the liver, blood, brain and diaphragm.

19.4. Parameterisation:

Cf. document “PBTK model refinement: parameterisation”.

19.5. Extrapolation rodents to human

Physiological and metabolic parameters were scaled as a function of body weight. When available, parameters derived for human studies (in vitro/in vivo) were utilised in the model.

19.6. Sensitivity analysis

Sensitivity analysis was not conducted.

19.7. Assessment, validation

To develop and validate the CPF PBPK model, pharmacokinetic and pharmacodynamic studies were conducted in both rats and humans. The time course of CPF and CPF-oxon in the blood and the activity of ChE in the plasma, and AChE in brains of male rats were determined following oral administration of 100, 50, 10, 5, 1 and 0.5 mg CPF/kg of body weight. An additional group of female rats were administered the same doses of CPF and plasma, RBC and selected tissue ChE activity was determined. A double-blind, placebo-controlled clinical pharmacokinetic study was also conducted in order to provide needed data to better define the pharmacokinetic of CPF in humans.

19.8. Questions:

Only the input parameters were scaled in order to describe the human PBPK model? Were there other changes in the model structure regarding humans except for the ones for the skin absorption?

19.9. Discussion:

- Additional experimental data, including better parameter estimates are needed in order to facilitate future model refinement.
- Only few pharmacokinetic studies have been conducted for model development and validation.
- The extend of absorption may vary depending on the conditions of the dose solution, dosing method and variations in species, gender or strain.
- Conducting studies that that better characterise the time course of specific esterase activities could improve the predictive capability of the PBPK model.

20. The implications of using a physiologically based pharmacokinetic (PBPK) model for pesticide risk assessment (Lu et al., 2010)

20.1. Chemical compound(s):

3,5,6-trichloro-2-pyridinol (TCPY), the specific metabolite of chlorpyrifos (CPF)

20.2. Species and stages:

Young children

20.3. Model structure, main assumptions and processes:

20.3.1. Structure

The PBPK model was developed using the PBPK model for CPF in rats and humans (Timchalk et al., 2002). Metabolism of CPF (and CPFO) was assigned to occur in the blood and liver, with the excreted metabolite, TCPY, lumped into a single compartment. To enable systematic extrapolation of the dose–urinary excretion behavior, the metabolite description was expanded from a volume-of-distribution concept to a physiologic description that can incorporate known differences at different life stages, such as between children and adults. The rat, adult, and child PBPK models were implemented using the U.S. Environmental Protection Agency's (U.S. EPA) Exposure Related Dose Estimating Model (ERDEM) (Blancato J.N. et al., 2006). The ERDEM platform consists of two parts: the Microsoft Windows-based graphical user interface and the model engine, which is built in Advanced Continuous Simulation Language. The parameters for the study participants and for their exposure scenarios were created in ERDEM as the model data sets (MDSs) to ensure consistent implementation and to facilitate review.

20.3.2. Exposure

Three concurrent exposure scenarios were developed: bolus ingestion (based on levels measured in three meals throughout the sampling day), inhalation, and rate ingestion for non-dietary routes (such as hand-to-mouth activity). The dermal route of exposure was not taken into account in the PBPK model simulation because CPF was not detected on any of the children's hands at the time sampling was taking place.

20.4. Parameterisation:

Cf. document "PBTK model refinement: parameterisation".

20.5. Extrapolation rodents to human

Physiological and metabolic parameters were scaled as a function of body weight to establish an initial value that was then adjusted based on model fit.

20.6. Sensitivity analysis

A parameter sensitivity analysis was performed to identify important parameters associated with urinary TCPY excretion and tissue-specific CPF dose metrics that were important to model behavior. A local analysis was applied and the magnitude of the parameter change was 1% of the baseline value. Responses of interest included peak concentrations of CPF in blood and TCPY urinary excretion rates at 8 and 24 hr after an oral CPF dose of 0.5 mg/kg. All model parameters were perturbed to investigate effects on model behavior.

20.7. Assessment, validation

The data used in the PBPK-model simulation were obtained from a cross-sectional pesticide exposure assessment study with repeated environmental and biologic sampling that was conducted in the U. S. state of Washington in 1998. Participants were recruited from a pool of children who had been enrolled in two previous assessment studies of pesticide exposure in Washington State. The PBPK model outputs for each MDS included the predicted cumulative excretion of TCPY (mmol) in urine for the duration of exposure (168 hr), as well as the estimated absorbed dose for each MDS. The cumulative TCPY excretion measured at each urine sample collection time point was calculated for each participant, and compared with the distribution of the predicted cumulative excretion of TCPY that was generated by the PBPK simulation.

20.8. Questions:

Which modifications were made in order the model to be applied to children?

20.9. Discussion:

- Studies are needed in order to investigate the existence of preformed OP urinary metabolites in the environment and food that may confound the results of OP pesticide exposure and risk assessment.
- Improvement of the quality of the exposure data used as model inputs. The validity of applying aggregate exposure measurements as inputs for PBPK model simulation and subsequent risk assessment is under question.

Anilines

21. A Novel Method for Assessing Drug Degradation Product Safety Using Physiologically-Based Pharmacokinetic Models and Stochastic Risk Assessment (Nguyen et al., 2015)

21.1. Chemical compound(s):

Aniline and structurally related compounds (PCA, 2,6-DMA, o-TOL, and PAP)

21.2. Species and stages:

PBPK models for rat and human

21.3. Model structure, main assumptions and processes:

21.3.1. Structure

The PBPK model in rat and human consisted of two major sub-models that describe disposition and input. In the disposition model, the relevant organs or tissues were selected. Compartments representing the adipose and liver are included in the model structure. To account for the target organ of toxicity, compartments for the spleen and kidney were also included. A disposition model in rats was constructed representing 14 compartments, including those for lungs, adipose, heart, brain, muscle, spleen, pancreas, stomach, gut, kidney, bone, skin, and thymus and two blood compartments (arterial and venous blood). The input model was adapted from the advanced compartmental absorption and transit model (ACAT) (Agoram et al., 2001) originally developed by Yu et al (1999). It consisted of nine compartments, including stomach, large intestine, seven segments of small intestine, and corresponding enterocyte or GI wall compartments.

21.3.2. Oral exposure

The input model consisted of nine compartments, including stomach, large intestine, seven segents of small intestine and corresponding enterocyte or GI wall compartments.

21.3.3. Distribution

The compounds were reported to be rapidly absorbed from the small intestine, and passively permeated through tissue and cellular membranes with no known transporter. Therefore, each tissue was assumed to be perfusion-rate limited.

21.3.4. Metabolism

Aniline and similarly structural compounds (PCA, 2,6-DMA, o-TOL, and PAP) are lipophilic and mainly metabolised in the liver. Aniline was reported to be metabolised in liver by acetylation and hydroxylation pathways.

21.3.5. Elimination

The model compounds were reported to be mainly eliminated via liver metabolism.

21.3.6. Binding

No reference about binding.

21.4. Parameterisation:

Cf. document “PBTK model refinement: parameterisation”.

21.5. Extrapolation rat to human

The scale up to human model was accomplished by adjusting the physiological parameters to human levels for healthy adult population. In particular, BW was set at 70 kg for male individuals and 60 kg for females. Other physiological parameters, such as tissue volumes and blood flows, were adjusted for males and females using corresponding reference values obtained from ICRP Publication 89 (Valentin, 2002). Tissue to plasma partition coefficients, protein fraction unbound, blood to plasma ratio, and effective permeability were assumed to be identical to those parameters in rat model, regardless of gender. Metabolic parameters were scaled from in vitro measurements using scaling factors for human population (Barter et al., 2007).

21.6. Sensitivity analysis

MC sampling was used. A total of 10,000 points were sampled from a joint normal distribution of 22 parameters that accounted for the physiological, metabolic, protein binding, permeability and tissue-to-plasma partition coefficient variability and uncertainty. The exposure metrics estimated from each simulation included the AUC for splenic exposure (aniline, o-TOL, PCA, and 2,6-DMA), the AUC for kidney exposure (PAP), and time-dependent aniline plasma concentration at selected oral doses from 0.15 to 2.25 mmol/kg. The model predictions were summarised with the mean and central 95% confidence intervals. At all dose levels, the reported blood concentrations were within the 2.5% and 97.5% quantiles of the prediction distributions. It is stressed that these intervals are not the result of fitting any of the model parameters to the data set, but rather the propagation of the uncertainty in the parameters to the model predictions.

21.7. Assessment, validation

The results were presented graphically.

- Effective permeability was calculated based on the MLR between caco-2 permeability and molecular descriptors.
- At a low aniline dose (0.15 mmol/kg), the model predictions of blood concentrations closely matched the observed data and displayed linear elimination kinetics.
- When the doses were increased, nonlinear elimination kinetics predictions were consistent with experimental data.
- The complexity of disposition kinetics in the distribution phase as well as the shape of the blood-level profiles was reasonably predicted.
- The use of PROB metric, which quantifies the probability that a randomly chosen human exposure at specific dose is greater than rat exposure at the critical dose provides a way to identify a critical human dose by considering what probability of failure (degradant toxicity) is tolerable for a given drug product. In other words: the benefit-risk decision can be rationally made.
- Using PBPK models and stochastic PROB metrics, the human reference dose was estimated to be larger than the value estimated by conventional risk assessment approach.

For model evaluation, a simple comparison of the forward prediction of the model at the initial estimates of the parameters to experimental data was conducted. No parameter optimisation (i.e., “fitting”) was involved. The model appeared to be in reasonable agreement with literature data.

21.8. Questions:

- Were the tissue/blood partition coefficients found to be the same for both rats and human?
- Were the disposition and input models the same for rats and human?
- What conclusions are made from the comparison of PROB method to the conventional risk assessment approach, which were used for estimating the human reference doses?

21.9. Discussion:

- The model consisted of two sub-models, the input and disposition models. Most of the input parameters were estimated using equations, which means that they may contain numerical errors. The parameters for human PBPK model were also derived from scaling up and extrapolation techniques, increasing by this way the uncertainty in predictions.
- 8 molecular descriptors are too many for QSAR development using a training set of 17 compounds. The excellent obtained correlation does not mean anything about the predictability of the model.

Brominated flame retardants

22. A physiologically based pharmacokinetic model for developmental exposure to BDE-47 in rats (Emond et al., 2010)

22.1. Chemical compound(s):

2,2',4,4'-tetrabromodiphenyl ether (BDE-47), that is a brominated flame retardant.

22.2. Species and stages:

Model developed in adult female pregnant and male/non-pregnant (male and non-pregnant considered as equivalent) rats.

22.3. Model structure, main assumptions and processes:

22.3.1. Structure

PBPK model comprising 8 main compartments: brain (sub-compartments: "brain blood", "brain tissue"), liver ("liver blood", "liver tissue"), adipose tissue (AT, sub-compartments "AT blood", "AT tissue"), kidney, placenta, fetus, blood, "rest of the body" (Figure).

The placenta and the fetus compartments were activated for the pregnant females.

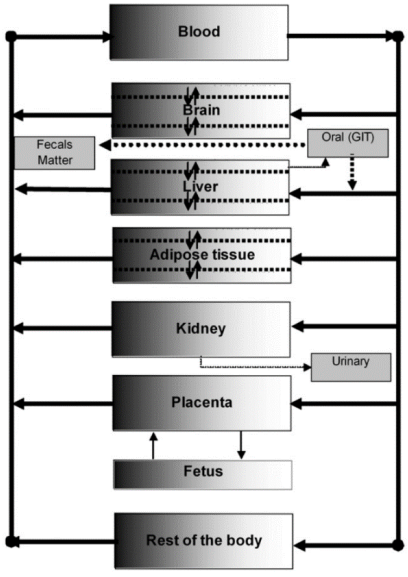

Figure 7: A conceptual representation of PBPK model for rats (Emond et al., 2010)

22.3.2. Oral exposure

Bolus in the gastrointestinal (GI) tract.

1st order rate of absorption from the GI tract to the liver.

22.3.3. Distribution

Most of the compartments were represented as perfusion-limited. In those compartments, the variation of the amount of the molecule in the compartment was calculated as a function of the blood flow to the tissue (Q_{tissue}, mL h^{-1}), the arterial concentration of the molecule (C_{art}, nmol mL^{-1}), the concentration of the molecule in the tissue (C_{tissue}, nmol mL^{-1}) and the partition coefficient of the molecule between the tissue and the blood ($PC_{tissue:blood}$, no units) (Eq 5).

Eq 5

$$\frac{dA_{tissue}}{dt} = Q_{tissue} \times (C_{art} - \frac{C_{tissue}}{PC_{tissue:blood}})$$

Liver, adipose tissue (AT), brain and fetus were represented as diffusion-limited*. The authors cited the same approach for the liver and the AT in (Emond et al., 2004), and the representation by this way of the blood-brain barrier limitation process in the brain. In these cases, a sub-compartment "tissue blood" and a sub-compartment "tissue cell" were represented, in which the variation of the amount of the molecule was represented respectively as shown in Eq 6 and Eq 7, depending on the blood flow to the tissue (Q_{tissue}, mL h^{-1}), the arterial concentration of the molecule (C_{art}, nmol mL^{-1}), the concentration of the molecule in the "tissue blood" sub-compartment ($C_{tissue\ blood}$, nmol mL^{-1}), the tissue permeability ($PA_{tissue\ cell}$, mL h^{-1}), the concentration of the molecule in the "tissue cell" sub-compartment ($C_{tissue\ cell}$, nmol mL^{-1}) and the partition coefficient of the molecule between the tissue cell and the tissue blood sub-compartments ($PC_{tissue:cell}$). The $PA_{tissue\ cell}$ was established in this model as a fraction of the tissue blood flow.

Eq 6

$$\frac{dA_{tissue\ blood}}{dt} = Q_{tissue} \times (C_{art} - C_{tissue\ blood}) - PA_{tissue\ cell} \times (C_{tissue\ blood} - \frac{C_{tissue\ cell}}{PC_{tissue:cell}})$$

Eq 7

$$\frac{dA_{tissue\ cell}}{dt} = PA_{tissue\ cell} \times (C_{tissue\ blood} - \frac{C_{tissue\ cell}}{PC_{tissue:cell}})$$

**"Bischoff (1975) demonstrated that for a membrane-limited case, the drop in blood concentration between entering the tissue, CB, and leaving the tissue, CTB, is negligible"* (Wang et al., 1997).

22.3.4. Metabolism

A flux of 1st order metabolism was represented as an exit from the "tissue cell" sub-compartment of the liver. This flux was calculated as the product of the arterial concentration of the molecule (C_{art}, nmol mL^{-1}), the blood flow to the liver (Q_{liver}, mL h^{-1}) and the extraction coefficient of the molecule in the liver (E, unitless).

22.3.5. Elimination

- First order elimination rate from the GI tract to the feces, calculated as the product of a constant of elimination of the molecule by the GI tract ($K_{elim\ fec}$, h^{-1}) and the amount of the molecule in the GI tract (lumen, nmol).
- First order elimination rate of the molecule from the kidney, calculated as the product of a clearance constant (Cl_{uri}, mL h^{-1}) and the concentration of the molecule in the systemic venous blood ($C_{ven\ systemic}$, nmol mL^{-1}).

22.3.6. Maternal transfer to the fetus

First order exchange of the molecule between the "placenta" and the "fetus" compartments. A clearance constant was used from the placenta to the fetus and vice versa. The retention of the molecule in the fetus depended on the fetus-blood partition coefficient ($PC_{fetus:blood}$, unitless).

22.3.7. Binding

No binding processes were represented.

22.3.8. Extrapolation non gestating-gestating stages

During gestation, variation of the body weight (BW) with the age and variation of the cardiac output as a function of the metabolic BW ($BW^{0.75}$). This change affected the rest of tissues, as their weight and blood flow were proportional to BW and cardiac output respectively.

22.4. Parameterisation:

Cf. document *"PBTK model refinement: parameterisation".*

22.5. Sensitivity analysis

One parameter each time (+/-2% initial value), analysis of the influence of each parameter on the AUC in the fetus.

22.6. Assessment, validation

The model was assessed on data from experimental treatments not previously used in the model and for different physiological stages:

- Non gestational stage: the exposure to the molecule at four doses (1, 10, 100 and 1000 µmol kg^{-1}) gave simulated results generally comprised within the standard deviations of the experimental results. The estimations had less good quality for adipose tissue and blood in some cases. The authors calculated that the error in the estimations at this physiological stage was within 20% of the experimental data.
- Gestational stage: three sets of data were used. The simulated results were comprised within the standard deviations of the experimental results for several tissues. Some tissues like the fetus, the liver and the rest of the body presented in some cases an error in the estimation comprised between 1 and 2.3 times the experimental values.

22.7. Questions:

- Why do they represent the liver and the adipose tissue as diffusion-limited compartments? It's not clarified either in this paper or in the cited reference Emond et al. (2004).

22.8. Discussion:

22.8.1. Structure

No clarification of the choice of representing the liver and the adipose tissue as diffusion-limited processes. On the other side, many ADME processes were represented as 1st order. Some of these processes could in reality follow 2nd order kinetics, and the liver and adipose tissue be perfusion-limited. The authors justified the 1st order kinetics for some processes like absorption and metabolism, but not systematically.

Detail: the units for the C_{tissue} (nmol mL^{-1}) and the $PC_{tissue:blood}$ (no units) would seem more realistic if the C_{tissue} was expressed on the basis of Kg^{-1}.

22.8.2. Sensitivity analysis

The influence of each parameter on the AUC of the fetus was assessed. The results suggested that this compartment was not very sensitive to each parameter. It seems logical that this compartment is not highly sensitive to most of the individual parameters since it was not directly irrigated by the systemic circulation but by the placenta, in a diffusion-limited process. It seems more appropriate to study the sensitivity on a component of the model like the blood, that is the compartment that takes in charge the distribution of the molecule in the whole body but not directly to the fetus.

22.8.3. Assessment

For most of the tissues except the blood in the pregnant rats for some doses, the experimental data corresponded only to one point of sampling. There was no sequential sampling that could let an assessment of the toxicokinetic curves, excepted for the blood during the gestational stage.

Generic PBPK models

23. INTEGRA PBTK model (Sarigiannis et al., 2014)

23.1. Chemical compound(s):

The INTEGRA generic PBPK model covers a broad range of compounds from different chemical families. These include: BPA, benzene, toluene, ethylbenzene, xylene, trichloromethane, phthalates, PAHs, TCDDs, BDEs, pesticides, parabens and perfluorinated compounds.

23.2. Species and stages:

The generic human PBTK model developed in INTEGRA is designed to describe in as much as possible detail the ADME processes occurring in the human body at different life stages, so as to be easily applicable to a broad variety of chemicals after proper parameterisation. In practice, it accounts for mother-fetus interaction, capturing all age dependent physiology changes, including the ones of the pregnant mother.

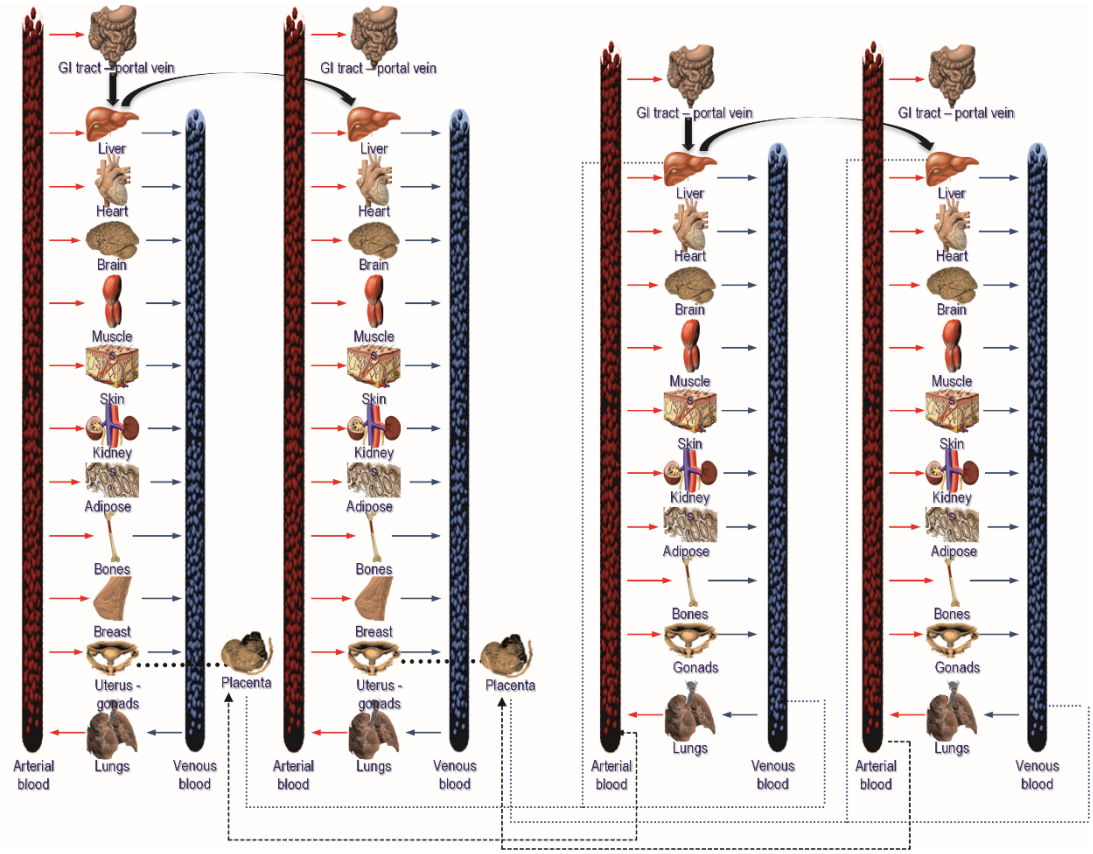

Figure 8: INTEGRA mother-fetus PBTK model

23.3. Model structure, main assumptions and processes:

23.3.1. Structure

All major human organs are included, as well as arterial, venous, and portal blood compartments. Xenobiotics and their metabolites are linked through the metabolising tissues. The model in its generic form includes the parent compound and up to three generations of potential metabolites. The mass balance equation for each compartment describes all appropriate parameters carrying biological significance, such as absorption, metabolism, elimination, and protein binding. In practice, in each tissue three mass balance equations are written, for (a) red blood cells, (b)

plasma and interstitial tissue and (c) cells. Specific organs were further divided in sub-compartments: liver is divided in up to 5 compartments so as to better describe the distribution of enzymes, and brain is divided in four sub-compartments, namely, main brain, globus palidus, cerebellum and pituitary, so as to better describe the permeability differences among the different brain regions. The model describes mother fetus interactions by modelling the intra-placental properties that govern the transfer of xenobiotics and their metabolites from the mother to the fetus as it grows. The anthropometric parameters of the models are time dependent, so as to provide a lifetime internal dose assessment, as well as to describe the continuously changing physiology of the mother and the developing fetus. The model include the diffusion flow from uterus to placenta and vice-versa during pregnancy (Beaudouin et al., 2010). Excretion via lactation is described as an output from the mammary tissue compartment through a partitioning process between mammary tissue and milk, and milk withdrawal by suckling, as described for PCBs in rats (Lee et al., 2007) and further adopted for humans (Verner et al., 2008).

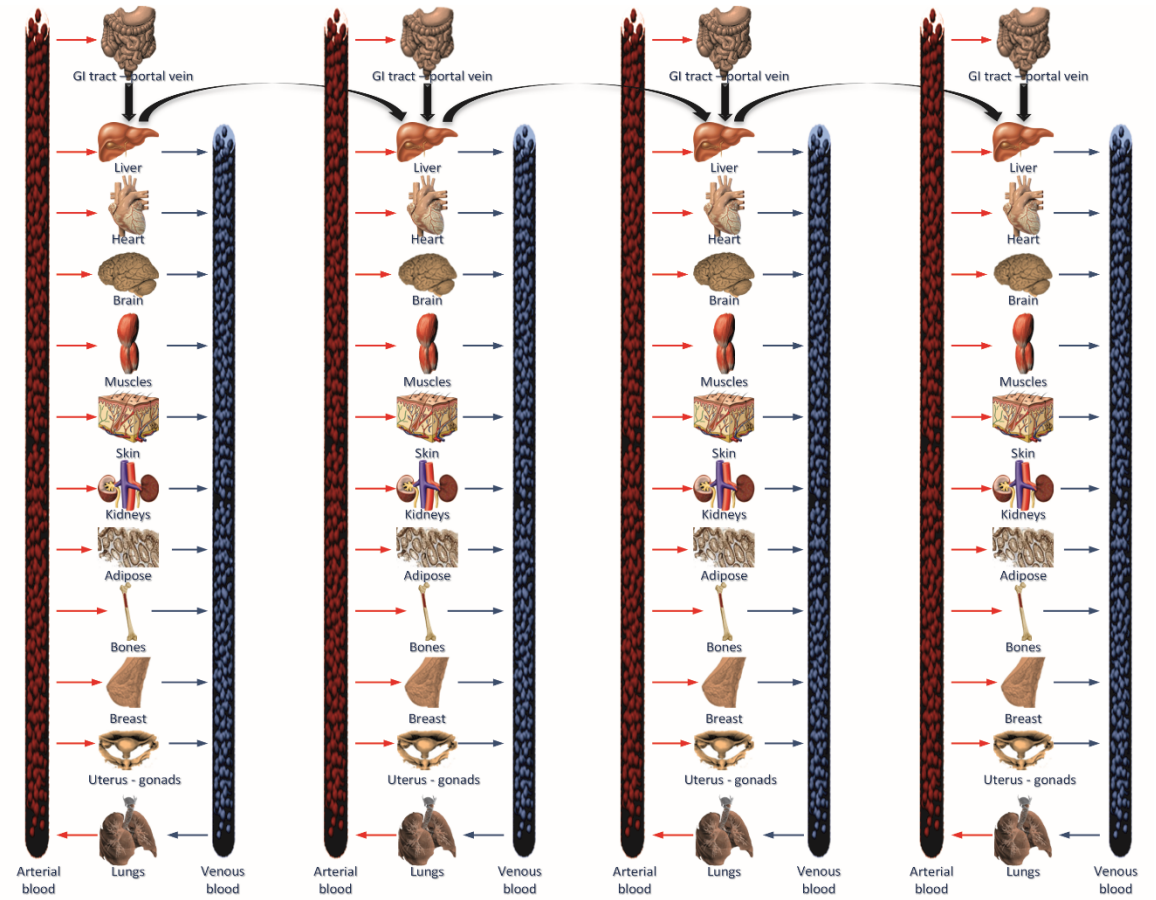

Figure 9: INTEGRA generic PBPK model structure: parent compound and three generations of metabolites

23.3.2. Exposure routes

The model includes also a detailed description for the three main routes of exposure. Inhalation takes into account absorption of gases and deposition fractions of particles across the different human respiratory tract regions based on particles size distribution. Absorption through the oral route is governed by the absorption rates of stomach and intestine. To better describe dermal absorption, skin has been modelled as a two layer structure, including stratum corneum that has been described as a “bricks and mortar” structure (Touitou, 2002) and viable epidermis (also accounting for metabolism), where the geometry of all layer microstructure has been explicitly described (Mitragotri et al., 2011).

23.3.3. Distribution

The fact that in each tissue three mass balance equations are written for (a) red blood cells, (b) plasma and interstitial tissue and (c) cells, allows the application of the model to both flow limited, as well as membrane-limited compounds, by just changing the parameterisation of the membrane permeability product.

23.3.4. Metabolism

Although the main metabolic organ is the liver, also other sites of metabolism might be considered (intestine, brain, skin, placenta) based on the presence or not of the enzymes involved in the metabolism of the compound of interest. Metabolism is described by saturable kinetics.

23.3.5. Elimination

Elimination is described by urine and feces excretion, as well as through lactation for females (when applicable).

23.3.6. Binding

Binding to red blood cells and plasma proteins are described by the equilibrium of concentration between red blood cells and plasma (accounting also for the hematocrit levels), as well as the fraction unbound in plasma.

23.4. Parameterisation:

The parameters related to organ volumes (***V***) and blood flows (***Q***) were taken from the ICRP (ICRP, 2002) report and Edginton and Ritter (2009) and fitted to time (*t in hours*) in order to derive continuous time depended non lineal polynomial formulas in the form of:

$V = a \cdot t^b + c \cdot t^d + e \cdot t + f$ for organ volumes

$Q = a \cdot t^b + c \cdot t + d$ for organ flows

Compound specific parameterisation of the model varies upon the compound of interest. For data rich compounds that experimental values have been obtained from toxicokinetic studies, or extrapolated from animal models, these parameters are used directly. For data poor chemicals, the main parameters of the model (partition coefficients of the tissue compartments and Michaelis-Menten kinetics) are derived by QSAR models (Papadaki et al., 2017; Sarigiannis et al., 2017).

23.5. Sensitivity analysis:

The modelling framework upon which INTEGRA is built supports global sensitivity analysis.

23.6. Assessment, validation:

The conservative nature of the bottom-up intake calculation is verified by estimating intake from real-life HBM data. The use of internal dosimetry coupled to the exposure reconstruction algorithm allowed the calculation of external and subsequently internal dose starting from the available HBM data.

23.7. Discussion:

- INTEGRA PBTK model is capturing major toxicokinetic interactions, allowing its applicability to a large chemical space upon successful parameterisation
- All 3 main exposure routes are explicitly detailed; this is of particular importance for multi-route, time-variable exposure scenarios
- It would be advisable to include more complex trees of metabolites

24. IndusChemFate (Jongeneelen and Berge, 2011)

24.1. Chemical compound(s):

This model has been designed primarily for neutral and predominantly ionic organic compounds.

24.2. Species and stages:

Humans

24.3. Model structure, main assumptions and processes:

24.3.1. Structure

The model contains 11 body compartments (lung, heart, brain, skin, adipose, muscles, bone, bone marrow, stomach and intestines (lumped), liver, and kidney). The model assumes a reference human of 70 kg.

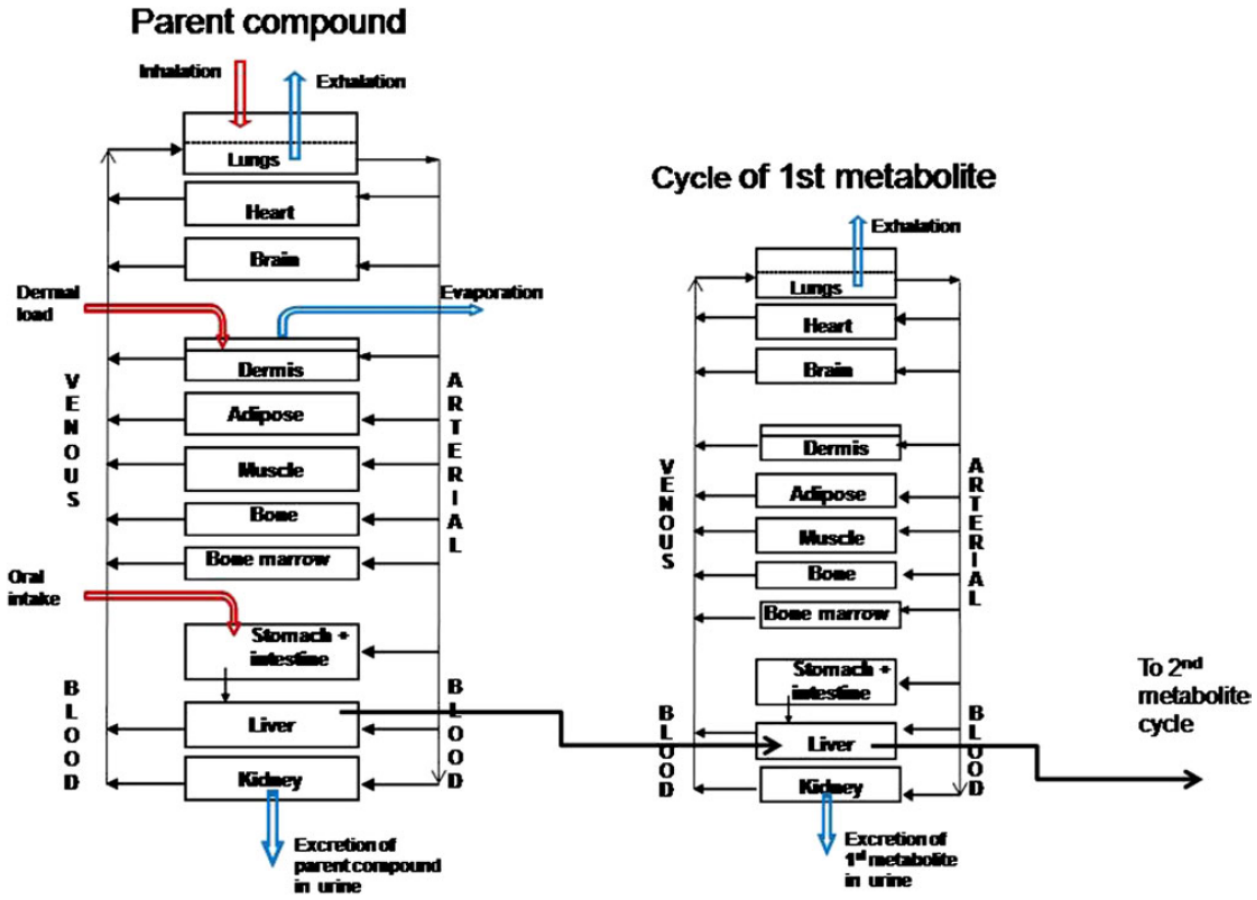

Figure 10: IndusChemFate model structure

24.3.2. Exposure

Tissue concentrations for each of the chemicals and metabolites can be simulated for either acute, occupational, or environmental exposure regimes with its typical duration, routes, concentrations, or dose rate. Inhalation in the IndusChemFate PBTK model is controlled by the concentration of the compound in the inhaled air, the alveolar ventilation, and the blood/air partition coefficient. In the model, the maximum concentration in inhaled air is limited at the level of saturated vapour pressure. For dermal absorption, a modified version of the algorithm developed by ten Berge (2009) was applied. This so-called Skinperm algorithm is a diffusion-based physiological model

that predicts absorption based on physical–chemical properties of the substance. It distinguishes two pathways of permeation through the skin: trans-cellular and inter-cellular. The physiological model considers the following processes: (1) Dermal deposition of a substance (liquid) on the skin, (2) Diffusion to the stratum corneum (SC), and (3) Absorption to the dermis/blood flow. The dermal absorption from the vapour phase is also considered. Direct transdermal uptake of vapour in the air might take place by diffusion. Oral intake of compounds is considered as a bolus dose that is applied to the intestinal lumen (via the stomach) and then absorbed into the intestinal tissue at a first order rate. From the intestines, the compound is released to the blood stream towards the liver (portal vein). The first order absorption rate is defined as the velocity at which the oral dose is absorbed by the intestinal tissue (as a fraction of the dose in the lumen per hour). Stomach and intestines are lumped in the model. The oral dose [in milligrams per kilogram body weight (BW)] and the absorption rate are the required input parameters for oral uptake in the model.

24.3.3. Distribution

For the blood:tissue partitioning, the QSPR algorithm as described by DeJongh et al. (1997) has been applied. They describe the distribution of compounds between blood and human body tissues as a function of water and lipid content of tissues and the n-octnnol:water partition coefficient (Kow).

24.3.4. Metabolism

Phase II metabolism with conjugation of metabolites generally increases the solubility. Enzymes produced by intestinal bacteria—such as b-glucuronidase, sulfatase, and various glycosidases—deconjugate these compounds in the intestines, releasing the parent compounds after which these are readily reabsorbed across the intestinal wall to the blood. This results in enterohepatic circulation (of conjugated phase II metabolites). In this model, a generic approach was applied: it incorporates enterohepatic circulation by defining the ratio of excretion to bile relative to excretion to the blood. This ratio is defined as the fraction of the amount of a metabolite in liver tissue that is excreted to the intestinal lumen via bile. In this approach, bile excretion means that there is an intestinal reabsorption.

24.3.5. Elimination

The chemical in the human body is eliminated in the model by two processes: metabolism (or biotransformation) and direct excretion in air or urine. Biotransformation is described by Michaelis–Menten saturable metabolism following the mathematical algorithms as described by Ramsey and Andersen (1984).

The (parent) compound is metabolised by a set of (iso)-enzymes. Usually, one or more metabolite(s) are produced. Metabolites may either undergo further metabolism or will be excreted. Contrary to many PBPK models, the occurrence of metabolism is not limited to the liver compartment but can be considered in any of the 11 model compartments. However, the default setting is metabolism in the liver only. When parallel metabolic pathways are involved, the V_{max} and k_M values for a specific metabolite production can be set as different from those for the parent compound. That is possible because the model considers both removal of the parent compound and production of metabolite as separate steps.

That means the biotransformation of the parent compound occurs for only x% into the metabolite of interest and for (100-x)% into other (unknown) metabolites. Substances can be excreted via urine, either unchanged as parent compound or as a metabolite. The model takes into account the renal clearance of substances by means of ultrafiltration in the glomeruli and possible resorption to the blood in the tubuli. The total renal clearance is assessed as the glomerular filtration minus the resorption in the tubuli. The model assumes that 8% of arterial blood becomes primary urine. The glomerular filtration rate in the IndusChemFate PBTK model is therefore set at 0.08 of the renal arterial blood flow. Tubular resorption restricts the renal clearance to 1% of the glomerular filtrate

(Griffiths, 1974). The tubular resorption is either set on or off. The selection is based on the octanol–water partition coefficient (log(Kow)) of the substance or metabolite of interest. The total volume of excreted urine in 24 h is set to 1.44 l. When the volatility is high, chemicals (and in a few cases a metabolite) will be exhaled. The exhaled concentration is a mixture of the inhaled air concentration (air that has not reached the alveoli) and alveolar air. The concentration of a compound in the alveolar space of the lungs is controlled by the blood concentration in the (arterial) lung blood and the blood/air partition coefficient. The amount of a compound that is exhaled is calculated by multiplying the alveolar concentration by the alveolar ventilation rate.

24.4. Parameterisation:

Cf. document “PBTK model refinement: parameterisation”.

24.5. Assessment, validation

Six experimental or observational studies with six different compounds were selected, e.g. the compounds pyrene (Jongeneelen et al., 1988), methyltert-butylether (MTBE) (Amberg et al., 1999), N-methyl-pyrrolidone (NMP) (Bader et al., 2008), ethanol (Kramer et al., 2007), 2-butoxyethanol (2-BE) (Franks et al., 2006) and n-heptane (Rossbach et al., 2010). The occupational exposure scenarios of the studies were different. The time course of the blood and urine concentrations of the parent compound and/or metabolites were simulated with the PBTK model IndusChemFate following the reported exposure scenario of the selected study. The results of the simulations (shape and height of the predicted concentrations) were compared with the reported experimental results.

24.6. Discussion:

- The simulations of experimental results show that it is feasible to apply the PBTK model IndusChemFate to multiple chemicals, including metabolites and different exposure regimes. The simulations show that blood and urine concentrations of various chemicals can be predicted, given an exposure scenario with certain airborne concentration and/or a dermal deposition dose rate.
- The uncertainty in the estimated metabolic rate constants may hamper the accurate simulation of metabolites.
- Regarding the width of the interindividual differences of body fluid concentrations, it seems acceptable that the accuracy of this PBTK model of approximately an order of magnitude is acceptable for first tier predictions of body fluid concentrations of chemicals.
- The model lacks detailed descriptions for specific protein binding, intestinal transport, interaction with intestinal flora, and excretion by feces that are important only for certain classes of chemicals.
- More detailed age dependent urinary excretion should be provided.

25. A stochastic whole-body physiologically based pharmacokinetic model (Beaudouin et al., 2010)

25.1. Chemical compound(s):

The general PBPK model is tested on two chemicals: 1,3-butadiene (BD), a volatile organic compound, and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), a persistent organic compound.

25.2. Species and stages:

Humans: fetus, children, adult women and men, pregnant women, elderly persons.

25.3. Model structure, main assumptions and processes:

25.3.1. Structure

General description: The model structure is identical for men and women, although an exception arises in case of pregnancy. This model proposes a detailed compartmentalisation of the human body with 22 organs. Two compartments integrate several entities. The urinary tract compartment includes the bladder, the ureters and the urethra, and the sexual organs compartment includes the testes, the epididymis and the prostate for men, and the ovaries, the fallopian tubes and the uterus for women. All tissue compartments are assumed to be well-mixed and blood flow-limited. The lungs were separated into two compartments to distinguish the pulmonary functions from the lungs anatomy (the tissues). Nineteen compartments are added to the general PBPK model to describe a woman's pregnancy and foetal development. They correspond to the placenta, the amniotic fluid and the foetus organs.

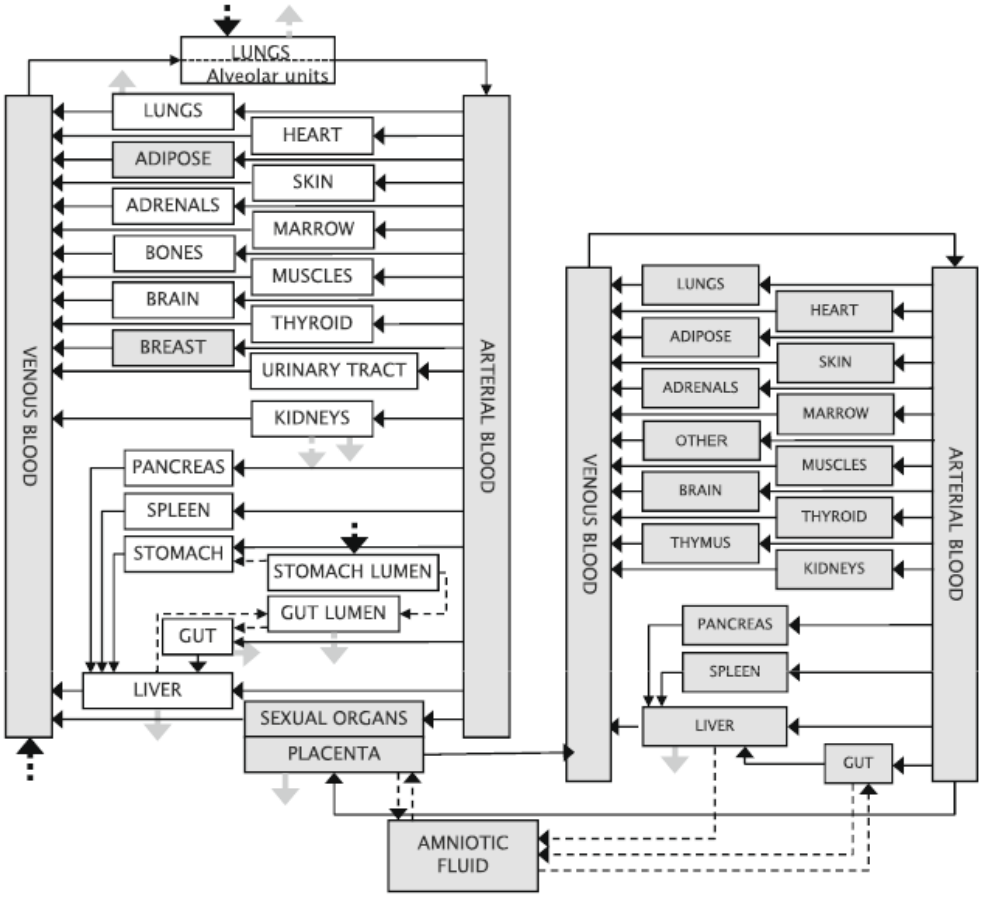

Figure 11: Structure of the stochastic whole-body physiologically based pharmacokinetic model developed by Beaudouin et al, (2010)

25.3.2. Exposure

Inhalation and ingestion were integrated in the mode. For inhalation, gas exchanges (inhalation and exhalation of contaminant, oxygenation of blood…) were modeled in the alveolar space and were assumed to be very rapid. The alveolar space is located between the venous blood and the lungs modeled as an organ. A simple model describes gas exchanges based on a one-directional airflow in the region of gas exchange and a rapid equilibrium between lung air and blood in the alveoli.

The gastrointestinal tract was subdivided into the stomach and the guts. Each of these was divided into 2 compartments: the lumen (in which the contaminant enters) and the wall (linked to the systemic circulation). The exchanges between the lumen and the wall were modeled as a diffusion by a first order reaction dependent of the concentration of contaminant in the stomach or gut lumen. Alternatively, a direct input can be made in the liver.

25.3.3. Distribution

The distribution is assumed to be evenly and homogeneously throughout the compartment volume and to be limited by perfusion, i.e., the tissue membranes present no barrier to diffusion. Blood flow is then the limiting factor to distribution in the various organs or tissues.

25.3.4. Metabolism and elimination

Elimination occurs via metabolism, urinary and faecal excretion, exhalation and, in case of lactation, milk production. Four sites of metabolism are modelled: liver, lungs, gut and placenta.

25.4. Parameterisation:

Quantitative relationships linking bodyweight, tissue volumes, or other physiological parameters with age were developed for childhood or for the whole life. Notable effects of aging on the bodyweight and tissue volumes, that are modelled, include skeletal muscle atrophy and variations of the adipose tissues. We assumed that all the organ volumes, except those two, do not evolve during adulthood. Aging atrophy of the muscle begins around 24 years old and thereafter accelerates, and the adipose volume starts to increase around age 20. The evolution of the cardiac output is described by a rapid increase from birth to adulthood, and then by a decrease modelling the effects of aging. Regional blood flows were assumed to change proportionally to tissue volumes.

Pregnancy impacts the parameterisation of four permanent compartments: adipose tissues, breast, sexual sexual organs and blood. During pregnancy, the weight of the ovaries and the fallopian tubes was assumed negligible in the sexual organs compartment compared to the weight of the uterus, so exchanges with the foetus occur via the whole sexual organs compartment.

Metabolism was assumed to be dependent on age but not gender.

A quantitative structure–activity relationship (QSAR) model developed by Poulin and Krishnan (1995a) was used to predict tissue:blood partition coefficients.

25.5. Sensitivity assessment

No sensitivity analysis was performed in this paper.

25.6. Assessment, validation

Several scenarios of exposure were tested (acute or chronic) on two chemical classes (VOC and dioxins) to assess the model predictability. The authors decided not to calibrate the PBPK model with experimental data in a statistical framework but to run the model with prior information on the compound, such as the molecular mass, the intake, the elimination or metabolic rates and the

octanol: water partition coefficient. For several exposure scenarios, experimental data were available in the literature. In general, a good agreement was obtained between the predictions and the actual data.

26. The MERLIN-Expo PBTK model (Brochot and Quindroit, 2018)

26.1. Chemical compound(s):

It was applied to inorganic chemicals (e.g. lead), perfluorinated compounds (PFOA, PFOS), persistent organic pollutants (PCBs, dioxins).

26.2. Species and stages:

Humans (general population, children at different ages)

26.3. Model structure, main assumptions and processes:

26.3.1. Structure

General description: **The 'Human' model** is a physiologically based pharmacokinetic (PBPK) model that aims to describe the fate of chemicals in the human body. The PBPK model implemented in MERLIN-Expo subdivides the body in 22 compartments representing organs connected through blood. The PBPK model accounts for the physiological or biochemical variations that arise throughout the growth and the development of an individual. This model is based on the model developed by Beaudouin et al. (2010) and has been improved to include new features (e.g., binding).

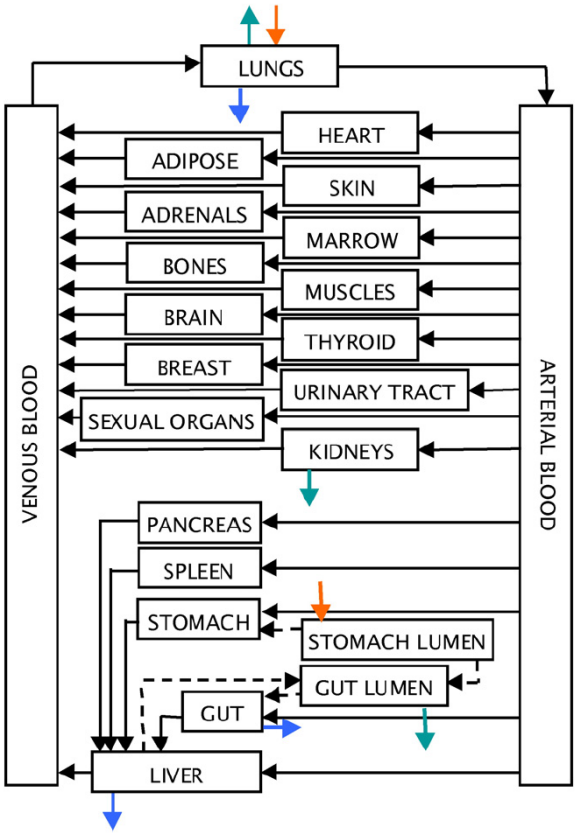

Figure 12: MerlinExpo PBTK model structure

26.3.2. Exposure

Absorption of the contaminants via inhalation was considered. Gas exchanges (inhalation and exhalation of contaminant, oxygenation of blood…) were modeled in the alveolar space and were assumed to be very rapid. The alveolar space is located between the venous blood and the lungs modeled as an organ. A simple model describes gas exchanges based on a one-direction airflow in the region of gas exchange and a rapid equilibrium between lung air and blood in the alveoli. Absorption by ingestion was also taken into account. The gastrointestinal tract was subdivided into the stomach and the guts. Each of these was divided into 2 compartments: the lumen (in which the contaminant enters) and the wall (linked to the systemic circulation). The exchanges between the lumen and the wall were modeled as a diffusion by a first order reaction dependent of the concentration of contaminant in the stomach or gut lumen. Alternatively, a direct input can be made in the liver.

26.3.3. Distribution

Distribution refers to the reversible partitioning of a compound into the various tissues of the body from the systemic circulation. Each organ or tissue can receive different doses of the compound and the compound can remain in the organs or tissues for a varying amount of time. The compound can be moved from the plasma to the tissue until equilibrium is established. The distribution is assumed to be evenly and homogeneously throughout the compartment volume and to be limited by perfusion, i.e., the tissue membranes present no barrier to diffusion. Blood flow is then the limiting factor to distribution in the various organs or tissues.

26.3.4. Metabolism

In this PBPK model, metabolism can occur in all compartments except in the gut and stomach lumen and in the alveolar space. Two equations are proposed to model metabolism either as a saturable (Michaelis-Menten equation) or a linear process (a first order reaction). The linear model assumes that the rate of metabolism is proportional to the change rate in the chemical concentration in the organ. The saturable Michaelis-Menten reaction implies that the reaction is essentially first order at low concentrations of the compound, and it approaches zero order after a certain high concentration.

26.3.5. Elimination

Excretion of the compounds refers to the removal of the compound and its metabolites from the body. As metabolism, excretion can occur in all organs/compartments except in the gut and stomach lumen and in the alveolar space and is described by a first-order reaction. This model assumes that the rate of excretion is proportional to the rate of change of the amount of the contaminant in the organ. Two specific excretion routes were also modeled: the biliary excretion and the excretion in feces. Contaminants excreted by bile enter in the gut lumen and can be reabsorbed.

26.4. Parameterisation:

MERLIN-Expo also contains a library of substances for which default values are provided and justified for each compound-specific parameter (e.g. partition coefficients).

26.5. Sensitivity assessment

Several sensitivity methods that are actually available were applied: ((ii) screening methods based on optimised experimental designs (e.g. Morris method), aiming at identifying non-influential parameters at low computational cost; (iii) global regression methods, relying on the strong assumption that the relationship between outputs and inputs is linear or monotonic (e.g., Standardised Regression Coefficients (SRC)); (iv) global variance-based methods (e.g., FAST, EFAST, Sobol'), considered as the most robust, but computationally expensive., as well as a

guidance document, allowing flexibility in the methods used according to the question that has to be addressed.

26.6. Assessment, validation

Model results were evaluated against available monitoring data (Venice, Belgium) to assess model reliability and its applicability to complex exposure scenario.

27. MENTOR-3P PBTK model (Xue et al., 2010)

27.1. Chemical compound(s):

Total and inorganic arsenic

27.2. Species and stages:

Humans

27.3. Model structure, main assumptions and processes:

27.3.1. Structure

A ‘‘flow-limited’’ PBPK formulation, representing a simplification of a generalised PBPK model of MENTOR-3P (Georgopoulos and Lioy, 2006), was adopted. The dynamics of four As circulating species (arsenates, arsenites, and the As metabolites MMA and DMA) in body compartments were captured using this PBPK model. Also characterised were the corresponding biomarker levels in urine.

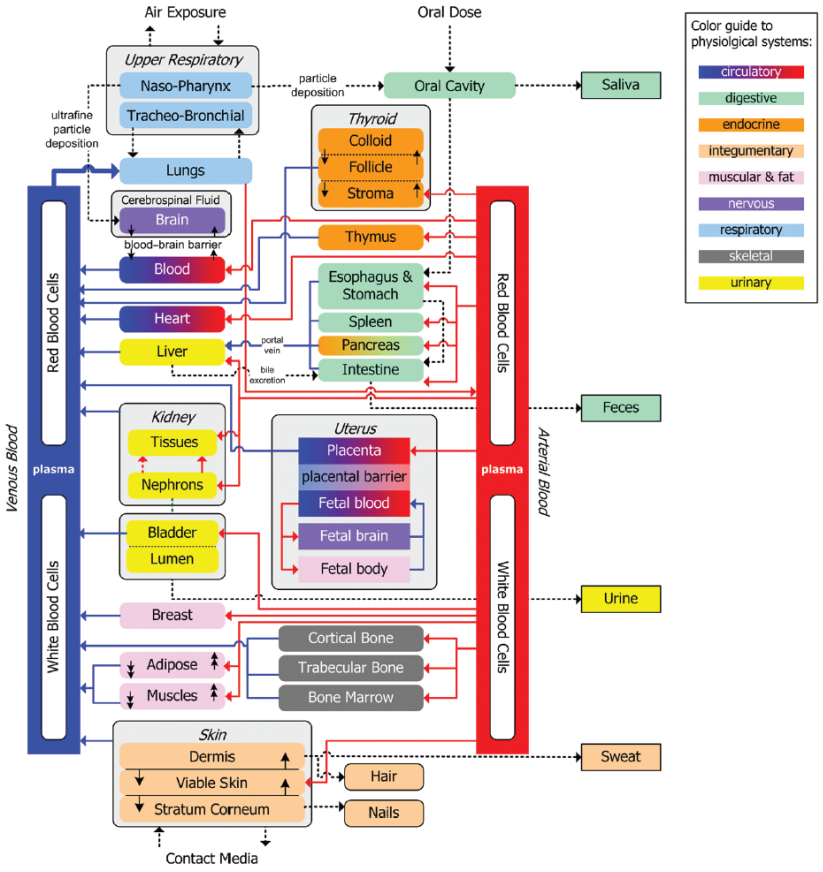

Figure 13: MENTOR-3P PBTK model structure

27.3.2. Oral exposure

Dietary and drinking water exposure. Total As residue data from the FDA’s ongoing Total Dietary Survey (TDS), also known as the market basket study (FDA 1991–2004), was used.

27.4. Parameterisation:

Cf. document “PBTK model refinement: parameterisation”.

27.5. Assessment, validation

Two types of model evaluation were conducted: a) SHEDS-Dietary predictions were compared with National Human Exposure Assessment Survey (NHEXAS) duplicate diet data; and b) linked SHEDS–MENTOR predictions were compared with NHANES biomonitoring data.

DISCUSSION

The present version of this document contains a synthesis on current PBTK models developed by different authors to represent the toxicokinetics of the first set of priority compounds determined in the HBM4EU project: phthalates/DINCH, bisphenols, PAHs, PFAS, BFRs, cadmium, chromium (VI), and pesticides (in the frame of mixtures). In addition, the available generic PBTK models, as well as their applicability domain are presented herein.

Most of the studied models were extrapolated to the human. Some of the models described herein were initially developed either for the rat or for the monkey, while two models realised an extrapolation between the non-pregnant and the pregnant physiological stages. This extrapolation included in both cases the variation of the body weight (BW) with the time of gestation and the variation of the cardiac output (CO) as a function of the metabolic BW ($BW^{0.75}$). Clewell et al. (2008) included specific equations for the growth of other components of the fetal or maternal organisms and, in the basis of *in vitro* results, modified the parameters of saturable metabolism from non-pregnant to pregnant stages.

The majority of the toxicokinetics processes represented in these models were considered as 1^{st} order kinetics. The representation of saturable kinetics was chosen in some cases, mainly for processes related to the metabolism and the elimination of some molecules. The choice of saturable kinetics for the different processes was not justified in some publications. With regards to the results of the model assessment, the choice of saturable instead of 1^{st} order renal resorption by Loccisano et al. (2011) is discussed later.

Either the oral, the inhaled and/or the dermal ways of exposure were represented.

The transfer of the molecule between the blood and the tissues was generally represented as perfusion-limited. It means that the transfer was a function of the blood flow to a specific tissue, the concentration of the molecule in the blood and in the tissue and the partition coefficient of the molecule between the tissue and the blood. Some authors represented the transfer to some compartments, or the transfer of a given metabolite as being diffusion-limited. In this case, the compartment was subdivided in two sub-compartments, one receiving the molecule directly by the blood irrigation, and the other sub-compartment receiving it from the previous sub-compartment with the participation of a permeability coefficient. The choice of the diffusion-limited distribution was not explained by the authors in some cases. Keys et al. (2000b) tested different model structures for the representation of the toxicokinetics of di(n-butyl) phthalate (DPB) and its metabolite mono(n-butyl) phthalate (MBP). In the case of the MBP, they decided to test a diffusion-limited model in reason of the high charge and the molecular weight of this molecule. Their results showed a better fit of the MBP kinetics with the diffusion-limited than with the perfusion-limited one. On the basis of Keys et al. (2000b) results, Clewell et al. (2008) selected a diffusion-limited model for the representation of the MBP toxicokinetics. In the gestational models studied, the transfer from the placenta to the fetus was represented as diffusion-limited. A good explanation for the choice of diffusion-limited transfer in some cases can be found in Heredia-Ortiz and Bouchard (2013): *"For each organ, it was determined whether the transfer was limited by tissue perfusion or diffusion (permeability), hence if a tissue: blood equilibrium was reached instantaneously or if the transfer to the tissue was limited by diffusion (permeability) of the molecule through the cell membranes"*. These authors based their choice for each tissue on the depuration curves obtained experimentally in rats by Marie et al. (2010).

Oppositely to other models that didn't include any binding mechanisms, the model of Loccisano et al. (2011) considered a free fraction (< 3%) of PFOA and PFOS in the plasma to take into account the high binding of these molecules to plasma proteins. The model of Teeguarden et al. (2005b)

included an explicit representation of the binding only in the uterus. This specificity is discussed later.

Reabsorption processes after the metabolism or the elimination of these molecules were represented in some models. These processes comprised the enterohepatic reabsorption from the (GI) tract to the liver and the renal resorption from a “filtrate” compartment to the kidney.

About the model structure, a too complex structure can be deleterious for the accuracy of the model. Effectively, each parameter value presents a given level of variability and the use of a high number of parameters (related to a complex model structure) increases the incertitude in the model.

Different ways to estimate the partition coefficients (PC) and the rate constants were used. They are developed in the *“PBTK model refinement: parameterisation”* document.

A sensitivity analysis was realised in most of the cases on the individual parameters and the results were normalised. The choice of the variables considered to test the sensitivity to each parameter is also an aspect to consider. In some cases in which saturable processes were represented, two analysis were realised for different doses. The objective was to test the sensitivity of the model to each parameter below and over a saturating dose. A simple and an interesting approach to analyse the results of the sensitivity analysis was realised by Hissink et al. (2009) , who classified the parameters from their S.A. results as being influent either on the body burden (similar influence on the concentrations of the molecule in different tissues) or on the partition of the molecule in the body (different impact in each tissue). Heredia-Ortiz et al. (2014) realised a stochastic variation of all the parameters simultaneously.

REFERENCES

Abraham, K., Mielke, H., Huisinga, W., Gundert-Remy, U., 2005. Elevated internal exposure of children in simulated acute inhalation of volatile organic compounds: effects of concentration and duration. Arch Toxicol 79, 63-73.

Agoram, B., Woltosz, W.S., Bolger, M.B., 2001. Predicting the impact of physiological and biochemical processes on oral drug bioavailability. Adv Drug Deliv Rev 50 Suppl 1, S41-67.

Amberg, A., Rosner, E., Dekant, W., 1999. Biotransformation and kinetics of excretion of methyl-tert-butyl ether in rats and humans. Toxicol Sci 51, 1-8.

Andra, S.S., Charisiadis, P., Karakitsios, S., Sarigiannis, D.A., Makris, K.C., 2015. Passive exposures of children to volatile trihalomethanes during domestic cleaning activities of their parents. Environmental research 136, 187-195.

ATSDR, 1995. Public Health Statement for Polycyclic Aromatic Hydrocarbons (PAHs).

ATSDR, 2002. Aniline. Division of Toxicology ToxFAQs.

ATSDR, 2011. Chromium Toxicity: What Are the Physiologic Effects of Chromium Exposure? Case Studies in Environmental Medicine (CSEM).

ATSDR, 2012. Public Health Statement: Chromium. Division of Toxicology and Human Health Sciences

ATSDR, 2017, Health Effects of PFAS, https://www.atsdr.cdc.gov/pfc/health_effects_pfcs.html,

Bader, M., Wrbitzky, R., Blaszkewicz, M., Schaper, M., van Thriel, C., 2008. Human volunteer study on the inhalational and dermal absorption of N-methyl-2-pyrrolidone (NMP) from the vapour phase. Arch Toxicol 82, 13-20.

Barter, Z.E., Bayliss, M.K., Beaune, P.H., Boobis, A.R., Carlile, D.J., Edwards, R.J., Houston, J.B., Lake, B.G., Lipscomb, J.C., Pelkonen, O.R., Tucker, G.T., Rostami-Hodjegan, A., 2007. Scaling factors for the extrapolation of in vivo metabolic drug clearance from in vitro data: reaching a consensus on values of human microsomal protein and hepatocellularity per gram of liver. Current drug metabolism 8, 33-45.

Beaudouin, R., Micallef, S., Brochot, C., 2010. A stochastic whole-body physiologically based pharmacokinetic model to assess the impact of inter-individual variability on tissue dosimetry over the human lifespan. Regulatory Toxicology and Pharmacology 57, 103-116.

Bechaux, C., Bodin, L., Clemencon, S., Crepet, A., 2014. PBPK and population modelling to interpret urine cadmium concentrations of the French population. Toxicol Appl Pharmacol 279, 364-372.

Bernareggi, A., Rowland, M., 1991. Physiologic modeling of cyclosporin kinetics in rat and man. J Pharmacokinet Biopharm 19, 21-50.

Blancato J.N., Power, F.W., Brown, R.N., Dary, C.C., 2006. Exposure Related Dose Estimating Model (ERDEM): A Physiologically-Based Pharmacokinetic and Pharmacodynamic (PBPK/PD) Model for Assessing Human Exposure and Risk.

Bogdanska, J., Borg, D., Sundstrom, M., Bergstrom, U., Halldin, K., Abedi-Valugerdi, M., Bergman, A., Nelson, B., DePierre, J., Nobel, S., 2011. Tissue distribution of S-35-labelled perfluorooctane

sulfonate in adult mice after oral exposure to a low environmentally relevant dose or a high experimental dose. Toxicology 284, 54-62.

Bois, F.Y., Jamei, M., Clewell, H.J., 2010. PBPK modelling of inter-individual variability in the pharmacokinetics of environmental chemicals. Toxicology 278, 256-267.

Brochot, C., Quindroit, P., 2018. Modelling the Fate of Chemicals in Humans Using a Lifetime Physiologically Based Pharmacokinetic (PBPK) Model in MERLIN-Expo, in: P. Ciffroy, A. Tediosi, E. Capri (Eds.), Modelling the Fate of Chemicals in the Environment and the Human Body. Springer International Publishing, Cham, pp. 215-257.

Campbell, J., Franzen, A., Van Landingham, C., Lumpkin, M., Crowell, S., Meredith, C., Loccisano, A., Gentry, R., Clewell, H., 2016. Predicting lung dosimetry of inhaled particleborne benzo[a]pyrene using physiologically based pharmacokinetic modeling. Inhal Toxicol 28, 520-535.

Castetbon, K., Vernay, M., Malon, A., Salanave, B., Deschamps, V., Roudier, C., Oleko, A., Szego, E., Hercberg, S., 2009. Dietary intake, physical activity and nutritional status in adults: the French nutrition and health survey (ENNS, 2006-2007). The British journal of nutrition 102, 733-743.

Choi, K., Joo, H., Campbell, J.L., Jr., Clewell, R.A., Andersen, M.E., Clewell, H.J., 3rd, 2012. In vitro metabolism of di(2-ethylhexyl) phthalate (DEHP) by various tissues and cytochrome P450s of human and rat. Toxicology in vitro : an international journal published in association with BIBRA 26, 315-322.

Ciffroy, P., Alfonso, B., Altenpohl, A., Banjac, Z., Bierkens, J., Brochot, C., Critto, A., De Wilde, T., Fait, G., Fierens, T., Garratt, J., Giubilato, E., Grange, E., Johansson, E., Radomyski, A., Reschwann, K., Suciu, N., Tanaka, T., Tediosi, A., Van Holderbeke, M., Verdonck, F., 2016. Modelling the exposure to chemicals for risk assessment: a comprehensive library of multimedia and PBPK models for integration, prediction, uncertainty and sensitivity analysis – the MERLIN-Expo tool. Science of The Total Environment 568, 770-784.

Clewell, H.J., Lee, T.-s., Carpenter, R.L., 1994. Sensitivity of Physiologically Based Pharmacokinetic Models to Variation in Model Parameters: Methylene Chloride. Risk Analysis 14, 521-531.

Clewell, R.A., Clewell, H.J., 3rd, 2008. Development and specification of physiologically based pharmacokinetic models for use in risk assessment. Regulatory toxicology and pharmacology : RTP 50, 129-143.

Clewell, R.A., Kremer, J.J., Williams, C.C., Campbell, J.L., Andersen, M.E., Borghoff, S.J., 2008. Tissue exposures to free and glucuronidated monobutylyphthalate in the pregnant and fetal rat following exposure to di-n-butylphthalate: Evaluation with a PBPK model. Toxicological Sciences 103, 241-259.

Coughlin, J.L., Thomas, P.E., Buckley, B., 2012a. Inhibition of genistein glucuronidation by bisphenol A in human and rat liver microsomes. Drug metabolism and disposition: the biological fate of chemicals 40, 481-485.

Coughlin, J.L., Thomas, P.E., Buckley, B., 2012b. Inhibition of Genistein Glucuronidation by Bisphenol A in Human and Rat Liver Microsomes. Drug Metabolism and Disposition 40, 481-485.

Court, M.H., Zhang, X., Ding, X., Yee, K.K., Hesse, L.M., Finel, M., 2012. Quantitative distribution of mRNAs encoding the 19 human UDP-glucuronosyltransferase enzymes in 26 adult and 3 fetal tissues. Xenobiotica 42, 266-277.

Crowell, S.R., Amin, S.G., Anderson, K.A., Krishnegowda, G., Sharma, A.K., Soelberg, J.J., Williams, D.E., Corley, R.A., 2011. Preliminary physiologically based pharmacokinetic models for benzo[a]pyrene and dibenzo[def,p]chrysene in rodents. Toxicol Appl Pharmacol 257, 365-376.

Csanady, G.A., Oberste-Frielinghaus, H.R., Semder, B., Baur, C., Schneider, K.T., Filser, J.G., 2002. Distribution and unspecific protein binding of the xenoestrogens bisphenol A and daidzein. Arch Toxicol 76, 299-305.

DeJongh, J., Verhaar, H.J.M., Hermens, J.L.M., 1997. A quantitative property-property relationship (QPPR) approach to estimate in vitro tissue blood partition coefficients of organic chemicals in rats and humans. Archives of Toxicology 72, 17-25.

Domingo, J.L., 2012. Health risks of dietary exposure to perfluorinated compounds. Environ Int 40, 187-195.

Droz, P.O., Wu, M.M., Cumberland, W.G., 1989. Variability in biological monitoring of organic-solvent exposure. 2. Application of a population physiological model. British Journal of Industrial Medicine 46, 547-558.

Edginton, A.N., Ritter, L., 2009a. Predicting plasma concentrations of bisphenol A in children younger than 2 years of age after typical feeding schedules, using a physiologically based toxicokinetic model. Environmental health perspectives 117, 645-652.

Edginton, A.N., Ritter, L., 2009b. Predicting plasma concentrations of bisphenol A in children younger than 2 years of age after typical feeding schedules, using a physiologically based toxicokinetic model. Environmental Health Perspectives 117, 645-652.

Edginton, A.N., Schmitt, W., Voith, B., Willmann, S., 2006a. A mechanistic approach for the scaling of clearance in children. Clin Pharmacokinet 45, 683-704.

Edginton, A.N., Schmitt, W., Willmann, S., 2006b. Development and evaluation of a generic physiologically based pharmacokinetic model for children. Clin Pharmacokinet 45, 1013-1034.

EFSA, 2015. Scientific Opinion on the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs: Executive summary.

Eissing, T., Kuepfer, L., Becker, C., Block, M., Coboeken, K., Gaub, T., Goerlitz, L., Jaeger, J., Loosen, R., Ludewig, B., Meyer, M., Niederalt, C., Sevestre, M., Siegmund, H.U., Solodenko, J., Thelen, K., Telle, U., Weiss, W., Wendl, T., Willmann, S., Lippert, J., 2011. A computational systems biology software platform for multiscale modeling and simulation: Integrating whole-body physiology, disease biology, and molecular reaction networks. Frontiers in Physiology FEB.

El-Masri, H.A., Kenyon, E.M., 2008. Development of a human physiologically based pharmacokinetic (PBPK) model for inorganic arsenic and its mono- and di-methylated metabolites. J Pharmacokinet Pharmacodyn 35, 31-68.

Emond, C., Birnbaum, L.S., DeVito, M.J., 2004. Physiologically based pharmacokinetic model for developmental exposures to TCDD in the rat. Toxicological Sciences 80, 115-133.

Emond, C., Raymer, J.H., Studabaker, W.B., Garner, C.E., Birnbaum, L.S., 2010. A physiologically based pharmacokinetic model for developmental exposure to BDE-47 in rats. Toxicology and Applied Pharmacology 242, 290-298.

Fabrega, F., Kumar, V., Schuhmacher, M., Domingo, J.L., Nadal, M., 2014. PBPK modeling for PFOS and PFOA: validation with human experimental data. Toxicol Lett 230, 244-251.

Fabrega, F., Nadal, M., Schuhmacher, M., Domingo, J.L., Kumar, V., 2016. Influence of the uncertainty in the validation of PBPK models: A case-study for PFOS and PFOA. Regulatory toxicology and pharmacology : RTP 77, 230-239.

FDA, 2014. Bisphenol A (BPA): Use in Food Contact Application.

Finley, B.L., Kerger, B.D., Katona, M.W., Gargas, M.L., Corbett, G.C., Paustenbach, D.J., 1997. Human ingestion of chromium (VI) in drinking water: pharmacokinetics following repeated exposure. Toxicol Appl Pharmacol 142, 151-159.

Fisher, J.W., Twaddle, N.C., Vanlandingham, M., Doerge, D.R., 2011. Pharmacokinetic modeling: prediction and evaluation of route dependent dosimetry of bisphenol A in monkeys with extrapolation to humans. Toxicol Appl Pharmacol 257, 122-136.

Franks, S.J., Spendiff, M.K., Cocker, J., Loizou, G.D., 2006. Physiologically based pharmacokinetic modelling of human exposure to 2-butoxyethanol. Toxicol Lett 162, 164-173.

Ganzleben, C., Antignac, J.P., Barouki, R., Castano, A., Fiddicke, U., Klanova, J., Lebret, E., Olea, N., Sarigiannis, D., Schoeters, G.R., Sepai, O., Tolonen, H., Kolossa-Gehring, M., 2017. Human biomonitoring as a tool to support chemicals regulation in the European Union. Int J Hyg Environ Health 220, 94-97.

Georgopoulos, P.G., Lioy, P.J., 2006. From a theoretical framework of human exposure and dose assessment to computational system implementation: the Modeling ENvironment for TOtal Risk Studies (MENTOR). Journal of toxicology and environmental health. Part B, Critical reviews 9, 457-483.

Georgopoulos, P.G., Sasso, A.F., Isukapalli, S.S., Lioy, P.J., Vallero, D.A., Okino, M., Reiter, L., 2008a. Reconstructing population exposures to environmental chemicals from biomarkers: challenges and opportunities. Journal of Exposure Science and Environmental Epidemiology 19, 149-171.

Georgopoulos, P.G., Wang, S.W., Yang, Y.C., Xue, J., Zartarian, V.G., McCurdy, T., Ozkaynak, H., 2008b. Biologically based modeling of multimedia, multipathway, multiroute population exposures to arsenic. Journal of Exposure Science and Environmental Epidemiology 18, 462-476.

Gilden, R.C., Huffling, K., Sattler, B., 2010. Pesticides and health risks. Journal of obstetric, gynecologic, and neonatal nursing : JOGNN 39, 103-110.

Harrison, J.H., Jr., Jollow, D.J., 1986. Role of aniline metabolites in aniline-induced hemolytic anemia. The Journal of pharmacology and experimental therapeutics 238, 1045-1054.

Harrison, J.H., Jr., Jollow, D.J., 1987. Contribution of aniline metabolites to aniline-induced methemoglobinemia. Mol Pharmacol 32, 423-431.

Hartung, T., Luechtefeld, T., Maertens, A., Kleensang, A., 2013. Integrated testing strategies for safety assessments. Altex 30, 3-18.

Heredia-Ortiz, R., Bouchard, M., 2013. Understanding the linked kinetics of benzo(a)pyrene and 3-hydroxybenzo(a)pyrene biomarker of exposure using physiologically-based pharmacokinetic modelling in rats. Journal of Pharmacokinetics and Pharmacodynamics 40, 669-682.

Heredia-Ortiz, R., Maitre, A., Barbeau, D., Lafontaine, M., Bouchard, M., 2014. Use of Physiologically-Based Pharmacokinetic Modeling to Simulate the Profiles of 3-Hydroxybenzo(a) pyrene in Workers Exposed to Polycyclic Aromatic Hydrocarbons. Plos One 9, e102570.

Heudorf, U., Mersch-Sundermann, V., Angerer, J., 2007. Phthalates: Toxicology and exposure. International Journal of Hygiene and Environmental Health 210, 623-634.

Hissink, A.M., Kulig, B.M., Kruse, J., Freidig, A.P., Verwei, M., Muijser, H., Lammers, J., McKee, R.H., Owen, D.E., Sweeney, L.M., Salmon, F., 2009. Physiologically Based Pharmacokinetic Modeling of Cyclohexane as a Tool for Integrating Animal and Human Test Data. International Journal of Toxicology 28, 498-509.

ICRP, 2002. Basic anatomical and physiological data for use in radiological protection: reference values, in: J. Valentin (Ed.), The International Commission on Radiological Protection.

Jarup, L., Akesson, A., 2009. Current status of cadmium as an environmental health problem. Toxicol Appl Pharmacol 238, 201-208.

Johnson, J.D., Gibson, S.J., Ober, R.E., 1984. Cholestyramine-enhanced fecal elimination of carbon-14 in rats after administration of ammonium [14C]perfluorooctanoate or potassium [14C]perfluorooctanesulfonate. Fundam Appl Toxicol 4, 972-976.

Jongeneelen, F.J., Anzion, R.B., Scheepers, P.T., Bos, R.P., Henderson, P.T., Nijenhuis, E.H., Veenstra, S.J., Brouns, R.M., Winkes, A., 1988. 1-Hydroxypyrene in urine as a biological indicator of exposure to polycyclic aromatic hydrocarbons in several work environments. The Annals of occupational hygiene 32, 35-43.

Jongeneelen, F.J., Berge, W.F.T., 2011. A generic, cross-chemical predictive PBTK model with multiple entry routes running as application in MS Excel; design of the model and comparison of predictions with experimental results. Annals of Occupational Hygiene 55, 841-864.

Jongeneelen, F.J., Ten Berge, W.F., 2011. A Generic, Cross-Chemical Predictive PBTK Model with Multiple Entry Routes Running as Application in MS Excel; Design of the Model and Comparison of Predictions with Experimental Results. Annals of Occupational Hygiene 55, 841-864.

Judson, R.S., Houck, K.A., Kavlock, R.J., Knudsen, T.B., Martin, M.T., Mortensen, H.M., Reif, D.M., Rotroff, D.M., Shah, I., Richard, A.M., Dix, D.J., 2010. In vitro screening of environmental chemicals for targeted testing prioritization: The toxcast project. Environmental Health Perspectives 118, 485-492.

Judson, R.S., Kavlock, R.J., Setzer, R.W., Cohen Hubal, E.A., Martin, M.T., Knudsen, T.B., Houck, K.A., Thomas, R.S., Wetmore, B.A., Dix, D.J., 2011. Estimating toxicity-related biological pathway altering doses for high-throughput chemical risk assessment. Chemical Research in Toxicology 24, 451-462.

Kamrin, M.A., 2009. Phthalate risks, phthalate regulation, and public health: a review. Journal of toxicology and environmental health. Part B, Critical reviews 12, 157-174.

Kawamoto, Y., Matsuyama, W., Wada, M., Hishikawa, J., Chan, M.P., Nakayama, A., Morisawa, S., 2007. Development of a physiologically based pharmacokinetic model for bisphenol A in pregnant mice. Toxicol Appl Pharmacol 224, 182-191.

Kearney, T.E., Manoguerra, A.S., Dunford, J.V., 1984. Chemically induced methemoglobinemia from aniline poisoning. Western Journal of Medicine 140, 282-286.

Keith, L.H., 1997. Environmental Endocrine Disruptors: A Handbook of Property Data. Wiley.

Kerger, B.D., Paustenbach, D.J., Corbett, G.E., Finley, B.L., 1996. Absorption and elimination of trivalent and hexavalent chromium in humans following ingestion of a bolus dose in drinking water. Toxicol Appl Pharmacol 141, 145-158.

Keys, D.A., Wallace, D.G., Kepler, T.B., Conolly, R.B., 2000a. Quantitative evaluation of alternative mechanisms of blood disposition of di(n-butyl) phthalate and mono(n-butyl) phthalate in rats. Toxicol Sci 53, 173-184.

Keys, D.A., Wallace, D.G., Kepler, T.B., Conolly, R.B., 2000b. Quantitative evaluation of alternative mechanisms of blood disposition of di(n-butyl) phthalate and mono(n-butyl) phthalate in rats. Toxicological Sciences 53, 173-184.

Kirman, C.R., Aylward, L.L., Suh, M., Harris, M.A., Thompson, C.M., Haws, L.C., Proctor, D.M., Lin, S.S., Parker, W., Hays, S.M., 2013a. Physiologically based pharmacokinetic model for humans orally exposed to chromium. Chem Biol Interact 204, 13-27.

Kirman, C.R., Hays, S.M., Aylward, L.L., Suh, M., Harris, M.A., Thompson, C.M., Haws, L.C., Proctor, D.M., 2012. Physiologically based pharmacokinetic model for rats and mice orally exposed to chromium. Chem Biol Interact 200, 45-64.

Kjellström, T., Nordberg, G.F., 1978. A kinetic model of cadmium metabolism in the human being. Environmental Research 16, 248-269.

Klaassen, C.D., 2007. Casarett & Doull's Toxicology: The Basic Science of Poisons, Seventh Edition. McGraw-Hill Education.

Koch, H.M., Angerer, J., Drexler, H., Eckstein, R., Weisbach, V., 2005. Di(2-ethylhexyl)phthalate (DEHP) exposure of voluntary plasma and platelet donors. Int J Hyg Environ Health 208, 489-498.

Koch, H.M., Drexler, H., Angerer, J., 2003. An estimation of the daily intake of di(2-ethylhexyl)phthalate (DEHP) and other phthalates in the general population. International Journal of Hygiene and Environmental Health 206, 77-83.

Kramer, A., Below, H., Bieber, N., Kampf, G., Toma, C.D., Huebner, N.-O., Assadian, O., 2007. Quantity of ethanol absorption after excessive hand disinfection using three commercially available hand rubs is minimal and below toxic levels for humans. BMC infectious diseases 7, 117-117.

Krauss, M., Schaller, S., Borchers, S., Findeisen, R., Lippert, J., Kuepfer, L., 2012. Integrating Cellular Metabolism into a Multiscale Whole-Body Model. PLoS Computational Biology 8.

Kudo, N., Sakai, A., Mitsumoto, A., Hibino, Y., Tsuda, T., Kawashima, Y., 2007. Tissue distribution and hepatic subcellular distribution of perfluorooctanoic acid at low dose are different from those at high dose in rats. Biological & Pharmaceutical Bulletin 30, 1535-1540.

Kurebayashi, H., Harada, R., Stewart, R.K., Numata, H., Ohno, Y., 2002. Disposition of a low dose of bisphenol a in male and female cynomolgus monkeys. Toxicol Sci 68, 32-42.

Kurebayashi, H., Okudaira, K., Ohno, Y., 2010. Species difference of metabolic clearance of bisphenol A using cryopreserved hepatocytes from rats, monkeys and humans. Toxicology Letters 198, 210-215.

Lafontaine, M., Gendre, C., Delsaut, P., Simon, P., 2004. URINARY 3-HYDROXYBENZO[A]PYRENE AS A BIOMARKER OF EXPOSURE TO POLYCYCLIC AROMATIC HYDROCARBONS: AN APPROACH FOR DETERMINING A BIOLOGICAL LIMIT VALUE. Polycyclic Aromatic Compounds 24, 441-450.

Langard, S., 1990. One hundred years of chromium and cancer: a review of epidemiological evidence and selected case reports. Am J Ind Med 17, 189-215.

Lee, C.H., Kim, S.H., Kwon, D.H., Jang, K.H., Chung, Y.H., Moon, J.D., 2013. Two Cases of Methemoglobinemia Induced by the Exposure to Nitrobenzene and Aniline. Annals of Occupational and Environmental Medicine 25, 31-31.

Lee, S.K., Ou, Y.C., Andersen, M.E., Yang, R.S.H., 2007. A physiologically based pharmacokinetic model for lactational transfer of PCB 153 with or without PCB 126 in mice. Archives of Toxicology 81, 101-111.

Leeder, J.S., 2009. Developmental pharmacogenetics: A general paradigm for application to neonatal pharmacology and toxicology. Clinical Pharmacology and Therapeutics 86, 678-682.

Loccisano, A.E., Campbell, J.L., Andersen, M.E., Clewell, H.J., 2011. Evaluation and prediction of pharmacokinetics of PFOA and PFOS in the monkey and human using a PBPK model. Regulatory Toxicology and Pharmacology 59, 157-175.

Loccisano, A.E., Campbell, J.L., Jr., Butenhoff, J.L., Andersen, M.E., Clewell, H.J., 3rd, 2012. Evaluation of placental and lactational pharmacokinetics of PFOA and PFOS in the pregnant, lactating, fetal and neonatal rat using a physiologically based pharmacokinetic model. Reprod Toxicol 33, 468-490.

Loccisano, A.E., Longnecker, M.P., Campbell, J.L., Andersen, M.E., Clewell, H.J., 2013a. Development of PBPK Models for PFOA and PFOS for Human Pregnancy and Lactation Life Stages. Journal of toxicology and environmental health. Part A 76, 25-57.

Loizou, G., Spendiff, M., Barton, H.A., Bessems, J., Bois, F.Y., d'Yvoire, M.B., Buist, H., Clewell, H.J., Meek, B., Gundert-Remy, U., Goerlitz, G., Schmitt, W., 2008. Development of good modelling practice for physiologically based pharmacokinetic models for use in risk assessment: The first steps. Regulatory Toxicology and Pharmacology 50, 400-411.

Lu, C., Holbrook, C.M., Andres, L.M., 2010. The implications of using a physiologically based pharmacokinetic (PBPK) model for pesticide risk assessment. Environ Health Perspect 118, 125-130.

Ma, T., Chambers, J.E., 1994. Kinetic parameters of desulfuration and dearylation of parathion and chlorpyrifos by rat liver microsomes. Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association 32, 763-767.

Ma, T., Chambers, J.E., 1995. A kinetic analysis of hepatic microsomal activation of parathion and chlorpyrifos in control and phenobarbital-treated rats. Journal of biochemical toxicology 10, 63-68.

McNally, K., R. Cotton, A. Hogg & G. Loizou (2014) PopGen: A virtual human population generator. *Toxicology,* 315**,** 70-85.

Maestri, L., Negri, S., Ferrari, M., Ghittori, S., Fabris, F., Danesino, P., Imbriani, M., 2006. Determination of perfluorooctanoic acid and perfluorooctanesulfonate in human tissues by liquid chromatography/single quadrupole mass spectrometry. Rapid communications in mass spectrometry : RCM 20, 2728-2734.

Mandiwana, K.L., Panichev, N., Panicheva, S., 2011. Determination of chromium(VI) in black, green and herbal teas. Food Chemistry 129, 1839-1843.

Marie, C., Bouchard, M., Heredia-Ortiz, R., Viau, C., Maître, A., 2010. A toxicokinetic study to elucidate 3-hydroxybenzo(a)pyrene atypical urinary excretion profile following intravenous injection of benzo(a)pyrene in rats. Journal of Applied Toxicology 30, 402-410.

Meeker, J.D., Sathyanarayana, S., Swan, S.H., 2009. Phthalates and other additives in plastics: human exposure and associated health outcomes. Philosophical transactions of the Royal Society of London. Series B, Biological sciences 364, 2097-2113.

Meulenberg, C.J., Vijverberg, H.P., 2000. Empirical relations predicting human and rat tissue:air partition coefficients of volatile organic compounds. Toxicol Appl Pharmacol 165, 206-216.

Mielke, H., Gundert-Remy, U., 2009. Bisphenol A levels in blood depend on age and exposure. Toxicology Letters 190, 32-40.

Mielke, H., Partosch, F., Gundert-Remy, U., 2011. The contribution of dermal exposure to the internal exposure of bisphenol A in man. Toxicology Letters 204, 190-198.

Mills, C.T., Morrison, J.M., Goldhaber, M.B., Ellefsen, K.J., 2011. Chromium(VI) generation in vadose zone soils and alluvial sediments of the southwestern Sacramento Valley, California: a potential source of geogenic Cr(VI) to groundwater. Applied Geochemistry 26, 1488-1501.

Minoia, C., Cavalleri, A., 1988. Chromium in urine, serum and red blood cells in the biological monitoring of workers exposed to different chromium valency states. Sci Total Environ 71, 323-327.

Mitragotri, S., Anissimov, Y.G., Bunge, A.L., Frasch, H.F., Guy, R.H., Hadgraft, J., Kasting, G.B., Lane, M.E., Roberts, M.S., 2011. Mathematical models of skin permeability: An overview. International Journal of Pharmaceutics 418, 115-129.

Mittermeier, A., Volkel, W., Fromme, H., 2016. Kinetics of the phthalate metabolites mono-2-ethylhexyl phthalate (MEHP) and mono-n-butyl phthalate (MnBP) in male subjects after a single oral dose. Toxicol Lett 252, 22-28.

Moreau, M., Leonard, J., Phillips, K.A., Campbell, J., Pendse, S.N., Nicolas, C., Phillips, M., Yoon, M., Tan, Y.M., Smith, S., Pudukodu, H., Isaacs, K., Clewell, H., 2017. Using exposure prediction tools to link exposure and dosimetry for risk-based decisions: A case study with phthalates. Chemosphere 184, 1194-1201.

Morgan, M.G., Henrion, M., Small, M., 1992. Uncertainty: A Guide to Dealing with Uncertainty in Quantitative Risk and Policy Analysis. Cambridge University Press.

Mortensen, S.R., Chanda, S.M., Hooper, M.J., Padilla, S., 1996. Maturational differences in chlorpyrifos-oxonase activity may contribute to age-related sensitivity to chlorpyrifos. Journal of biochemical toxicology 11, 279-287.

National Research Council, 2008. Phthalates and Cumulative Risk Assessment: The Tasks Ahead. The National Academies Press, Washington, DC.

Nguyen, H.Q., Stamatis, S.D., Kirsch, L.E., 2015. A Novel Method for Assessing Drug Degradation Product Safety Using Physiologically-Based Pharmacokinetic Models and Stochastic Risk Assessment. Journal of Pharmaceutical Sciences 104, 3101-3119.

Nicolopoulou-Stamati, P., Maipas, S., Kotampasi, C., Stamatis, P., Hens, L., 2016. Chemical Pesticides and Human Health: The Urgent Need for a New Concept in Agriculture. Frontiers in Public Health 4, 148.

Nordberg, G.F., Fowler, B.A., Nordberg, M., 2014. Handbook on the Toxicology of Metals. Elsevier Science.

O'Flaherty, E.J., 1993. Physiologically based models for bone-seeking elements. IV. Kinetics of lead disposition in humans. Toxicol Appl Pharmacol 118, 16-29.

O'Flaherty, E.J., 1996. A physiologically based model of chromium kinetics in the rat. Toxicol Appl Pharmacol 138, 54-64.

O'Flaherty, E.J., Kerger, B.D., Hays, S.M., Paustenbach, D.J., 2001. A physiologically based model for the ingestion of chromium(III) and chromium(VI) by humans. Toxicological sciences : an official journal of the Society of Toxicology 60, 196-213.

O'Flaherty, E.J., 1995. Chromium Toxicokinetics, in: R.A. Goyer, M.G. Cherian (Eds.), Toxicology of Metals: Biochemical Aspects. Springer Berlin Heidelberg, Berlin, Heidelberg, pp. 215-228.

Oze, C., Bird, D.K., Fendorf, S., 2007. Genesis of hexavalent chromium from natural sources in soil and groundwater. Proc Natl Acad Sci U S A 104, 6544-6549.

Papadaki, K.C., Karakitsios, S.P., Sarigiannis, D.A., 2017. Modeling of adipose/blood partition coefficient for environmental chemicals. Food and Chemical Toxicology 110, 274-285.

Paustenbach, D.J., Hays, S., Kerger, B.D., Finley, B., 1999. An analysis of inter-individual variability in uptake and elimination of chromium from human volunteers. Toxicologist 30.

Pettersson, S., Söderholm, B., Persson, J.E., Eriksson, S., Fritjofsson, Å., 1973. Testicular Blood Flow in Man Measured with Venous Occlusion Plethysmography and Xenon. Scandinavian Journal of Urology and Nephrology 7, 115-119.

Peyret, T., Krishnan, K., 2011. QSARs for PBPK modelling of environmental contaminants. SAR and QSAR in Environmental Research 22, 129-169.

Pond, A.L., Chambers, H.W., Chambers, J.E., 1995. Organophosphate detoxication potential of various rat tissues via A-esterase and aliesterase activities. Toxicol Lett 78, 245-252.

Pottenger, L.H., Domoradzki, J.Y., Markham, D.A., Hansen, S.C., Cagen, S.Z., Waechter, J.M., 2000. The relative bioavailability and metabolism of bisphenol A in rats is dependent upon the route of administration. Toxicological Sciences 54, 3-18.

Poulin, P., Krishnan, K., 1995a. An algorithm for predicting tissue: Blood partition coefficients of organic chemicals from n-octanol: Water partition coefficient data. Journal of Toxicology and Environmental Health 46, 117-129.

Poulin, P., Krishnan, K., 1995b. A biologically-based algorithm for predicting human tissue: blood partition coefficients of organic chemicals. Human & experimental toxicology 14, 273-280.

Poulin, P., Krishnan, K., 1996. Molecular Structure-Based Prediction of the Partition Coefficients of Organic Chemicals for Physiological Pharmacokinetic Models. Toxicology Methods 6, 117-137.

Poulin, P., Theil, F.P., 2000. A priori prediction of tissue:plasma partition coefficients of drugs to facilitate the use of physiologically-based pharmacokinetic models in drug discovery. J Pharm Sci 89, 16-35.

Price, K., Krishnan, K., 2011. 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 22, 107-128.

Ramsey, J.C., Andersen, M.E., 1984. A physiologically based description of the inhalation pharmacokinetics of styrene in rats and humans. Toxicology and Applied Pharmacology 73, 159-175.

Rodgers, T., Leahy, D., Rowland, M., 2005. Physiologically based pharmacokinetic modeling 1: Predicting the tissue distribution of moderate-to-strong bases. Journal of Pharmaceutical Sciences 94, 1259-1276.

Rodgers, T., Rowland, M., 2006. Physiologically based pharmacokinetic modelling 2: Predicting the tissue distribution of acids, very weak bases, neutrals and zwitterions. Journal of Pharmaceutical Sciences 95, 1238-1257.

Ruiz, P., Fowler, B.A., Osterloh, J.D., Fisher, J., Mumtaz, M., 2010a. Physiologically based pharmacokinetic (PBPK) tool kit for environmental pollutants--metals. SAR QSAR Environ Res 21, 603-618.

Ruiz, P., Mumtaz, M., Osterloh, J., Fisher, J., Fowler, B.A., 2010b. Interpreting NHANES biomonitoring data, cadmium. Toxicol Lett 198, 44-48.

Sanborn, M., Kerr, K.J., Sanin, L.H., Cole, D.C., Bassil, K.L., Vakil, C., 2007. Non-cancer health effects of pesticides: systematic review and implications for family doctors. Canadian family physician Medecin de famille canadien 53, 1712-1720.

Sarigiannis, D., Gotti, A., Karakitsios, S., 2011. A Computational Framework for Aggregate and Cumulative Exposure Assessment. Epidemiology 22, S96-S97.

Sarigiannis, D., Karakitsios, S., 2011. Perinatal Exposure to Bisphenol A: The Route of Administration Makes the Dose. Epidemiology 22, S172.

Sarigiannis, D., Karakitsios, S., Gotti, A., Loizou, G., Cherrie, J., Smolders, R., De Brouwere, K., Galea, K., Jones, K., Handakas, E., Papadaki, K., Sleeuwenhoek, A., 2014. Integra: From global scale contamination to tissue dose, Proceedings - 7th International Congress on Environmental Modelling and Software: Bold Visions for Environmental Modeling, iEMSs 2014, pp. 1001-1008.

Sarigiannis, D.A., 2017. Assessing the impact of hazardous waste on children's health: The exposome paradigm. Environ Res 158, 531-541.

Sarigiannis, D.A., Gotti, A., 2008. Biology-based dose-response models for health risk assessment of chemical mixtures. Fresenius Environmental Bulletin 17, 1439-1451.

Sarigiannis, D.A., Hansen, U., 2012. Considering the cumulative risk of mixtures of chemicals - A challenge for policy makers. Environmental Health: A Global Access Science Source 11.

Sarigiannis, D.A., Karakitsios, S.P., 2012. A dynamic physiology based pharmacokinetic model for assessing lifelong internal dose, AIChE 2012, Pittsburgh, PA.

Sarigiannis, D.A., Karakitsios, S.P., Handakas, E., Simou, K., Solomou, E., Gotti, A., 2016. Integrated exposure and risk characterization of bisphenol-A in Europe. Food and Chemical Toxicology 98, 134-147.

Sarigiannis, D.A., Papadaki, K., Kontoroupis, P., Karakitsios, S.P., 2017. Development of QSARs for parameterizing Physiology Based ToxicoKinetic models. Food and Chemical Toxicology 106, 114-124.

Sasso, A.F., Isukapalli, S.S., Georgopoulos, P.G., 2010. A generalized physiologically-based toxicokinetic modeling system for chemical mixtures containing metals. Theoretical Biology and Medical Modelling 7.

Satarug, S., Garrett, S.H., Sens, M.A., Sens, D.A., 2010. Cadmium, environmental exposure, and health outcomes. Environ Health Perspect 118, 182-190.

Schmitt, W., 2008. General approach for the calculation of tissue to plasma partition coefficients. Toxicology in Vitro 22, 457-467.

Sharma, R.P., Schuhmacher, M., Kumar, V., 2017. Developing integrated PBPK/PD coupled mechanistic pathway model (miRNA-BDNF): An approach towards system toxicology. Toxicol Lett 280, 79-91.

Sharma, R.P., Schuhmacher, M., Kumar, V., 2018a. The development of a pregnancy PBPK Model for Bisphenol A and its evaluation with the available biomonitoring data. Science of Total Environment *in press*.

Sharma, R.P., Schuhmacher, M., Kumar, V., 2018b. Physiology based Pharmacokinetic (PBPK) modeling for DEHP metabolites integrating its in vitro metabolism: a bottom up modeling approach. Toxicology Letters *Submitted*.

Shin, B.S., Kim, C.H., Jun, Y.S., Kim, D.H., Lee, B.M., Yoon, C.H., Park, E.H., Lee, B.M., Yoon, C.H., Park, E.H., Lee, K.C., Han, S.Y., Park, K.L., Kim, H.S., Yoo, S.D., 2004a. Physiologically based pharmacokinetics of bisphenol A. Journal of Toxicology and Environmental Health - Part A 67, 1971-1985.

Shin, B.S., Kim, C.H., Jun, Y.S., Kim, D.H., Lee, B.M., Yoon, C.H., Park, E.H., Lee, K.C., Han, S.Y., Park, K.L., Kim, H.S., Yoo, S.D., 2004b. Physiologically based pharmacokinetics of bisphenol A. Journal of toxicology and environmental health. Part A 67, 1971-1985.

Stern, A.H., 2010. A quantitative assessment of the carcinogenicity of hexavalent chromium by the oral route and its relevance to human exposure. Environ Res 110, 798-807.

Sultatos, L.G., 1994. Mammalian toxicology of organophosphorus pesticides. J Toxicol Environ Health 43, 271-289.

Sultatos, L.G., Murphy, S.D., 1983. Kinetic analyses of the microsomal biotransformation of the phosphorothioate insecticides chlorpyrifos and parathion. Fundam Appl Toxicol 3, 16-21.

Swan, S.H., 2008. Environmental phthalate exposure in relation to reproductive outcomes and other health endpoints in humans. Environmental research 108, 177-184.

Tan, Y.M., Liao, K., Conolly, R., Blount, B., Mason, A., Clewell, H., 2006. Use of a physiologically based pharmacokinetic model to identify exposures consistent with human biomonitoring data for chloroform. Journal of Toxicology and Environmental Health - Part A: Current Issues 69, 1727-1756.

Teeguarden, J.G., Waechter, J.M., Clewell, H.J., Covington, T.R., Barton, H.A., 2005a. Evaluation of oral and intravenous route pharmacokinetics, plasma protein binding, and uterine tissue dose metrics of bisphenol A: A physiologically based pharmacokinetic approach. Toxicological Sciences 85, 823-838.

Teeguarden, J.G., Waechter Jr, J.M., Clewell III, H.J., Covington, T.R., Barton, H.A., 2005b. Evaluation of oral and intravenous route pharmacokinetics, plasma protein binding, and uterine

tissue dose metrics of bisphenol A: A physiologically based pharmacokinetic approach. Toxicological Sciences 85, 823-838.

ten Berge, W., 2009. A simple dermal absorption model: derivation and application. Chemosphere 75, 1440-1445.

Thayer, K.A., Doerge, D.R., Hunt, D., Schurman, S.H., Twaddle, N.C., Churchwell, M.I., Garantziotis, S., Kissling, G.E., Easterling, M.R., Bucher, J.R., Birnbaum, L.S., 2015. Pharmacokinetics of Bisphenol A in Humans Following a Single Oral Administration. Environment international 83, 107-115.

Timchalk, C., Nolan, R.J., Mendrala, A.L., Dittenber, D.A., Brzak, K.A., Mattsson, J.L., 2002. A Physiologically based pharmacokinetic and pharmacodynamic (PBPK/PD) model for the organophosphate insecticide chlorpyrifos in rats and humans. Toxicological sciences : an official journal of the Society of Toxicology 66, 34-53.

Touitou, E., 2002. Drug delivery across the skin. Expert Opinion on Biological Therapy 2, 723-733.

Upmeier, A., Degen, G.H., Diel, P., Michna, H., Bolt, H.M., 2000. Toxicokinetics of bisphenol A in female DA/Han rats after a single i.v. and oral administration. Archives of Toxicology 74, 431-436.

USEPA, 2013. Provisional Guidance for Quantitative Risk Assessment of Polycyclic Aromatic Hydrocarbons.

Valcke, M., Krishnan, K., 2011. Evaluation of the impact of the exposure route on the human kinetic adjustment factor. Regulatory Toxicology and Pharmacology 59, 258-269.

Valentin, J., 2002. Basic anatomical and physiological data for use in radiological protection: reference values. A report of age- and gender-related differences in the anatomical and physiological characteristics of reference individuals. ICRP Publication 89. Ann ICRP 32, 5-265.

Vanden Heuvel, J.P., Kuslikis, B.I., Van Rafelghem, M.J., Peterson, R.E., 1991. Tissue distribution, metabolism, and elimination of perfluorooctanoic acid in male and female rats. Journal of biochemical toxicology 6, 83-92.

Ventura, C., Latino, D.A.R.S., Martins, F., 2013. Comparison of Multiple Linear Regressions and Neural Networks based QSAR models for the design of new antitubercular compounds. European journal of medicinal chemistry 70, 831-845.

Verner, M.A., Charbonneau, M., Lopez-Carrillo, L., Haddad, S., 2008. Physiologically based pharmacokinetic modeling of persistent organic pollutants for lifetime exposure assessment: A new tool in breast cancer epidemiologic studies. Environmental Health Perspectives 116, 886-892.

Wagner, J.G., 1973. Properties of Michaelis-Menten equation and its integrated form which are useful in pharmacokinetics. Journal of Pharmacokinetics and Biopharmaceutics 1, 103-121.

Wang, X.F., Santostefano, M.J., Evans, M.V., Richardson, V.M., Diliberto, J.J., Birnbaum, L.S., 1997. Determination of parameters responsible for pharmacokinetic behavior of TCDD in female Sprague-Dawley rats. Toxicology and Applied Pharmacology 147, 151-168.

WHO, 2010. Exposure to highly hazardous pesticides: A major public health concern, Geneva, Switzerland.

Willhite, C.C., Ball, G.L., McLellan, C.J., 2008. Derivation of a bisphenol A oral reference dose (RfD) and drinking-water equivalent concentration. Journal of toxicology and environmental health. Part B, Critical reviews 11, 69-146.

Willmann, S., Lippert, J., Sevestre, M., Solodenko, J., Fois, F., Schmitt, W., 2003a. PK-Sim®: A physiologically based pharmacokinetic 'whole-body' model. Drug Discovery Today: BIOSILICO 1, 121-124.

Willmann, S., Schmitt, W., Keldenich, J., Dressman, J.B., 2003b. A Physiologic Model for Simulating Gastrointestinal Flow and Drug Absorption in Rats. Pharmaceutical Research 20, 1766-1771.

Willmann, S., Schmitt, W., Keldenich, J., Lippert, J., Dressman, J.B., 2004a. A physiological model for the estimation of the fraction dose absorbed in humans. J Med Chem 47, 4022-4031.

Willmann, S., Schmitt, W., Keldenich, J., Lippert, J., Dressman, J.B., 2004b. A physiological model for the estimation of the fraction dose absorbed in humans. Journal of Medicinal Chemistry 47, 4022-4031.

World Health Organization, 2010. WHO Guidelines for Indoor Air Quality: Selected Pollutants. WHO.

Xue, J., Zartarian, V., Wang, S.W., Liu, S.V., Georgopoulos, P., 2010. Probabilistic modeling of dietary arsenic exposure and dose and evaluation with 2003-2004 NHANES data. Environmental Health Perspectives 118, 345-350.

Yang, X., Doerge, D.R., Teeguarden, J.G., Fisher, J.W., 2015. Development of a physiologically based pharmacokinetic model for assessment of human exposure to bisphenol A. Toxicol Appl Pharmacol 289, 442-456.

Yang, Y., Xu, X., Georgopoulos, P.G., 2010. A Bayesian population PBPK model for multiroute chloroform exposure. Journal of Exposure Science and Environmental Epidemiology 20, 326-341.

Yu, D., 1999a. A pharmacokinetic modeling of inorganic arsenic: a short-term oral exposure model for humans. Chemosphere 39, 2737-2747.

Yu, D., 1999b. A Physiologically Based Pharmacokinetic Model of Inorganic Arsenic. Regulatory Toxicology and Pharmacology 29, 128-141.

Yu, L.X., Amidon, G.L., 1999. A compartmental absorption and transit model for estimating oral drug absorption. International journal of pharmaceutics 186, 119-125.

14 ANNEX 2: PBTK model refinement: parameterisation

Table of Contents

1. Introduction

In the frame of the HBM4EU project, precisely the WP12, a previous document (title: *"PBTK models review"*) has been developed which summarises different PBTK models that represent the toxicokinetics of the priority compounds in the animal and/or the human.

The current document presents the main ways of estimation of the different parameters applied in the studied models. This document aims to contribute to the PBTK model refinement (deliverable 12.3 in the annex 1 of the project). Several strategies have been utilised by the various model developers, and some distinct examples of the main strategies are illustrated below. These strategies, in summary pertain for:

- Calculation from in vivo experimental data
- Calculation from in vitro experimental data
- Utilisation of values from the bibliography
- Use of Quantitative Structure Activity Relationships (QSARs)
- Fitting of parameters on the basis of experimental data

1.1. Calculation from *in vivo* experimental data

In their model representing the pharmacokinetics of PFOA and PFOS, Loccisano et al. (2011) estimated the partition coefficients between the tissue and the plasma ($PC_{tissue:\ plasma}$) from experimental data in mice and in rats (cf. 2.3.1). These authors estimated the $PC_{tissue:\ blood}$ by dividing the measured concentration of the molecule in the corresponding tissue by the concentration in the serum or in the blood. This approach was also applied by Clewell et al. (2008) to estimate the values of some $PC_{tissue:\ plasma}$ of the mono-butylphthalate (MBP) from the experimental values obtained by Williams and Blanchfield (1975). The precise calculations that Clewell et al. (2008) applied to obtain the PC values from the data measured 4 h after the exposure were not specified.

1.2. Calculation from *in vitro* experimental data

Teeguarden et al. (2005) used the value of $PC_{liver:\ blood}$ of BPA in the liver that had been measured *in vitro* by Csanady et al. (2002) by using blood and tissues from humans. *In vitro* incubations of the molecule with a) blood and b) a mixture of blood and of a given tissue, at known volumes of each matrix, were realised. The $PC_{tissue:\ blood}$ was determined when the molecule attained the equilibrium concentrations in both matrices. As discussed in the previous document, knowing that the donors of blood and of tissues were not the same individuals, it would have been useful to verify that the body composition was equivalent in the donors of tissues and of blood. In the case of the BPA, the binding is an important process that have an influence on the $PC_{tissue:\ blood}$ values. In this aspect, Teeguarden et al. (2005) indicated: *"The resulting partition coefficients (from Csanady et al., 2002) account for the net affect of processes controlling apparent partitioning (e.g., binding to plasma proteins)"*. That's the reason by which the binding to plasma proteins was not explicitly represented in general in the model.

1.3. Utilisation of values from the bibliography

In their model developed to represent the toxicokinetics of the 2,2',4,4'-tetrabromodiphenyl ether (BDE-47) in the rat, Emond et al. (2010) applied for several parameters (among which, the partition coefficients between the blood and the tissues and some permeability constants) the values applied in a model representing the toxicokinetics of the TCDD in the rat (Emond et al., 2004)

(2.22). In this previous model, Emond et al. (2004) used experimental toxicokinetics data on TCDD in rats to estimate these values. The direct utilisation of these values from one model to another can be discussed. From one side, Emond et al. (2004) developed their model for a different molecule, the TCDD. From another side, the structure of both models was different (ex. lower number of compartments, diffusion-limited compartments of placenta and rest of body in Emond et al., 2004). The application of the data from Emond et al. (2004) in the model of Emond et al. (2010) was more difficult to justify for the “rest of the body” partition coefficient, as this compartment did not englobe the same tissues in both models.

1.4. Use of Quantitative Structure Activity Relationships (QSARs)

Clewell et al. (2008) applied for the $PC_{tissue:\ plasma}$ of the di-n-butylphthalate (DBP) and its main metabolite, the mono-butylphthalate (MBP), the values estimated algorithmically by Keys et al. (2000). These estimations were realised by applying the n-Octanol: water partition coefficient (K_{ow}) of the studied molecules in the algorithms proposed by Poulin and Krishnan (1995).

In the model representing the toxicokinetics of the cyclohexane in the rat, Hissink et al. (2009) calculated the tissue: air partition coefficients ($PC_{tissue:\ air}$) by the equations proposed previously by other authors (Droz et al., 1989). These equations used the values of the water: air, olive oil: air and blood: air partition coefficients. The values of the $PC_{tissue:\ blood}$ were calculated as the quotient of the $PC_{tissue:\ air}$ by the $PC_{blood:\ air}$.

1.5. Fitting of parameters on the basis of experimental data

All the studied models have used this approach for a several parameters. By this way, the metabolic constants V_{max} and K_m were obtained by Hissink et al. (2009) by visually fitting them in the model to experimental data in rats obtained by the same authors. A limited number of parameters was fitted to experimental data in the models of Teeguarden et al. (2005) (2.6.2) or Loccisano et al. (2011) (2.3.2). These authors fitted the parameters on the basis of different sets of experimental data. It was also the case in the model of Heredia-Ortiz et al. (2013, 2014) on the toxicokinetics of the Benzo(a)pyrene (BaP) and its main metabolites (1). In this model, the determination of the parameter values was organised and realised by group of parameters. Each group of parameters was fitted to experimental data obtained by a given exposure route. The selection made (groups of parameters, experimental study for each group) seems a good choice. The extremely high value of the estimated PC for the lungs is discussed in the review document on the PBPK models. Clewell et al. (2008), used also a sequential approach by which the most pertinent data sets were used for several parameters, that can let a more accurate fitting than a global fitting of all the unknown parameters simultaneously. In this model, too many kinetic parameters (4 partition coefficients and 30 kinetic rate constants) were unknown and should be fitted to *in vivo* kinetic data. This fitting was realised by visual examination, what is less precise than applying a statistic method (this aspect was also discussed by the authors). In the model of Emond et al. (2010), several unknown parameters were simultaneously fitted to experimental data (2.22). These data were obtained in different strains of rat for male and pregnant female. The fitting of a high number of parameters gives place to a considerable degree of incertitude in the obtained values and the interpretation of each parameter value. For example, the E value was different for male and pregnant female of different strains. The authors indicated it could be motivated by differences in the strain, in the physiological stage, and even that this different E value could be compensating for differences in other processes not represented in the model.

2. Detailed parameterisation per PBPK model

PAHS

2.1. Use of Physiologically-Based Pharmacokinetic Modeling to Simulate the Profiles of 3-Hydroxybenzo(a)pyrene in Workers Exposed to Polycyclic Aromatic Hydrocarbons (Heredia-Ortiz et al., 2014)

2.1.1. Partition and permeability coefficients:

Fitted to experimental data from the literature (Marie et al., 2010), obtained after intravenous (IV) exposure in rats (Heredia-Ortiz and Bouchard, 2013; Marie et al., 2010).

2.1.2. Rate constants:

- Rate of hepatic metabolism fitted to experimental data from the literature, obtained after intravenous (IV) exposure in rats (Heredia-Ortiz and Bouchard, 2013; Marie et al., 2010).
- Absorption rates and fractions: fitted to experimental data from the literature, obtained by different studies after intra-tracheal (respiratory), dermal and oral exposure in rats (Heredia-Ortiz and Bouchard, 2013).

2.2. Predicting lung dosimetry pf inhaled particleborne benzo(a)pyrene using physiologically based pharmacokinetic modeling (Campbell et al., 2016)

2.2.1. Partition coefficients:

Tissue/blood partition coefficients were calculated based on octanol/water partition coefficients and tissue composition.

2.2.2. Rate constants:

Rate constants were set based on data from the published literature. The affinity constant, K_m, was used as reported; however, the V_{max} required scaling to the tissue. Scaling of the V_{max} was accomplished by multiplying the reported rate by the tissue-specific microsomal protein content per gram of tissue for liver or lung and then by the tissue volume.

Perfluorinated compounds

2.3. Evaluation and prediction of pharmacokinetics of PFOA and PFOS in the monkey and human using a PBPK model (Loccisano et al., 2011)

2.3.1. Partition coefficients:

- The $PC_{tissue:\ plasma}$ for PFOA were estimated from *in vivo* concentration data (μg g^{-1}) in rats (Kudo et al., 2007). The rats were administered a single IV dose of PFOA. Different doses (from 0.041 to 16.56 mg kg BW^{-1}) were tested. The tissues were sampled 2 h. after the dose administration. Loccisano et al. (2011) estimated the $PC_{tissue:\ blood}$ from the data of the rats administered the lowest dose. They divided the concentration of the molecule in the corresponding tissue by the concentration in the serum. Not clear the origin of the estimated PC for the skin, as Kudo et al. (2007) didn't analyse this tissue. Uncertainty in the estimated PC for the "rest of body" compartment, that comprised less tissues in Kudo et al. (2007) than in the present model.
- The $PC_{tissue:\ blood}$ for PFOS were estimated from tissue concentration data in mice (DePierre, 2009, personal communication). This source of data has not been found, but (Bogdanska et al., 2011) contains data that most probably correspond to the same experiment. Adult male mice received PFOS in their diet at either an environmentally relevant dose (0.031 mg kg BW^{-1} d^{-1}) or a high dose (23 mg kg BW^{-1} d^{-1}) for a period of 1 to 5 days. The $PC_{tissue:\ blood}$ were estimated by dividing the concentration of the molecule in the corresponding tissue by the concentration in the blood. The verification of the individual values suggests that Loccisano et al. (2011) estimated the PC generally from the data obtained in the mice exposed to the lowest dose. It's not clear how they estimated the PC for the "rest of body" compartment from these data.

2.3.2. Rate constants:

- The constant of maximum resorption in the filtrate compartment (V_{max}, mg h^{-1} $kg^{-0.75}$) was fitted to plasma concentration in monkey. The Michaelis-Menten affinity constant K_t (mg L^{-1}) was fitted to plasma and urine concentration data in monkeys.
- The urinary elimination rate constant (K_{urinec}, $kg^{0.25}$ h^{-1}) was fitted to urine data in monkeys.
- The free fraction of chemical in the plasma ("Free") was fitted to plasma concentration data from the monkey.
- The clearance rate from the plasma to the filtrate compartment and from the filtrate compartment to the "urine storage" was fixed as being 20% of the kidney blood flow.

2.4. Development of PBPK Models for PFOA and PFOS for Human Pregnancy and Lactation Life Stages (Loccisano et al., 2013)

2.4.1. Partition coefficients:

The partition coefficients for liver, kidney, skin, fat, rest tissues and placenta were estimated from tissue concentration data in rats. No data were available for PFOA or PFOS partitioning into mammary tissue. This was estimated from mouse tissue data. Tissue/blood partition coefficients were similar for the tissues examined across species; thus, the same pcs were used in the human model. Milk/plasma partition coefficients were calibrated from three human biomonitoring studies where the concentrations of PFOA and PFOS were measured in both maternal plasma and milk.

2.4.2. Rate constants:

Due to lack of data in humans, the rate constants used in the human models were the same as those estimated for the pregnant rat. The parameters for placental transfer were scaled to fetal body weight$^{0.75}$.

2.5. PBPK modeling for PFOS and PFOA: Validation with human experimental data (Fabrega et al., 2014)

2.5.1. Partition coefficients:

Parameterisation data were regarding rats and were taken from Loccisano et al. (2011). New partition coefficients coming from human autopsy tissues (Maestri et al., 2006) were also applied and compared with partition coefficient data from rats.

2.5.2. Rate constants:

Parameterisation data were regarding rats and were taken from Loccisano et al. (2011).

Bisphenols

2.6. Evaluation of Oral and Intravenous Route Pharmacokinetics, Plasma Protein Binding, and Uterine Tissue Dose Metrics of Bisphenol A: A Physiologically Based Pharmacokinetic Approach (Teeguarden et al., 2005a)

2.6.1. Partition coefficients:

The partition coefficient values were obtained from Csanady et al. (2002). These authors estimated the $PC_{tissue:\ blood}$ for the BPA by an *in vitro* experiment, using blood and different tissues from humans. *In vitro* incubations of the molecule with a) blood and b) a mixture of blood and of a given tissue, at known volumes of each matrix, were realised. The $PC_{tissue:\ blood}$ was determined when the molecule attained the equilibrium concentrations in both matrices. Teeguarden et al. (2005) used the $PC_{liver:\ blood}$ for the liver. For the uterus and the body compartments there were no measured values. The authors applied the $PC_{muscle:\ blood}$ for these compartments. They applied the same values for the rat as estimated from human data.

2.6.2. Rate constants:

- Absorption:
  - Rat: uptake rate ($kg^{0.25}\ h^{-1}$) fitted to oral rat pharmacokinetic data (Pottenger et al., 2000).
  - Human: the uptake rate estimated from rat data was directly applied for human.
- Volume of distribution:
  - BPA: the body compartment was estimated by difference (body = 1 - remaining tissues - bone). In rat: fitting to IV kinetic data. Not specified but probably fitted on human data for the human model.
  - BPAG (fraction of BW), rat: the value estimated for human was directly applied to the rat, in the absence of rat data.
  - BPAG (fraction of BW), human: value estimated by fitting to human data.
- Binding to plasma proteins:
  - Rat: the plasma binding protein content (BmaxA, µM) and the BPA: binding protein disassociation constant (KDA, µM) were estimated from the human values using for the estimation experimental data in rats.
  - Human: the values of BmaxA (µM) and KDA (µM) in humans were estimated *in vitro* by Csanady et al. (2002).
- Metabolism:
  - Rat: different values of V_{max} were estimated to be used either for oral or for IV exposure. For oral exposure, this parameter was fitted to experimental data after oral exposure in rats (Pottenger et al., 2000) and presented different values for males and females. V_{max} for IV exposure fitted to toxicokinetics data in rats obtained after IV exposure (Upmeier et al., 2000). The Michaelis-Menten constant (K_m, mg L^{-1}) was estimated as the middle of the range values reported by Kuester and Sipes (2003) for rats and humans.
  - Human: V_{max} fitted to human data. The Michaelis-Menten constant (K_m, mg L^{-1}) was estimated as the middle of the range values reported by Kuester and Sipes (2003) for rats and humans.
- Excretion:
  - Rat: fitted to experimental data after oral exposure in rats (Pottenger et al., 2000). Different values for male and female rats. The authors indicated: *"The*

pharmacokinetics of BPA are complicated by interspecies differences in the biliary elimination of BPAG…" (Teeguarden et al., 2005a).
    - Human: estimated on the basis of (human) experimental data.
- Enterohepatic recirculation:
    - Rat: fitted to experimental data after oral exposure in rats (Pottenger et al., 2000).
    - Human: estimated on the basis of (human) experimental data.

2.7. Physiologically Based Pharmacokinetics of Bisphenol A (Shin et al., 2004b)

2.7.1. Partition coefficients:

Blood/serum partition ratios, tissue/serum partition coefficients and tissue/blood partition ratios were determined for rats using in vivo experiments.

2.7.2. Rate constants:

Blood flow rates of tissues in a 0.25-kg rat were obtained from the literature, as were the blood volume, tissue volume, and blood flow rates to tissues in a 70-kg man (Bernareggi and Rowland, 1991; Pettersson et al., 1973).

2.8. Development of a physiologically based pharmacokinetic model for assessment of human exposure to bisphenol A (Yang et al., 2015)

2.8.1. Partition coefficients:

Tissue-to-serum distribution ratios for BPA used in the original model (Fisher et al., 2011) were used in this study (Table 2). For skin, the partition coefficient was adopted from Mielke et al. (2011), where it was calculated using the algorithm developed by Schmitt (2008).

2.8.2. Rate constants:

The physiological model parameters for adult humans were taken from the published literature or set to the study-specific values, with the exception of the percent body fat (V_{FatC}), which was estimated using a linear regression equation as a function of age and natural log transformed body mass index (BMI). The Michaelis constant (K_{mliver}, nM) for hepatic BPA glucuronidation was set equal to the reported K_m value of 45,800 nM, experimentally determined using pooled male and female human liver microsomes (Coughlin et al., 2012a). The maximum reaction velocity for hepatic glucuronidation ($V_{maxliverC}$) was derived from a reported in vitro maximal velocity of 4.71 nmol/min/mg protein (Coughlin et al., 2012a), by accounting for microsomal protein content of the human liver (32 mg microsomal protein/g liver) (Barter et al., 2007) and model predicted liver weight (2.132 kg, for a man with body weight of 82 kg). To describe the sulfation of BPA in the liver, the Michaelis constant ($K_{mlivers}$, nM) was set to the reported Km value of 10,100 nM, experimentally determined using cryopreserved hepatocytes of humans (Kurebayashi et al., 2010). The maximum reaction velocity for hepatic sulfation ($V_{maxliversC}$) was derived from a reported in vitro maximal velocity of 149 nmol/h/g liver (Kurebayashi et al., 2010), by accounting for model predicted liver weight (2.132 kg, for aman with bodyweight of 82 kg).

2.9. Predicting plasma concentrations of bisphenol A in children younger than 2 years of age after typical feeding schedules, using a Physiologically Based Toxicokinetic Model (Edginton and Ritter, 2009a)

2.9.1. Partition coefficients:

The algorithms of Rodgers and Rowland (2006) and Rodgers et al. (2005) were used for estimating tissue/plasma partition coefficients.

2.9.2. Rate constants:

Rate constants are not mentioned.

2.10. Integrated exposure and risk characterisation of bisphenol-A in Europe (Sarigiannis et al., 2016b)

2.10.1. Partition coefficients:

Tissue/blood partition coefficients were derived from literature (Edginton and Ritter, 2009a).

2.10.2. Rate constants:

Rate constants, intrinsic and renal clearance were derived from literature (Edginton and Ritter, 2009a).

2.11. The development of a pregnancy PBPK Model for Bisphenol A and its evaluation with the available biomonitoring data (Sharma et al., 2018a)

2.11.1. Partition coefficients:

The partition coefficient (PC) for liver, fat, brain, and skin were taken from the study done by Fisher et al., (2011). The placental and kidney partition coefficient for BPA were taken from Csanády et al., (2002) and the BPAS was not distributed to fetus tissues. However, to measure BPAG concentration in the fetus plasma, BPAG was distributed to maternal placenta using placenta partition coefficient taken from the previous mice study (Kawamoto et al., 2007). For other fetus compartments, partition coefficients were kept similar to as mother's organs partition coefficients.

2.11.2. Rate constants:

The transfer rate constants from maternal to fetus for BPA and BPAG in this model were taken from the pregnant mice PBPK model and scaled to fetal body weight (Kawamoto et al., 2007), as there is no available human data. The rate of reaction for both glucuronidation and sulfation for the PBPK model was derived by IVIVE scaling approach. The current hepatic in-vitro cell line data were used for deriving maximum reaction velocity (Coughlin et al., 2012b). The deconjugation of the BPAG to BPA was based on first-order rate transfer constant. The half-life of the chemicals is used to establish the rate of deconjugation estimated to be 0.35 hr-1 (k = 0.693/t1/2). The human hepatocyte in-vitro data was scaled to calculate the fetus liver metabolic activity. For the scaling of Vmax, the reported fetus microsomal protein content was used in place of adult microsomal content.

Cadmium

2.12. A Kinetic Model of Cadmium Metabolism in the Human Being (Kjellström and Nordberg, 1978)

2.12.1. Partition coefficients:

To find the coefficient values that would be most reasonable to be used in the model as fixed values, calculated concentrations of cadmium in different compartments were compared with empirical data from different exposure situations.

2.12.2. Rate constants:

Rate constants (absorption rate) were found by empirical data.

2.13. PBPK and population modelling to interpret urine cadmium concentrations of the French population (Bechaux et al., 2014)

2.13.1. Partition coefficients:

Tissue partitioning data was taken from literature (Kjellström and Nordberg, 1978; Ruiz et al., 2010b).

2.13.2. Rate constants:

Rate constants (rate of cadmium transfer in/to tissues) were taken from literature (Kjellström and Nordberg, 1978; Ruiz et al., 2010b).

2.14. Physiologically based pharmacokinetic (PBPK) tool kit for environmental pollutants - metals (Ruiz et al. 2010)

2.14.1. Partition coefficients:

Human physiological describing the blood and tissue partitioning of Cd were taken from the literature.

2.14.2. Rate constants:

Human physiological describing the absorption and distribution of Cd were taken from the literature.

Chromium (VI)

2.15. A Physiologically Based Model for the Ingestion of Chromium (III) and Chromium (VI) by humans (O'Flaherty et al., 2001)

2.15.1. Partition coefficients:

2.15.2. Rate constants:

Rates of deposition were estimated the same with the ones used in the rat kinetic model (O'Flaherty, 1996). The absorption rate constants, the clearance constants into and out of tissues, the reduction rate constants and urinary clearance were estimated based on data from experimental studies of human chromium kinetics (Finley et al., 1997b; Kerger et al., 1996; Paustenbach et al., 1999).

2.16. Physiologically based pharmacokinetic model for humans orally exposed to chromium (Kirman et al., 2013)

2.16.1. Partition coefficients:

Model parameter values were set based on: (1) data from the published literature; (2) by adjusting parameter values to obtain fits to the key data sets; and (3) professional judgment.

2.16.2. Rate constants:

Model parameter values like metabolic constants reduction rates were assumed to be equal to the estimated ones in rats and some other limited literature data.

Phthalates

2.17. Using exposure prediction tools to link exposure and dosimetry for risk based decisions: A case study with phthalates (Moreau et al. 2017)

2.17.1. Partition coefficients:

All model parameters were randomly sampled, and a distribution of phthalate urine concentrations was generated by running the PBPK model for several iterations. The partitioning parameters in the MC analysis either were distributed lognormally. To exclude physiologically implausible values, CV was assumed to be 50%. with parameters truncated at ± 1.95 SD.

2.17.2. Rate constants:

All model parameters were randomly sampled, and a distribution of phthalate urine concentrations was generated by running the PBPK model for several iterations. The metabolic constants and metabolic clearance in the MC analysis either were distributed lognormally. To exclude physiologically implausible values, CV was assumed to be 50%. with parameters truncated at ± 1.95 SD.

2.18. Physiology based Pharmacokinetic (PBPK) modeling for DEHP metabolites integrating its in vitro metabolism: a bottom up modeling approach (Sharma et al., 2018b)

2.18.1. Partition coefficients:

The partition coefficients for DEHP were estimated using the algorithm based on tissue composition method (Poulin and Krishnan, 1995b; Poulin and Krishnan, 1996; Poulin and Theil, 2000). A log ko/w of 7.6 was used for the estimation of tissue: plasma partition coefficient. The distribution of MEHP was done using partition coefficient values measured experimentally via vial – equilibration method by Keys et al. (2000a).

2.18.2. Rate constants:

The transfer of the metabolites formed in the liver to the blood was described by first order uptake rate and these parameters were calibrated against the Koch et al. (2003) data. The excretion rate for the MEHP and other metabolites were described using first order rate equation using elimination rate constants. They were obtained by using the relationship of elimination rate constant and chemical's plasma half-life i.e. ratio of ln2 (0.693)/t1/2 (half-life). The mean half-lives for MEHP, 5-OH MEHP and 5-CX MEPP and 5-oxo MEHP was estimated previously by Lorber et al., (2010) in his model experiments using the above mentioned relationship. Those values were used initially for the simulation of model and if necessary parameters were optimised by fitting to the time course of concentration of chemicals in plasma and cumulative excretion profile in urine reported in Koch et al., (2005) study. The elimination rate constant for MEHP was measured using half-life, estimated by Mittermeier et al. (2016). The in vitro intestinal and hepatic metabolic rates for different metabolites were reported by Coi et al. (Choi et al., 2012) in human intestinal and hepatocyte cell line. The in-vitro in-vivo extrapolation (IVIVE) method, which generally involves scaling of in-vitro Vmax value to in-vivo that utilises physiological specific parameters such as tissue specific Microsomal protein content or cytosol protein, specific tissue volume and, body weight. Based on in-vitro studies of DEHP in the gut and liver, an IVIVE approach was implemented to derive model parameter such as Vmax, describing the maximum rate of

metabolism. The estimated parameters (V_{max} in-vitro), maximum rate of reaction were scaled to the whole body based on the MSP (microsomal protein) and cytosol content of liver and gut.

Pesticides

2.19. A Physiologically Based Pharmacokinetic and Pharmacodynamic (PBPK/PD) Model for the Organophosphate Insecticide Chlorpyrifos in Rats and Humans (Timchalk et al., 2002)

2.19.1. Partition coefficients:

The partition coefficients for CPF and CPF-oxon were estimated based on their octanol/water partitioning coefficients and tissue lipid content based on an algorithm by Poulin and Krishnan (1995a).

2.19.2. Rate constants:

A range of Km and Vamx parameters has been determined in vitro, utilising tissue obtained from both mice and rats (Ma and Chambers, 1994, 1995; Mortensen et al., 1996; Pond et al., 1995; Sultatos, 1994; Sultatos and Murphy, 1983). The selection of a reasonable set of model parameters was determined by evaluating the overall goodness of fit of the model against the experimental data over the range of reported rate constants for enzyme affinity and activities.

2.20. The implications of using a physiologically based pharmacokinetic (PBPK) model for pesticide risk assessment (Lu et al., 2010)

2.20.1. Partition coefficients:

The partition coefficients were estimated based on their octanol/water partitioning coefficients and tissue lipid content based on an algorithm by Poulin and Krishnan (1995a).

2.20.2. Rate constants:

Glucuronic conjugation and the urinary excretion rate parameters were based on TCPY data in rats and in adult humans.

Anilines

2.21. A Novel Method for Assessing Drug Degradation Product Safety Using Physiologically-Based Pharmacokinetic Models and Stochastic Risk Assessment (Nguyen et al., 2015)

2.21.1. Partition coefficients:

The $PC_{tissue:\ plasma}$ were estimated using the mechanistic tissue composition-based equation for acids, very weak bases, neutral compounds, and some zwitterions from the model of Rodgers and Rowland (2006). The Kpu values in rats and humans were estimated for 14 tissues (adipose, bone, brain, gut, heart, kidney, liver, lung, muscle, pancreas, skin, spleen, stomach, and thymus) using residual blood adjusted rat tissue composition data for both species along with fraction unbound in plasma and blood to plasma ratio values. Blood to plasma ratio of aniline in rats was obtained from literature (Harrison and Jollow, 1986) which is equal to 1. Other model compounds (such as PCA, o-TOL, 2,6-DMA, and PAP) were assumed to distribute equally in plasma and erythrocytes.

2.21.2. Rate constants:

The maximal velocity (V_{max}) and Michaelis constant (K_m) values were determined in vitro in rat liver microsomes (aniline, PCA, 2,6-DMA, and o-TOL) or in rat hepatocytes (PAP) by measuring the rate of substrate depletion. Enzyme kinetic parameters (V_{max}, K_m) were estimated by fitting the Michaelis–Menten equation to all depletion curves simultaneously with Bayesian parameter estimation via Markov Chain Monte Carlo (MCMC) sampling.

Brominated Flame Retardants

2.22. A physiologically based pharmacokinetic model for developmental exposure to BDE-47 in rats (Emond et al., 2010)

2.22.1. Partition coefficients:

Either directly applied those used for TCDD in a previous model (Emond et al., 2004), which were estimated on the basis of experimental toxicokinetics data of TCDD in rats (Wang et al., 1997), or fitted.

2.22.2. Rate constants:

- Constant of absorption in the GI tract: fitted.
- Tissue permeability constant: either applied directly those used for TCDD in a previous model (Emond et al., 2004) or estimated on the basis of experimental data.
- Extraction coefficient of the molecule in the liver: estimated on the basis of experimental data.
- Constant of elimination of the molecule by the GI tract. Not clearly specified the origin of this value.
- Constant of clearance from the kidney. Not clearly specified the origin of this value.
- Constant of placenta-fetus transfer. Not clearly specified the origin of this value.

Generic PBPK models

2.23. INTEGRA PBPK model (Sarigiannis et al., 2014)

2.23.1. Partition coefficients:

Compound specific parameterisation of the model varies upon the compound of interest. For data rich compounds that experimental values have been obtained from toxicokinetic studies, or extrapolated from animal models, these parameters are used directly. For data poor chemicals, the partition coefficients of the tissue compartments are derived by advanced QSAR models that couple the Abraham solvation equation with artificial neural networks (Sarigiannis et al., 2017) and in particular for the adipose tissue (which has a dominant influence in the distribution volume of lipophilic compounds) multiple descriptors with artificial neural networks (Papadaki et al., 2017).

2.23.2. Rate constants:

Similarly to before, compound specific parameterisation of the model varies upon the compound of interest, depending on whether we have to deal with data rich or data poor compounds. For data poor chemicals, the Michaelis-menten kinetics are derived by advanced QSAR models that couple the Abraham solvation equation with artificial neural networks (Sarigiannis et al., 2017). The particular model has been proved particularly efficient for capturing the complex biological interactions that govern metabolism and enzyme-substrate dynamics.

2.24. IndusChemFate (Jongeneelen and Berge, 2011)

2.24.1. Partition coefficients:

The partition coefficients of the parent compound and its metabolites (blood/air and tissue/blood partition coefficients of 11 organs) are estimated by means of quantitative structure–property relationship, in which five easily available physicochemical properties of the compound are the independent parameters. A novel QSPR to estimate the blood/air partition coefficient has been derived. A wide range of VOCs with measured blood/air values for humans from many sources were reported in the paper of Meulenberg and Vijverberg (2000). For the blood/tissue partitioning, the QSPR algorithm as described by DeJongh et al. (1997) has been applied.

2.24.2. Rate constants:

Maximum velocity of metabolism and the Michaelis–Menten constant are preferably taken form experimental data with human tissue. Metabolic rate should at preference be derived in experiments measurements with microsomal liver fractions or with isolated hepatocytes. However, such in vitro measurements of the metabolic rate are not always available. Therefore, optimised Vmax and kM values from fitting procedures were used as a second-best estimate.

2.25. A stochastic whole-body physiologically based pharmacokinetic model (Beaudouin et al., 2010)

2.25.1. Partition coefficients:

A quantitative structure–activity relationship (QSAR) model developed by Poulin and Krishnan (1995a) was used to predict tissue/blood partition coefficients.

2.25.2. Rate constants:

Rate constants were determined using in vivo and in vitro experiments.

2.26. MerlinExpo PBTK model (Brochot and Quindroit, 2018)

2.26.1. Partition coefficients:

MERLIN-Expo also contains a library of substances for which default values are provided and justified for each compound-specific parameter (e.g. partition coefficients).

2.26.2. Rate constants:

MERLIN-Expo also contains a library of substances for which default values are provided and justified for each compound-specific parameter.

2.27. MENTOR-3P PBTK model (Xue et al., 2010)

2.27.1. Partition coefficients:

The model parameters (partition coefficients) were employed from literature (Yu, 1999a; Yu, 1999b).

2.27.2. Rate constants:

The model parameters (metabolic rates) were found in literature (Yu, 1999a; Yu, 1999b).

REFERENCES

Abraham, K., Mielke, H., Huisinga, W., Gundert-Remy, U., 2005. Elevated internal exposure of children in simulated acute inhalation of volatile organic compounds: effects of concentration and duration. Archives of toxicology 79, 63-73.

Agoram, B., Woltosz, W.S., Bolger, M.B., 2001. Predicting the impact of physiological and biochemical processes on oral drug bioavailability. Advanced drug delivery reviews 50 Suppl 1, S41-67.

Amberg, A., Rosner, E., Dekant, W., 1999. Biotransformation and kinetics of excretion of methyl-tert-butyl ether in rats and humans. Toxicol Sci 51, 1-8.

Andra, S.S., Charisiadis, P., Karakitsios, S., Sarigiannis, D.A., Makris, K.C., 2015. Passive exposures of children to volatile trihalomethanes during domestic cleaning activities of their parents. Environ Res 136, 187-195.

ATSDR, 1995. Public Health Statement for Polycyclic Aromatic Hydrocarbons (PAHs).

ATSDR, 2002. Aniline. Division of Toxicology ToxFAQs.

ATSDR, 2011. Chromium Toxicity: What Are the Physiologic Effects of Chromium Exposure? Case Studies in Environmental Medicine (CSEM).

ATSDR, 2012. Public Health Statement: Chromium. Division of Toxicology and Human Health Sciences

ATSDR, 2017, Health Effects of PFAS, https://www.atsdr.cdc.gov/pfc/health_effects_pfcs.html,

Bader, M., Wrbitzky, R., Blaszkewicz, M., Schaper, M., van Thriel, C., 2008. Human volunteer study on the inhalational and dermal absorption of N-methyl-2-pyrrolidone (NMP) from the vapour phase. Arch Toxicol 82, 13-20.

Bartell, S.M., Calafat, A.M., Lyu, C., Kato, K., Ryan, P.B., Steenland, K., 2010. Rate of decline in serum PFOA concentrations after granular activated carbon filtration at two public water systems in Ohio and West Virginia. Environ Health Perspect 118, 222-228.

Barter, Z.E., Bayliss, M.K., Beaune, P.H., Boobis, A.R., Carlile, D.J., Edwards, R.J., Houston, J.B., Lake, B.G., Lipscomb, J.C., Pelkonen, O.R., Tucker, G.T., Rostami-Hodjegan, A., 2007. Scaling factors for the extrapolation of in vivo metabolic drug clearance from in vitro data: reaching a consensus on values of human microsomal protein and hepatocellularity per gram of liver. Current drug metabolism 8, 33-45.

Beaudouin, R., Micallef, S., Brochot, C., 2010. A stochastic whole-body physiologically based pharmacokinetic model to assess the impact of inter-individual variability on tissue dosimetry over the human lifespan. Regulatory Toxicology and Pharmacology 57, 103-116.

Bechaux, C., Bodin, L., Clemencon, S., Crepet, A., 2014. PBPK and population modelling to interpret urine cadmium concentrations of the French population. Toxicol Appl Pharmacol 279, 364-372.

Bernareggi, A., Rowland, M., 1991. Physiologic modeling of cyclosporin kinetics in rat and man. J Pharmacokinet Biopharm 19, 21-50.

Blancato J.N., Power, F.W., Brown, R.N., Dary, C.C., 2006. Exposure Related Dose Estimating Model (ERDEM): A Physiologically-Based Pharmacokinetic and Pharmacodynamic (PBPK/PD) Model for Assessing Human Exposure and Risk.

Bogdanska, J., Borg, D., Sundstrom, M., Bergstrom, U., Halldin, K., Abedi-Valugerdi, M., Bergman, A., Nelson, B., DePierre, J., Nobel, S., 2011. Tissue distribution of S-35-labelled perfluorooctane sulfonate in adult mice after oral exposure to a low environmentally relevant dose or a high experimental dose. Toxicology 284, 54-62.

Bois, F.Y., Jamei, M., Clewell, H.J., 2010. PBPK modelling of inter-individual variability in the pharmacokinetics of environmental chemicals. Toxicology 278, 256-267.

Brochot, C., Quindroit, P., 2018. Modelling the Fate of Chemicals in Humans Using a Lifetime Physiologically Based Pharmacokinetic (PBPK) Model in MERLIN-Expo, in: P. Ciffroy, A. Tediosi, E. Capri (Eds.), Modelling the Fate of Chemicals in the Environment and the Human Body. Springer International Publishing, Cham, pp. 215-257.

Campbell, J., Franzen, A., Van Landingham, C., Lumpkin, M., Crowell, S., Meredith, C., Loccisano, A., Gentry, R., Clewell, H., 2016. Predicting lung dosimetry of inhaled particleborne benzo[a]pyrene using physiologically based pharmacokinetic modeling. Inhal Toxicol 28, 520-535.

Castetbon, K., Vernay, M., Malon, A., Salanave, B., Deschamps, V., Roudier, C., Oleko, A., Szego, E., Hercberg, S., 2009. Dietary intake, physical activity and nutritional status in adults: the French nutrition and health survey (ENNS, 2006-2007). The British journal of nutrition 102, 733-743.

CDC, 2009. Centers for Disease Control and Prevention, Fourth national report on human exposure to environmental chemicals. National Center for Environmental Health, Division of Laboratory Sciences, Atlanta, Georgia.

Choi, K., Joo, H., Campbell, J.L., Jr., Clewell, R.A., Andersen, M.E., Clewell, H.J., 3rd, 2012. In vitro metabolism of di(2-ethylhexyl) phthalate (DEHP) by various tissues and cytochrome P450s of human and rat. Toxicology in vitro : an international journal published in association with BIBRA 26, 315-322.

Ciffroy, P., Alfonso, B., Altenpohl, A., Banjac, Z., Bierkens, J., Brochot, C., Critto, A., De Wilde, T., Fait, G., Fierens, T., Garratt, J., Giubilato, E., Grange, E., Johansson, E., Radomyski, A., Reschwann, K., Suciu, N., Tanaka, T., Tediosi, A., Van Holderbeke, M., Verdonck, F., 2016. Modelling the exposure to chemicals for risk assessment: a comprehensive library of multimedia and PBPK models for integration, prediction, uncertainty and sensitivity analysis – the MERLIN-Expo tool. Science of The Total Environment 568, 770-784.

Clewell, H.J., Lee, T.-s., Carpenter, R.L., 1994. Sensitivity of Physiologically Based Pharmacokinetic Models to Variation in Model Parameters: Methylene Chloride. Risk Analysis 14, 521-531.

Clewell, R.A., Clewell, H.J., 3rd, 2008. Development and specification of physiologically based pharmacokinetic models for use in risk assessment. Regulatory toxicology and pharmacology : RTP 50, 129-143.

Clewell, R.A., Kremer, J.J., Williams, C.C., Campbell, J.L., Andersen, M.E., Borghoff, S.J., 2008. Tissue exposures to free and glucuronidated monobutylyphthalate in the pregnant and fetal rat following exposure to di-n-butylphthalate: Evaluation with a PBPK model. Toxicological Sciences 103, 241-259.

Coughlin, J.L., Thomas, P.E., Buckley, B., 2012a. Inhibition of Genistein Glucuronidation by Bisphenol A in Human and Rat Liver Microsomes. Drug Metabolism and Disposition 40, 481-485.

Coughlin, J.L., Thomas, P.E., Buckley, B., 2012b. Inhibition of genistein glucuronidation by bisphenol A in human and rat liver microsomes. Drug metabolism and disposition: the biological fate of chemicals 40, 481-485.

Court, M.H., Zhang, X., Ding, X., Yee, K.K., Hesse, L.M., Finel, M., 2012. Quantitative distribution of mRNAs encoding the 19 human UDP-glucuronosyltransferase enzymes in 26 adult and 3 fetal tissues. Xenobiotica 42, 266-277.

Crowell, S.R., Amin, S.G., Anderson, K.A., Krishnegowda, G., Sharma, A.K., Soelberg, J.J., Williams, D.E., Corley, R.A., 2011. Preliminary physiologically based pharmacokinetic models for benzo[a]pyrene and dibenzo[def,p]chrysene in rodents. Toxicol Appl Pharmacol 257, 365-376.

Csanady, G.A., Oberste-Frielinghaus, H.R., Semder, B., Baur, C., Schneider, K.T., Filser, J.G., 2002. Distribution and unspecific protein binding of the xenoestrogens bisphenol A and daidzein. Arch Toxicol 76, 299-305.

DeJongh, J., Verhaar, H.J.M., Hermens, J.L.M., 1997. A quantitative property-property relationship (QPPR) approach to estimate in vitro tissue blood partition coefficients of organic chemicals in rats and humans. Archives of Toxicology 72, 17-25.

Domingo, J.L., 2012. Health risks of dietary exposure to perfluorinated compounds. Environ Int 40, 187-195.

Droz, P.O., Wu, M.M., Cumberland, W.G., 1989. Variability in biological monitoring of organic-solvent exposure. 2. Application of a population physiological model. British Journal of Industrial Medicine 46, 547-558.

Edginton, A.N., Ritter, L., 2009a. Predicting plasma concentrations of bisphenol A in children younger than 2 years of age after typical feeding schedules, using a physiologically based toxicokinetic model. Environmental health perspectives 117, 645-652.

Edginton, A.N., Ritter, L., 2009b. Predicting plasma concentrations of bisphenol A in children younger than 2 years of age after typical feeding schedules, using a physiologically based toxicokinetic model. Environmental Health Perspectives 117, 645-652.

Edginton, A.N., Schmitt, W., Voith, B., Willmann, S., 2006a. A mechanistic approach for the scaling of clearance in children. Clinical pharmacokinetics 45, 683-704.

Edginton, A.N., Schmitt, W., Willmann, S., 2006b. Development and evaluation of a generic physiologically based pharmacokinetic model for children. Clinical pharmacokinetics 45, 1013-1034.

EFSA, 2015. Scientific Opinion on the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs: Executive summary.

Eissing, T., Kuepfer, L., Becker, C., Block, M., Coboeken, K., Gaub, T., Goerlitz, L., Jaeger, J., Loosen, R., Ludewig, B., Meyer, M., Niederalt, C., Sevestre, M., Siegmund, H.U., Solodenko, J., Thelen, K., Telle, U., Weiss, W., Wendl, T., Willmann, S., Lippert, J., 2011. A computational systems biology software platform for multiscale modeling and simulation: Integrating whole-body physiology, disease biology, and molecular reaction networks. Frontiers in Physiology 2, 1-10.

El-Masri, H.A., Kenyon, E.M., 2008. Development of a human physiologically based pharmacokinetic (PBPK) model for inorganic arsenic and its mono- and di-methylated metabolites. J Pharmacokinet Pharmacodyn 35, 31-68.

Elinder, C.G., Lind, B., Kjellstrom, T., Linnman, L., Friberg, L., 1976. Cadmium in kidney cortex, liver, and pancreas from Swedish autopsies. Estimation of biological half time in kidney cortex, considering calorie intake and smoking habits. Arch Environ Health 31, 292-302.

Emond, C., Birnbaum, L.S., DeVito, M.J., 2004. Physiologically based pharmacokinetic model for developmental exposures to TCDD in the rat. Toxicological Sciences 80, 115-133.

Emond, C., Raymer, J.H., Studabaker, W.B., Garner, C.E., Birnbaum, L.S., 2010. A physiologically based pharmacokinetic model for developmental exposure to BDE-47 in rats. Toxicology and Applied Pharmacology 242, 290-298.

Ericson, I., Gómez, M., Nadal, M., van Bavel, B., Lindström, G., Domingo, J.L., 2007. Perfluorinated chemicals in blood of residents in Catalonia (Spain) in relation to age and gender: A pilot study. Environment International 33, 616-623.

Fabrega, F., Kumar, V., Schuhmacher, M., Domingo, J.L., Nadal, M., 2014. PBPK modeling for PFOS and PFOA: validation with human experimental data. Toxicol Lett 230, 244-251.

Fabrega, F., Nadal, M., Schuhmacher, M., Domingo, J.L., Kumar, V., 2016. Influence of the uncertainty in the validation of PBPK models: A case-study for PFOS and PFOA. Regulatory toxicology and pharmacology : RTP 77, 230-239.

FDA, 2014. Bisphenol A (BPA): Use in Food Contact Application.

Finley, B.L., Kerger, B.D., Katona, M.W., Gargas, M.L., Corbett, G.C., Paustenbach, D.J., 1997a. Human Ingestion of Chromium (VI) in Drinking Water: Pharmacokinetics Following Repeated Exposure. Toxicology and Applied Pharmacology 142, 151-159.

Finley, B.L., Kerger, B.D., Katona, M.W., Gargas, M.L., Corbett, G.C., Paustenbach, D.J., 1997b. Human ingestion of chromium (VI) in drinking water: pharmacokinetics following repeated exposure. Toxicol Appl Pharmacol 142, 151-159.

Fisher, J.W., Twaddle, N.C., Vanlandingham, M., Doerge, D.R., 2011. Pharmacokinetic modeling: prediction and evaluation of route dependent dosimetry of bisphenol A in monkeys with extrapolation to humans. Toxicol Appl Pharmacol 257, 122-136.

Franks, S.J., Spendiff, M.K., Cocker, J., Loizou, G.D., 2006. Physiologically based pharmacokinetic modelling of human exposure to 2-butoxyethanol. Toxicol Lett 162, 164-173.

Ganzleben, C., Antignac, J.P., Barouki, R., Castano, A., Fiddicke, U., Klanova, J., Lebret, E., Olea, N., Sarigiannis, D., Schoeters, G.R., Sepai, O., Tolonen, H., Kolossa-Gehring, M., 2017. Human biomonitoring as a tool to support chemicals regulation in the European Union. Int J Hyg Environ Health 220, 94-97.

Georgopoulos, P.G., Lioy, P.J., 2006. From a theoretical framework of human exposure and dose assessment to computational system implementation: the Modeling ENvironment for TOtal Risk Studies (MENTOR). Journal of toxicology and environmental health. Part B, Critical reviews 9, 457-483.

Georgopoulos, P.G., Sasso, A.F., Isukapalli, S.S., Lioy, P.J., Vallero, D.A., Okino, M., Reiter, L., 2008a. Reconstructing population exposures to environmental chemicals from biomarkers: challenges and opportunities. Journal of Exposure Science and Environmental Epidemiology 19, 149-171.

Georgopoulos, P.G., Wang, S.W., Yang, Y.C., Xue, J., Zartarian, V.G., McCurdy, T., Ozkaynak, H., 2008b. Biologically based modeling of multimedia, multipathway, multiroute population exposures to arsenic. Journal of Exposure Science and Environmental Epidemiology 18, 462-476.

Gilden, R.C., Huffling, K., Sattler, B., 2010. Pesticides and health risks. Journal of obstetric, gynecologic, and neonatal nursing : JOGNN 39, 103-110.

Harrison, J.H., Jr., Jollow, D.J., 1986. Role of aniline metabolites in aniline-induced hemolytic anemia. The Journal of pharmacology and experimental therapeutics 238, 1045-1054.

Harrison, J.H., Jr., Jollow, D.J., 1987. Contribution of aniline metabolites to aniline-induced methemoglobinemia. Mol Pharmacol 32, 423-431.

Hartung, T., Luechtefeld, T., Maertens, A., Kleensang, A., 2013. Integrated testing strategies for safety assessments. Altex 30, 3-18.

Heredia-Ortiz, R., Bouchard, M., 2013. Understanding the linked kinetics of benzo(a)pyrene and 3-hydroxybenzo(a)pyrene biomarker of exposure using physiologically-based pharmacokinetic modelling in rats. Journal of Pharmacokinetics and Pharmacodynamics 40, 669-682.

Heredia-Ortiz, R., Maitre, A., Barbeau, D., Lafontaine, M., Bouchard, M., 2014. Use of Physiologically-Based Pharmacokinetic Modeling to Simulate the Profiles of 3-Hydroxybenzo(a) pyrene in Workers Exposed to Polycyclic Aromatic Hydrocarbons. Plos One 9, e102570.

Heudorf, U., Mersch-Sundermann, V., Angerer, J., 2007. Phthalates: Toxicology and exposure. International Journal of Hygiene and Environmental Health 210, 623-634.

Hissink, A.M., Kulig, B.M., Kruse, J., Freidig, A.P., Verwei, M., Muijser, H., Lammers, J., McKee, R.H., Owen, D.E., Sweeney, L.M., Salmon, F., 2009. Physiologically Based Pharmacokinetic Modeling of Cyclohexane as a Tool for Integrating Animal and Human Test Data. International Journal of Toxicology 28, 498-509.

ICRP, 2002. Basic anatomical and physiological data for use in radiological protection: reference values, in: J. Valentin (Ed.), The International Commission on Radiological Protection, Ottawa, Ontario, Canada.

Jarup, L., Akesson, A., 2009. Current status of cadmium as an environmental health problem. Toxicol Appl Pharmacol 238, 201-208.

Johnson, J.D., Gibson, S.J., Ober, R.E., 1984. Cholestyramine-enhanced fecal elimination of carbon-14 in rats after administration of ammonium [14C]perfluorooctanoate or potassium [14C]perfluorooctanesulfonate. Fundam Appl Toxicol 4, 972-976.

Jongeneelen, F.J., Anzion, R.B., Scheepers, P.T., Bos, R.P., Henderson, P.T., Nijenhuis, E.H., Veenstra, S.J., Brouns, R.M., Winkes, A., 1988. 1-Hydroxypyrene in urine as a biological indicator of exposure to polycyclic aromatic hydrocarbons in several work environments. The Annals of occupational hygiene 32, 35-43.

Jongeneelen, F.J., Berge, W.F.T., 2011. A generic, cross-chemical predictive PBTK model with multiple entry routes running as application in MS Excel; design of the model and comparison of predictions with experimental results. Annals of Occupational Hygiene 55, 841-864.

Jongeneelen, F.J., Ten Berge, W.F., 2011. A Generic, Cross-Chemical Predictive PBTK Model with Multiple Entry Routes Running as Application in MS Excel; Design of the Model and Comparison of Predictions with Experimental Results. Annals of Occupational Hygiene 55, 841-864.

Judson, R.S., Houck, K.A., Kavlock, R.J., Knudsen, T.B., Martin, M.T., Mortensen, H.M., Reif, D.M., Rotroff, D.M., Shah, I., Richard, A.M., Dix, D.J., 2010. In vitro screening of environmental chemicals for targeted testing prioritization: The toxcast project. Environmental Health Perspectives 118, 485-492.

Judson, R.S., Kavlock, R.J., Setzer, R.W., Cohen Hubal, E.A., Martin, M.T., Knudsen, T.B., Houck, K.A., Thomas, R.S., Wetmore, B.A., Dix, D.J., 2011. Estimating toxicity-related biological pathway altering doses for high-throughput chemical risk assessment. Chemical Research in Toxicology 24, 451-462.

Kamrin, M.A., 2009. Phthalate risks, phthalate regulation, and public health: a review. Journal of toxicology and environmental health. Part B, Critical reviews 12, 157-174.

Kawamoto, Y., Matsuyama, W., Wada, M., Hishikawa, J., Chan, M.P., Nakayama, A., Morisawa, S., 2007. Development of a physiologically based pharmacokinetic model for bisphenol A in pregnant mice. Toxicol Appl Pharmacol 224, 182-191.

Kearney, T.E., Manoguerra, A.S., Dunford, J.V., 1984. Chemically induced methemoglobinemia from aniline poisoning. Western Journal of Medicine 140, 282-286.

Keith, L.H., 1997. Environmental Endocrine Disruptors: A Handbook of Property Data. Wiley.

Kerger, B.D., Paustenbach, D.J., Corbett, G.E., Finley, B.L., 1996. Absorption and elimination of trivalent and hexavalent chromium in humans following ingestion of a bolus dose in drinking water. Toxicol Appl Pharmacol 141, 145-158.

Keys, D.A., Wallace, D.G., Kepler, T.B., Conolly, R.B., 2000a. Quantitative evaluation of alternative mechanisms of blood disposition of di(n-butyl) phthalate and mono(n-butyl) phthalate in rats. Toxicol Sci 53, 173-184.

Keys, D.A., Wallace, D.G., Kepler, T.B., Conolly, R.B., 2000b. Quantitative evaluation of alternative mechanisms of blood disposition of di(n-butyl) phthalate and mono(n-butyl) phthalate in rats. Toxicological Sciences 53, 173-184.

Kirman, C.R., Aylward, L.L., Suh, M., Harris, M.A., Thompson, C.M., Haws, L.C., Proctor, D.M., Lin, S.S., Parker, W., Hays, S.M., 2013. Physiologically based pharmacokinetic model for humans orally exposed to chromium. Chemico-Biological Interactions 204, 13-27.

Kirman, C.R., Hays, S.M., Aylward, L.L., Suh, M., Harris, M.A., Thompson, C.M., Haws, L.C., Proctor, D.M., 2012. Physiologically based pharmacokinetic model for rats and mice orally exposed to chromium. Chemico-biological interactions 200, 45-64.

Kjellström, T., Evrin, P.-E., Rahnster, B., 1977. Dose-response analysis of cadmium-induced tubular proteinuria: A study of urinary β2-microglobulin excretion among workers in a battery factory. Environmental Research 13, 303-317.

Kjellström, T., Nordberg, G.F., 1978. A kinetic model of cadmium metabolism in the human being. Environmental Research 16, 248-269.

Klaassen, C.D., 2007. Casarett & Doull's Toxicology: The Basic Science of Poisons, Seventh Edition. McGraw-Hill Education.

Koch, H.M., Angerer, J., Drexler, H., Eckstein, R., Weisbach, V., 2005. Di(2-ethylhexyl)phthalate (DEHP) exposure of voluntary plasma and platelet donors. Int J Hyg Environ Health 208, 489-498.

Koch, H.M., Drexler, H., Angerer, J., 2003. An estimation of the daily intake of di(2-ethylhexyl)phthalate (DEHP) and other phthalates in the general population. International Journal of Hygiene and Environmental Health 206, 77-83.

Kramer, A., Below, H., Bieber, N., Kampf, G., Toma, C.D., Huebner, N.-O., Assadian, O., 2007. Quantity of ethanol absorption after excessive hand disinfection using three commercially available hand rubs is minimal and below toxic levels for humans. BMC infectious diseases 7, 117-117.

Krauss, M., Schaller, S., Borchers, S., Findeisen, R., Lippert, J., Kuepfer, L., 2012. Integrating Cellular Metabolism into a Multiscale Whole-Body Model. PLoS Computational Biology 8.

Kudo, N., Sakai, A., Mitsumoto, A., Hibino, Y., Tsuda, T., Kawashima, Y., 2007. Tissue distribution and hepatic subcellular distribution of perfluorooctanoic acid at low dose are different from those at high dose in rats. Biological & Pharmaceutical Bulletin 30, 1535-1540.

Kurebayashi, H., Harada, R., Stewart, R.K., Numata, H., Ohno, Y., 2002. Disposition of a low dose of bisphenol a in male and female cynomolgus monkeys. Toxicol Sci 68, 32-42.

Kurebayashi, H., Okudaira, K., Ohno, Y., 2010. Species difference of metabolic clearance of bisphenol A using cryopreserved hepatocytes from rats, monkeys and humans. Toxicology Letters 198, 210-215.

Lafontaine, M., Champmartin, C., Simon, P., Delsaut, P., Funck-Brentano, C., 2006. 3-Hydroxybenzo[a]pyrene in the urine of smokers and non-smokers. Toxicol Lett 162, 181-185.

Lafontaine, M., Gendre, C., Delsaut, P., Simon, P., 2004. URINARY 3-HYDROXYBENZO[A]PYRENE AS A BIOMARKER OF EXPOSURE TO POLYCYCLIC AROMATIC HYDROCARBONS: AN APPROACH FOR DETERMINING A BIOLOGICAL LIMIT VALUE. Polycyclic Aromatic Compounds 24, 441-450.

Langard, S., 1990. One hundred years of chromium and cancer: a review of epidemiological evidence and selected case reports. Am J Ind Med 17, 189-215.

Lee, C.H., Kim, S.H., Kwon, D.H., Jang, K.H., Chung, Y.H., Moon, J.D., 2013. Two Cases of Methemoglobinemia Induced by the Exposure to Nitrobenzene and Aniline. Annals of Occupational and Environmental Medicine 25, 31-31.

Lee, S.K., Ou, Y.C., Andersen, M.E., Yang, R.S.H., 2007. A physiologically based pharmacokinetic model for lactational transfer of PCB 153 with or without PCB 126 in mice. Archives of Toxicology 81, 101-111.

Leeder, J.S., 2009. Developmental pharmacogenetics: A general paradigm for application to neonatal pharmacology and toxicology. Clinical Pharmacology and Therapeutics 86, 678-682.

Loccisano, A.E., Campbell, J.L., Andersen, M.E., Clewell, H.J., 2011. Evaluation and prediction of pharmacokinetics of PFOA and PFOS in the monkey and human using a PBPK model. Regulatory Toxicology and Pharmacology 59, 157-175.

Loccisano, A.E., Campbell, J.L., Jr., Butenhoff, J.L., Andersen, M.E., Clewell, H.J., 3rd, 2012. Evaluation of placental and lactational pharmacokinetics of PFOA and PFOS in the pregnant, lactating, fetal and neonatal rat using a physiologically based pharmacokinetic model. Reprod Toxicol 33, 468-490.

Loccisano, A.E., Longnecker, M.P., Campbell, J.L., Andersen, M.E., Clewell, H.J., 2013. Development of pbpk models for pfoa and pfos for human pregnancy and lactation life stages. Journal of Toxicology and Environmental Health - Part A: Current Issues 76, 25-57.

Loizou, G., Spendiff, M., Barton, H.A., Bessems, J., Bois, F.Y., d'Yvoire, M.B., Buist, H., Clewell, H.J., Meek, B., Gundert-Remy, U., Goerlitz, G., Schmitt, W., 2008. Development of good modelling practice for physiologically based pharmacokinetic models for use in risk assessment: The first steps. Regulatory Toxicology and Pharmacology 50, 400-411.

Lu, C., Holbrook, C.M., Andres, L.M., 2010. The implications of using a physiologically based pharmacokinetic (PBPK) model for pesticide risk assessment. Environ Health Perspect 118, 125-130.

Ma, T., Chambers, J.E., 1994. Kinetic parameters of desulfuration and dearylation of parathion and chlorpyrifos by rat liver microsomes. Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association 32, 763-767.

Ma, T., Chambers, J.E., 1995. A kinetic analysis of hepatic microsomal activation of parathion and chlorpyrifos in control and phenobarbital-treated rats. Journal of biochemical toxicology 10, 63-68.

Maestri, L., Negri, S., Ferrari, M., Ghittori, S., Fabris, F., Danesino, P., Imbriani, M., 2006. Determination of perfluorooctanoic acid and perfluorooctanesulfonate in human tissues by liquid chromatography/single quadrupole mass spectrometry. Rapid communications in mass spectrometry : RCM 20, 2728-2734.

Mandiwana, K.L., Panichev, N., Panicheva, S., 2011. Determination of chromium(VI) in black, green and herbal teas. Food Chemistry 129, 1839-1843.

Marie, C., Bouchard, M., Heredia-Ortiz, R., Viau, C., Maître, A., 2010. A toxicokinetic study to elucidate 3-hydroxybenzo(a)pyrene atypical urinary excretion profile following intravenous injection of benzo(a)pyrene in rats. Journal of Applied Toxicology 30, 402-410.

Meeker, J.D., Sathyanarayana, S., Swan, S.H., 2009. Phthalates and other additives in plastics: human exposure and associated health outcomes. Philosophical transactions of the Royal Society of London. Series B, Biological sciences 364, 2097-2113.

Meulenberg, C.J., Vijverberg, H.P., 2000. Empirical relations predicting human and rat tissue:air partition coefficients of volatile organic compounds. Toxicol Appl Pharmacol 165, 206-216.

Mielke, H., Gundert-Remy, U., 2009. Bisphenol A levels in blood depend on age and exposure. Toxicology Letters 190, 32-40.

Mielke, H., Partosch, F., Gundert-Remy, U., 2011. The contribution of dermal exposure to the internal exposure of bisphenol A in man. Toxicology Letters 204, 190-198.

Mills, C.T., Morrison, J.M., Goldhaber, M.B., Ellefsen, K.J., 2011. Chromium(VI) generation in vadose zone soils and alluvial sediments of the southwestern Sacramento Valley, California: a potential source of geogenic Cr(VI) to groundwater. Applied Geochemistry 26, 1488-1501.

Minoia, C., Cavalleri, A., 1988. Chromium in urine, serum and red blood cells in the biological monitoring of workers exposed to different chromium valency states. Sci Total Environ 71, 323-327.

Mitragotri, S., Anissimov, Y.G., Bunge, A.L., Frasch, H.F., Guy, R.H., Hadgraft, J., Kasting, G.B., Lane, M.E., Roberts, M.S., 2011. Mathematical models of skin permeability: An overview. International Journal of Pharmaceutics 418, 115-129.

Mittermeier, A., Volkel, W., Fromme, H., 2016. Kinetics of the phthalate metabolites mono-2-ethylhexyl phthalate (MEHP) and mono-n-butyl phthalate (MnBP) in male subjects after a single oral dose. Toxicol Lett 252, 22-28.

Moreau, M., Leonard, J., Phillips, K.A., Campbell, J., Pendse, S.N., Nicolas, C., Phillips, M., Yoon, M., Tan, Y.M., Smith, S., Pudukodu, H., Isaacs, K., Clewell, H., 2017. Using exposure prediction tools to link exposure and dosimetry for risk-based decisions: A case study with phthalates. Chemosphere 184, 1194-1201.

Morgan, M.G., Henrion, M., Small, M., 1992. Uncertainty: A Guide to Dealing with Uncertainty in Quantitative Risk and Policy Analysis. Cambridge University Press.

Mortensen, S.R., Chanda, S.M., Hooper, M.J., Padilla, S., 1996. Maturational differences in chlorpyrifos-oxonase activity may contribute to age-related sensitivity to chlorpyrifos. Journal of biochemical toxicology 11, 279-287.

National Research Council, 2008. Phthalates and Cumulative Risk Assessment: The Tasks Ahead. The National Academies Press, Washington, DC.

Nguyen, H.Q., Stamatis, S.D., Kirsch, L.E., 2015. A Novel Method for Assessing Drug Degradation Product Safety Using Physiologically-Based Pharmacokinetic Models and Stochastic Risk Assessment. Journal of Pharmaceutical Sciences 104, 3101-3119.

Nicolopoulou-Stamati, P., Maipas, S., Kotampasi, C., Stamatis, P., Hens, L., 2016. Chemical Pesticides and Human Health: The Urgent Need for a New Concept in Agriculture. Frontiers in Public Health 4, 148.

Nolan, R.J., Rick, D.L., Freshour, N.L., Saunders, J.H., 1984. Chlorpyrifos: pharmacokinetics in human volunteers. Toxicol Appl Pharmacol 73, 8-15.

Nordberg, G.F., Fowler, B.A., Nordberg, M., 2014. Handbook on the Toxicology of Metals. Elsevier Science.

O'Flaherty, E.J., 1993. Physiologically based models for bone-seeking elements. IV. Kinetics of lead disposition in humans. Toxicol Appl Pharmacol 118, 16-29.

O'Flaherty, E.J., 1996. A physiologically based model of chromium kinetics in the rat. Toxicol Appl Pharmacol 138, 54-64.

O'Flaherty, E.J., Kerger, B.D., Hays, S.M., Paustenbach, D.J., 2001. A physiologically based model for the ingestion of chromium(III) and chromium(VI) by humans. Toxicological sciences : an official journal of the Society of Toxicology 60, 196-213.

O'Flaherty, E.J., 1995. Chromium Toxicokinetics, in: R.A. Goyer, M.G. Cherian (Eds.), Toxicology of Metals: Biochemical Aspects. Springer Berlin Heidelberg, Berlin, Heidelberg, pp. 215-228.

Olsen, G.W., Burris, J.M., Ehresman, D.J., Froehlich, J.W., Seacat, A.M., Butenhoff, J.L., Zobel, L.R., 2007. Half-life of serum elimination of perfluorooctanesulfonate,perfluorohexanesulfonate, and perfluorooctanoate in retired fluorochemical production workers. Environ Health Perspect 115, 1298-1305.

Oze, C., Bird, D.K., Fendorf, S., 2007. Genesis of hexavalent chromium from natural sources in soil and groundwater. Proc Natl Acad Sci U S A 104, 6544-6549.

Papadaki, K.C., Karakitsios, S.P., Sarigiannis, D.A., 2017. Modeling of adipose/blood partition coefficient for environmental chemicals. Food and Chemical Toxicology 110, 274-285.

Paustenbach, D.J., Hays, S., Kerger, B.D., Finley, B., 1999. An analysis of inter-individual variability in uptake and elimination of chromium from human volunteers. Toxicologist 30.

Paustenbach, D.J., Hays, S.M., Brien, B.A., Dodge, D.G., Kerger, B.D., 1996. Observation of steady state in blood and urine following human ingestion of hexavalent chromium in drinking water. Journal of toxicology and environmental health 49, 453-461.

Payan, J.P., Marty, J.P., Fabry, J.P., Beydon, D., Boudry, I., Ferrari, E., Canel, F., Grandclaude, M.C., Vincent, C.M., 2001. In vivo and in vitro percutaneous absorption of [(14)C]di-N-butylphthalate in rat. Drug metabolism and disposition: the biological fate of chemicals 29, 843-854.

Pérez, F., Nadal, M., Navarro-Ortega, A., Fàbrega, F., Domingo, J.L., Barceló, D., Farré, M., 2013. Accumulation of perfluoroalkyl substances in human tissues. Environment International 59, 354-362.

Pettersson, S., Söderholm, B., Persson, J.E., Eriksson, S., Fritjofsson, Å., 1973. Testicular Blood Flow in Man Measured with Venous Occlusion Plethysmography and Xenon. Scandinavian Journal of Urology and Nephrology 7, 115-119.

Peyret, T., Krishnan, K., 2011. QSARs for PBPK modelling of environmental contaminants. SAR and QSAR in Environmental Research 22, 129-169.

Pond, A.L., Chambers, H.W., Chambers, J.E., 1995. Organophosphate detoxication potential of various rat tissues via A-esterase and aliesterase activities. Toxicol Lett 78, 245-252.

Pottenger, L.H., Domoradzki, J.Y., Markham, D.A., Hansen, S.C., Cagen, S.Z., Waechter, J.M., 2000. The relative bioavailability and metabolism of bisphenol A in rats is dependent upon the route of administration. Toxicological Sciences 54, 3-18.

Poulin, P., Krishnan, K., 1995a. An algorithm for predicting tissue: Blood partition coefficients of organic chemicals from n-octanol: Water partition coefficient data. Journal of toxicology and environmental health 46, 117-129.

Poulin, P., Krishnan, K., 1995b. A biologically-based algorithm for predicting human tissue: blood partition coefficients of organic chemicals. Human & experimental toxicology 14, 273-280.

Poulin, P., Krishnan, K., 1996. Molecular Structure-Based Prediction of the Partition Coefficients of Organic Chemicals for Physiological Pharmacokinetic Models. Toxicology Methods 6, 117-137.

Poulin, P., Theil, F.P., 2000. A priori prediction of tissue:plasma partition coefficients of drugs to facilitate the use of physiologically-based pharmacokinetic models in drug discovery. J Pharm Sci 89, 16-35.

Price, K., Krishnan, K., 2011. 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 22, 107-128.

Ramsey, J.C., Andersen, M.E., 1984. A physiologically based description of the inhalation pharmacokinetics of styrene in rats and humans. Toxicology and Applied Pharmacology 73, 159-175.

Rodgers, T., Leahy, D., Rowland, M., 2005. Physiologically based pharmacokinetic modeling 1: Predicting the tissue distribution of moderate-to-strong bases. Journal of Pharmaceutical Sciences 94, 1259-1276.

Rodgers, T., Rowland, M., 2006. Physiologically based pharmacokinetic modelling 2: Predicting the tissue distribution of acids, very weak bases, neutrals and zwitterions. Journal of Pharmaceutical Sciences 95, 1238-1257.

Ruiz, P., Fowler, B.A., Osterloh, J.D., Fisher, J., Mumtaz, M., 2010a. Physiologically based pharmacokinetic (PBPK) tool kit for environmental pollutants--metals. SAR QSAR Environ Res 21, 603-618.

Ruiz, P., Mumtaz, M., Osterloh, J., Fisher, J., Fowler, B.A., 2010b. Interpreting NHANES biomonitoring data, cadmium. Toxicol Lett 198, 44-48.

Sanborn, M., Kerr, K.J., Sanin, L.H., Cole, D.C., Bassil, K.L., Vakil, C., 2007. Non-cancer health effects of pesticides: systematic review and implications for family doctors. Canadian family physician Medecin de famille canadien 53, 1712-1720.

Sarigiannis, D., Gotti, A., Karakitsios, S., 2011. A Computational Framework for Aggregate and Cumulative Exposure Assessment. Epidemiology 22, S96-S97.

Sarigiannis, D., Karakitsios, S., 2011. Perinatal Exposure to Bisphenol A: The Route of Administration Makes the Dose. Epidemiology 22, S172.

Sarigiannis, D., Karakitsios, S., Gotti, A., Loizou, G., Cherrie, J., Smolders, R., De Brouwere, K., Galea, K., Jones, K., Handakas, E., Papadaki, K., Sleeuwenhoek, A., 2014. Integra: From global scale contamination to tissue dose, Proceedings - 7th International Congress on Environmental Modelling and Software: Bold Visions for Environmental Modeling, iEMSs 2014, pp. 1001-1008.

Sarigiannis, D.A., 2017. Assessing the impact of hazardous waste on children's health: The exposome paradigm. Environ Res 158, 531-541.

Sarigiannis, D.A., Gotti, A., 2008. Biology-based dose-response models for health risk assessment of chemical mixtures. Fresenius Environmental Bulletin 17, 1439-1451.

Sarigiannis, D.A., Hansen, U., 2012. Considering the cumulative risk of mixtures of chemicals - A challenge for policy makers. Environmental Health: A Global Access Science Source 11.

Sarigiannis, D.A., Karakitsios, S.P., 2012. A dynamic physiology based pharmacokinetic model for assessing lifelong internal dose, AIChE 2012, Pittsburgh, PA.

Sarigiannis, D.A., Karakitsios, S.P., Handakas, E., Simou, K., Solomou, E., Gotti, A., 2016. Integrated exposure and risk characterization of bisphenol-A in Europe. Food and Chemical Toxicology 98, 134-147.

Sarigiannis, D.A., Papadaki, K., Kontoroupis, P., Karakitsios, S.P., 2017. Development of QSARs for parameterizing Physiology Based ToxicoKinetic models. Food and Chemical Toxicology 106, 114-124.

Sasso, A.F., Isukapalli, S.S., Georgopoulos, P.G., 2010. A generalized physiologically-based toxicokinetic modeling system for chemical mixtures containing metals. Theoretical Biology and Medical Modelling 7.

Satarug, S., Garrett, S.H., Sens, M.A., Sens, D.A., 2010. Cadmium, environmental exposure, and health outcomes. Environ Health Perspect 118, 182-190.

Schmitt, W., 2008. General approach for the calculation of tissue to plasma partition coefficients. Toxicology in Vitro 22, 457-467.

Sharma, R.P., Schuhmacher, M., Kumar, V., 2017. Developing integrated PBPK/PD coupled mechanistic pathway model (miRNA-BDNF): An approach towards system toxicology. Toxicol Lett 280, 79-91.

Sharma, R.P., Schuhmacher, M., Kumar, V., 2018a. The development of a pregnancy PBPK Model for Bisphenol A and its evaluation with the available biomonitoring data. Science of Total Environment *in press*.

Sharma, R.P., Schuhmacher, M., Kumar, V., 2018b. Physiology based Pharmacokinetic (PBPK) modeling for DEHP metabolites integrating its in vitro metabolism: a bottom up modeling approach. Toxicology Letters *Submitted*.

Shin, B.S., Kim, C.H., Jun, Y.S., Kim, D.H., Lee, B.M., Yoon, C.H., Park, E.H., Lee, B.M., Yoon, C.H., Park, E.H., Lee, K.C., Han, S.Y., Park, K.L., Kim, H.S., Yoo, S.D., 2004a. Physiologically based pharmacokinetics of bisphenol A. Journal of Toxicology and Environmental Health - Part A 67, 1971-1985.

Shin, B.S., Kim, C.H., Jun, Y.S., Kim, D.H., Lee, B.M., Yoon, C.H., Park, E.H., Lee, K.C., Han, S.Y., Park, K.L., Kim, H.S., Yoo, S.D., 2004b. Physiologically based pharmacokinetics of bisphenol A. Journal of toxicology and environmental health. Part A 67, 1971-1985.

Stern, A.H., 2010. A quantitative assessment of the carcinogenicity of hexavalent chromium by the oral route and its relevance to human exposure. Environ Res 110, 798-807.

Sultatos, L.G., 1994. Mammalian toxicology of organophosphorus pesticides. Journal of toxicology and environmental health 43, 271-289.

Sultatos, L.G., Murphy, S.D., 1983. Kinetic analyses of the microsomal biotransformation of the phosphorothioate insecticides chlorpyrifos and parathion. Fundam Appl Toxicol 3, 16-21.

Swan, S.H., 2008. Environmental phthalate exposure in relation to reproductive outcomes and other health endpoints in humans. Environmental research 108, 177-184.

Tan, Y.M., Liao, K., Conolly, R., Blount, B., Mason, A., Clewell, H., 2006. Use of a physiologically based pharmacokinetic model to identify exposures consistent with human biomonitoring data for chloroform. Journal of Toxicology and Environmental Health - Part A: Current Issues 69, 1727-1756.

Teeguarden, J.G., Waechter, J.M., Clewell, H.J., Covington, T.R., Barton, H.A., 2005a. Evaluation of oral and intravenous route pharmacokinetics, plasma protein binding, and uterine tissue dose metrics of bisphenol A: A physiologically based pharmacokinetic approach. Toxicological Sciences 85, 823-838.

Teeguarden, J.G., Waechter Jr, J.M., Clewell III, H.J., Covington, T.R., Barton, H.A., 2005b. Evaluation of oral and intravenous route pharmacokinetics, plasma protein binding, and uterine tissue dose metrics of bisphenol A: A physiologically based pharmacokinetic approach. Toxicological Sciences 85, 823-838.

ten Berge, W., 2009. A simple dermal absorption model: derivation and application. Chemosphere 75, 1440-1445.

Thayer, K.A., Doerge, D.R., Hunt, D., Schurman, S.H., Twaddle, N.C., Churchwell, M.I., Garantziotis, S., Kissling, G.E., Easterling, M.R., Bucher, J.R., Birnbaum, L.S., 2015. Pharmacokinetics of Bisphenol A in Humans Following a Single Oral Administration. Environment international 83, 107-115.

Timchalk, C., Nolan, R.J., Mendrala, A.L., Dittenber, D.A., Brzak, K.A., Mattsson, J.L., 2002. A Physiologically based pharmacokinetic and pharmacodynamic (PBPK/PD) model for the organophosphate insecticide chlorpyrifos in rats and humans. Toxicological sciences : an official journal of the Society of Toxicology 66, 34-53.

Touitou, E., 2002. Drug delivery across the skin. Expert Opinion on Biological Therapy 2, 723-733.

Upmeier, A., Degen, G.H., Diel, P., Michna, H., Bolt, H.M., 2000. Toxicokinetics of bisphenol A in female DA/Han rats after a single i.v. and oral administration. Archives of Toxicology 74, 431-436.

USEPA, 2013. Provisional Guidance for Quantitative Risk Assessment of Polycyclic Aromatic Hydrocarbons.

Valcke, M., Krishnan, K., 2011. Evaluation of the impact of the exposure route on the human kinetic adjustment factor. Regulatory Toxicology and Pharmacology 59, 258-269.

Valentin, J., 2002. Basic anatomical and physiological data for use in radiological protection: reference values. A report of age- and gender-related differences in the anatomical and physiological characteristics of reference individuals. ICRP Publication 89. Ann ICRP 32, 5-265.

Vanden Heuvel, J.P., Kuslikis, B.I., Van Rafelghem, M.J., Peterson, R.E., 1991. Tissue distribution, metabolism, and elimination of perfluorooctanoic acid in male and female rats. Journal of biochemical toxicology 6, 83-92.

Ventura, C., Latino, D.A.R.S., Martins, F., 2013. Comparison of Multiple Linear Regressions and Neural Networks based QSAR models for the design of new antitubercular compounds. European journal of medicinal chemistry 70, 831-845.

Verner, M.A., Charbonneau, M., Lopez-Carrillo, L., Haddad, S., 2008. Physiologically based pharmacokinetic modeling of persistent organic pollutants for lifetime exposure assessment: A new tool in breast cancer epidemiologic studies. Environmental Health Perspectives 116, 886-892.

Völkel, W., Colnot, T., Csanády, G.A., Filser, J.G., Dekant, W., 2002. Metabolism and Kinetics of Bisphenol A in Humans at Low Doses Following Oral Administration. Chemical Research in Toxicology 15, 1281-1287.

Wagner, J.G., 1973. Properties of Michaelis-Menten equation and its integrated form which are useful in pharmacokinetics. Journal of Pharmacokinetics and Biopharmaceutics 1, 103-121.

Wang, X.F., Santostefano, M.J., Evans, M.V., Richardson, V.M., Diliberto, J.J., Birnbaum, L.S., 1997. Determination of parameters responsible for pharmacokinetic behavior of TCDD in female Sprague-Dawley rats. Toxicology and Applied Pharmacology 147, 151-168.

WHO, 2010. Exposure to highly hazardous pesticides: A major public health concern, Geneva, Switzerland.

Willhite, C.C., Ball, G.L., McLellan, C.J., 2008. Derivation of a bisphenol A oral reference dose (RfD) and drinking-water equivalent concentration. Journal of toxicology and environmental health. Part B, Critical reviews 11, 69-146.

Willmann, S., Lippert, J., Sevestre, M., Solodenko, J., Fois, F., Schmitt, W., 2003a. PK-Sim®: A physiologically based pharmacokinetic 'whole-body' model. Drug Discovery Today: BIOSILICO 1, 121-124.

Willmann, S., Schmitt, W., Keldenich, J., Dressman, J.B., 2003b. A Physiologic Model for Simulating Gastrointestinal Flow and Drug Absorption in Rats. Pharmaceutical Research 20, 1766-1771.

Willmann, S., Schmitt, W., Keldenich, J., Lippert, J., Dressman, J.B., 2004a. A physiological model for the estimation of the fraction dose absorbed in humans. Journal of Medicinal Chemistry 47, 4022-4031.

Willmann, S., Schmitt, W., Keldenich, J., Lippert, J., Dressman, J.B., 2004b. A physiological model for the estimation of the fraction dose absorbed in humans. J Med Chem 47, 4022-4031.

World Health Organization, 2010. WHO Guidelines for Indoor Air Quality: Selected Pollutants. WHO.

Xue, J., Zartarian, V., Wang, S.W., Liu, S.V., Georgopoulos, P., 2010. Probabilistic modeling of dietary arsenic exposure and dose and evaluation with 2003-2004 NHANES data. Environmental Health Perspectives 118, 345-350.

Yang, X., Doerge, D.R., Teeguarden, J.G., Fisher, J.W., 2015. Development of a physiologically based pharmacokinetic model for assessment of human exposure to bisphenol A. Toxicol Appl Pharmacol 289, 442-456.

Yang, Y., Xu, X., Georgopoulos, P.G., 2010. A Bayesian population PBPK model for multiroute chloroform exposure. Journal of Exposure Science and Environmental Epidemiology 20, 326-341.

Yano, B.L., Young, J.T., Mattsson, J.L., 2000. Lack of Carcinogenicity of Chlorpyrifos Insecticide in a High-Dose, 2-Year Dietary Toxicity Study in Fischer 344 Rats. Toxicological Sciences 53, 135-144.

Yu, D., 1999a. A pharmacokinetic modeling of inorganic arsenic: a short-term oral exposure model for humans. Chemosphere 39, 2737-2747.

Yu, D., 1999b. A Physiologically Based Pharmacokinetic Model of Inorganic Arsenic. Regulatory Toxicology and Pharmacology 29, 128-141.

Yu, L.X., Amidon, G.L., 1999. A compartmental absorption and transit model for estimating oral drug absorption. International journal of pharmaceutics 186, 119-125.