



SOT FDA Colloquia on Emerging Toxicological Science Challenges in Food and Ingredient Safety

OECD Guidance on the Characterisation, Validation, and Reporting of Physiologically Based Kinetic (PBK) Models

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No Conflict of Interest

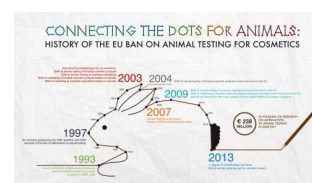
OECD Document not yet endorsed, still in draft

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Premise

- Risk assessment can and should be based on non-animal data
- This implies the need to interpret and use *in vitro* toxicity data in combination with biokinetic data
- Biokinetic (ADME) data can be generated by *in silico* and *in vitro* models
- Mathematical modelling is the only way to accurately integrate and use non-animal data
- Robust and reliable mathematical models are available ...

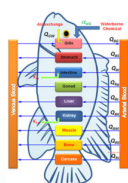
Picture source: https://ec.europa.eu/growth/sectors/cosmetics/animal-testing_en
<https://www.sciencemag.org/news/2019/09/us-epa-eliminate-all-mammal-testing-2035>



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What Kinds of Models Are In Scope?



Physiologically based kinetic (PBK) model

Throughout this presentation the more general term PBK will be used. Noting that PBK, PBPK, PBBK and PBTK are synonyms.

Physiologically based pharmacokinetic (PBPK) is the most widely used term for kinetic models describing the absorption, distribution, metabolism and excretion of a drug within the body. Although widely used in the pharmaceutical sector, the "PBPK" term is not strictly correct in the area of chemical risk assessment. An alternative is "PBTK" with the TK representing toxicokinetic, but this is not appropriate either (Clewley & Clewley, 2008). More general terms, such as physiologically based biokinetic (PBBK) or physiologically based kinetic (PBK), are thus more appropriate.

Premise

- but guidance is needed to promote model credibility in a decision-making context

Pictures source: <https://ec.europa.eu/jrc/en/publication/eurl-ecvam-workshop-new-generation-physiologically-based-kinetic-models-risk-assessment> (human)
<https://www.frontiersin.org/articles/10.3389/fmars.2015.00114/full> (fish)

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A Bit of History Behind the Document–Part I

- EURL ECVAM Strategy Document on Toxicokinetics (2015)
 - Objectives to enable prediction of systemic toxicity by applying new approach methods
- Workshop on physiologically based kinetic modelling (2016)
 - Establishing model credibility, dealing with uncertainty



Pictures source: <https://ec.europa.eu/jrc/en/publication/eurl-ecvam-workshop-new-generation-physiologically-based-kinetic-models-risk-assessment>



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A Bit of History Behind the Document–Part II

Survey of PBK model use in science and regulation (2017)

- 93 respondents
- Need for guidance on reporting, use, and reviewing the new generation PBK Models



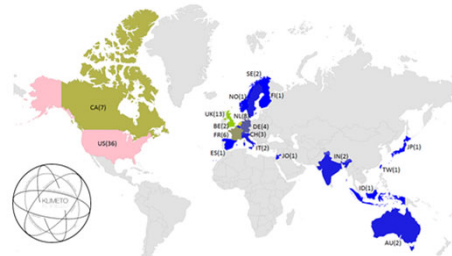
Regulatory Toxicology and Pharmacology
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Investigating the state of physiologically based kinetic modelling practices and challenges associated with gaining regulatory acceptance of model applications

Alicia Paini ¹, R. B. Jeremy A. Leonard ², Tomas Klimont ³, Yu-Mei Tan ⁴, Andrew Worth ⁴

Pictures source: <https://www.sciencedirect.com/science/article/pii/S0273230017302696>
<https://chemicalwatch.com/62129/regulatory-agencies-reluctant-to-use-mathematical-models-of-organisms>



<https://apps.klimeto.com/pbk/>

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Regulatory agencies reluctant to use mathematical models of organisms

JRC survey highlights need for new PBK guidelines

30 November 2017 / Alternative approaches to testing, Europe, United States

Regulatory agencies remain reluctant to use physiologically based kinetic (PBK) models, according to an expert survey by the European Commission's Joint Research Centre (JRC).

Widely used in industry and academia, PBK mathematical models describe how chemicals pass through the body, which is represented as a series of interconnected compartments. The models are favoured



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OECD Guidance Document on the Characterisation, Validation, and Reporting of Physiologically Based Models for Regulatory Applications

Typical PBK models	New Generation PBK models
Calibration and evaluation of the model rely on <i>in vivo</i> data	Development of the model rely on <i>in vitro</i> or <i>in silico</i> methods
Model structure reflects a balance between the principles of parsimony and plausibility	Model structure reflects mechanistic understanding of biology and biochemistry
“Familiar uncertainty”	“Unfamiliar Uncertainty”

The aim of this document is to provide guidance on the characterisation, validation, and reporting of Physiologically Based Kinetic (PBK) models intended for use in the regulatory assessment of chemicals in cases where no *in vivo* kinetic data are available for model validation.



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Regulatory Applications

Potential Applications	
1	Extrapolating across doses or exposure scenarios
2	Route-to-route extrapolation
3	Interspecies extrapolation (and modification of default assessment factors)
4	Intraspecies extrapolation (accounting for population variability)
5	<i>In vivo</i> extrapolation of <i>in vitro</i> toxicity data – Q(IVIVE)
6	Setting safe levels of a chemical based on tissue dosimetry (in humans or animals)
7	Interpreting human and wildlife biomonitoring data by retrospectively reconstructing the external dose or exposure (reverse dosimetry)
8	Predicting biologically-relevant doses at target tissues

Builds on Existing Guidance

	EPA 2006	WHO 2010	EFSA 2014	CEN 2015	EMA/FDA 2018
Scope	Model application in risk assessment	Model application in risk assessment	Good Modelling Practices	Reporting of multimedia models	PBK model platform evaluation
Applications	Interspecies Extrapolation Intraspecies Variability Route-to-Route Extrapolation Duration Adjustment High-Dose to Low-Dose Extrapolation.	Interspecies extrapolation Interindividual variability High dose to low dose extrapolation; Route-to-route extrapolation.	Environmental	Environmental and human models	Drug submission

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OECD PBK Model Guidance Structure

Introduction

Chapter 2 (PBK modelling workflow) summarises the steps taken to characterise and validate PBK models using physicochemical and biochemical data from *in vitro* and *in silico* methods.

Chapter 3 (regulatory assessment of PBK models) presents a template for reporting models and a checklist for evaluating their validity and applicability, according to context of use.

Case Studies



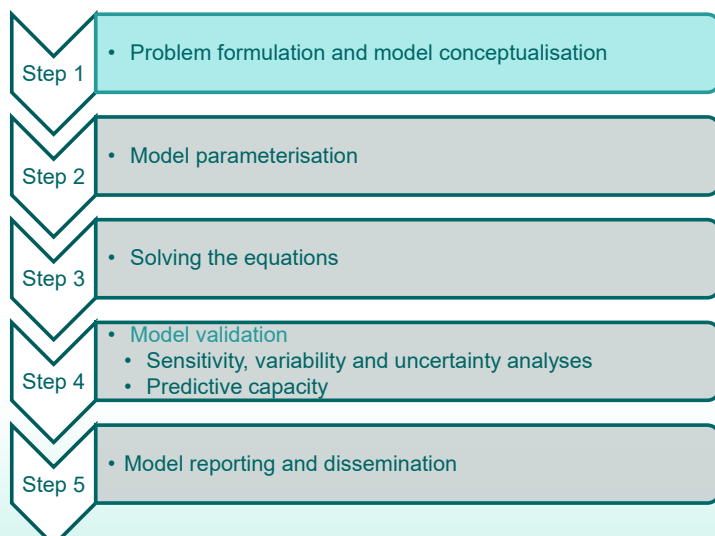
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Into the Guidance: Model Workflow

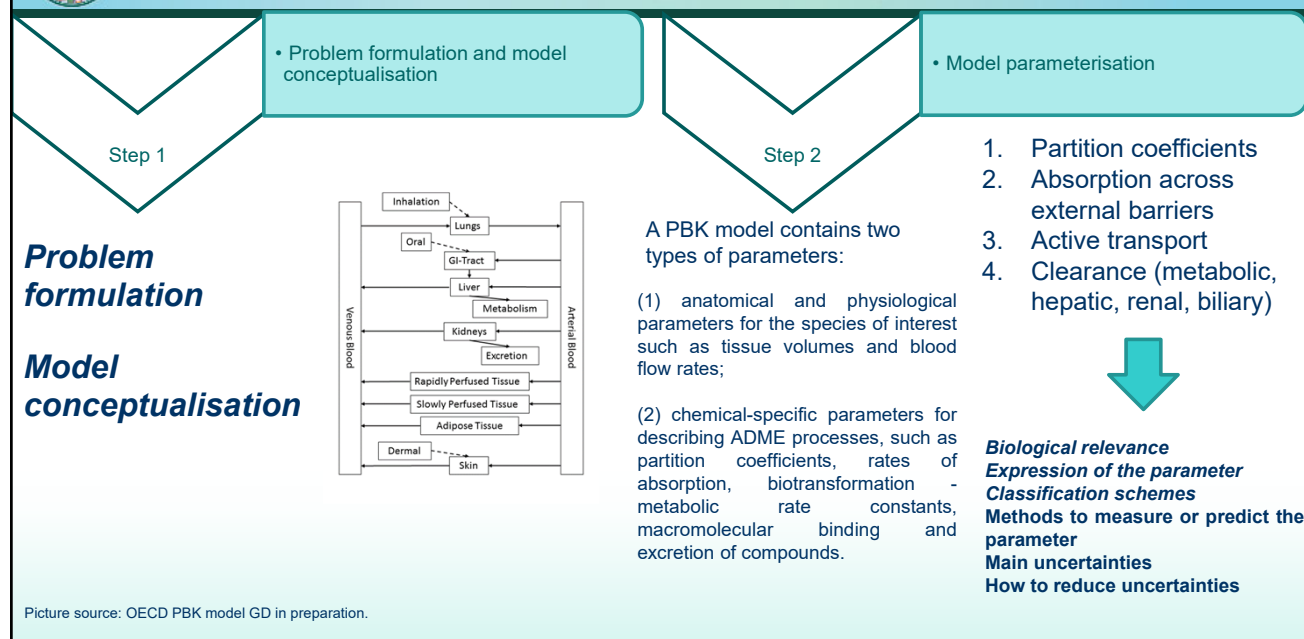


Scientific workflow for characterising and validating PBK models, with emphasis on the use of *in vitro* and *in silico* data for absorption, distribution, metabolism, and excretion (ADME) parameters, and in scenarios where *in vivo* kinetic data are limited or unavailable to parameterise model parameters

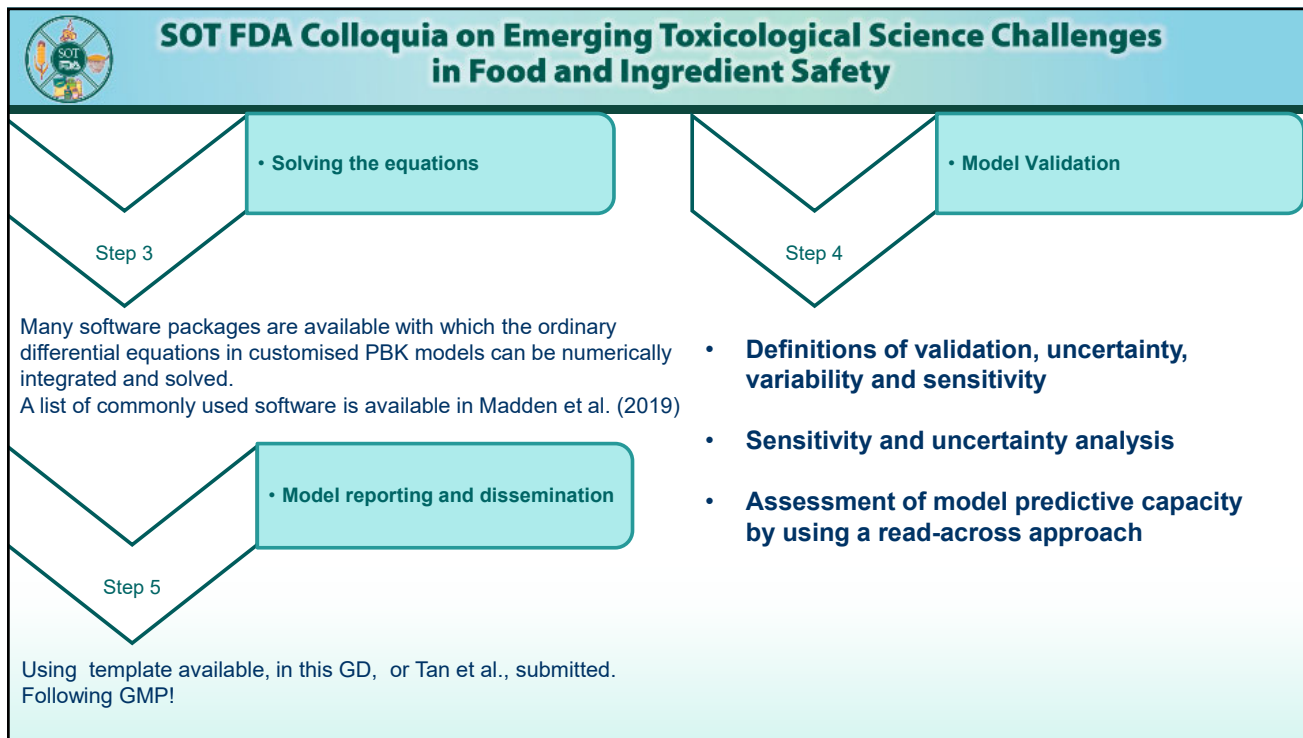
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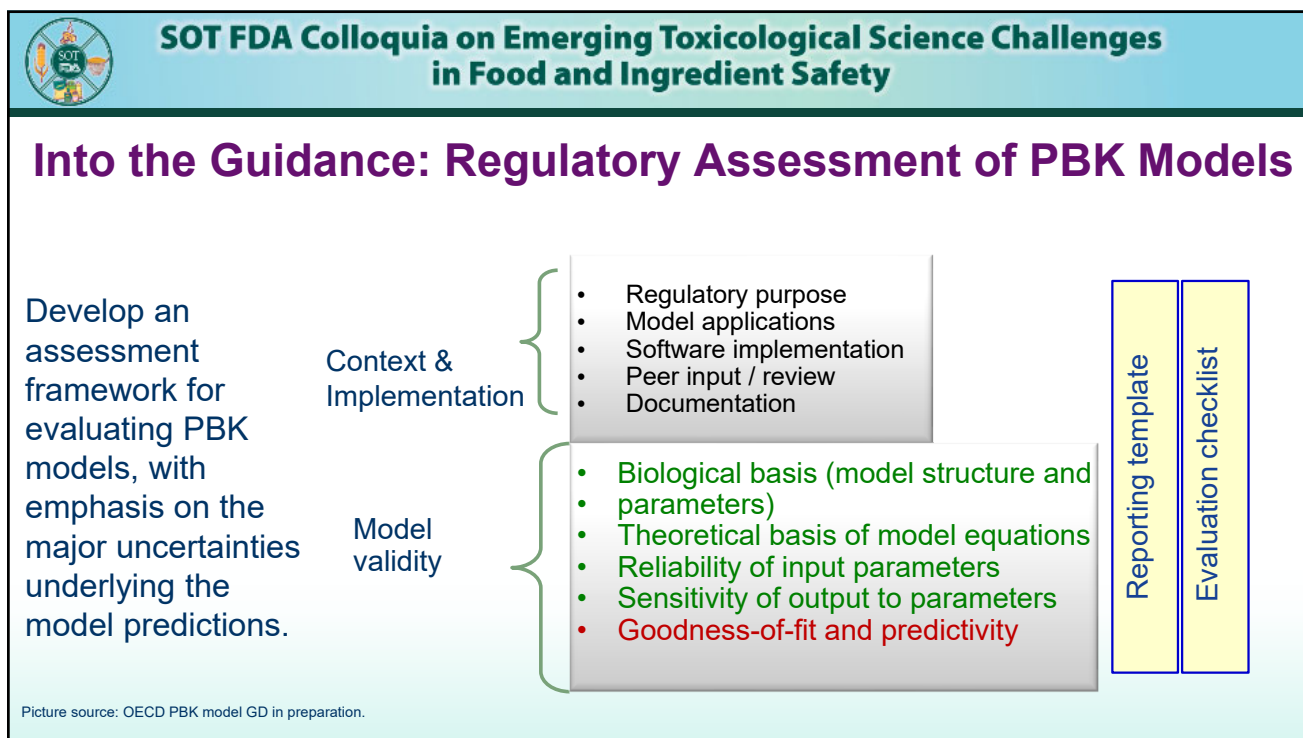
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Context and Implementation

PBK model code should be provided to ensure that:

- the model code (i.e., equations and parameter values) are devoid of syntax or mathematical errors;
- the values and units of input parameters are accurate;
- the chemical mass balance and blood flow balance are respected at all times; and
- there is no solver or numerical error.

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Model Validity

- Biological basis (model structure and parameters)
- Theoretical basis of model equations
- Reliability of input parameters
- Sensitivity and uncertainty analysis:
 - Application of OAT or GSA have a great impact on drawing conclusion on model validity.
- Goodness-of-fit and predictivity

Confidence matrix for the input parameters (adapted from WHO, 2010).

		Uncertainty in variability of the input parameter estimates		
		High	Medium	Low
SENSITIVITY	High		Parameter 1	Parameter 3 Parameter 4 Parameter 7
	Medium		Parameter 2	Parameter 10
	Low			Parameter 12 Parameter 13

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PBK Model Evaluation Tool Box

1. Model Reporting Template

Confidence Matrix

		Uncertainty in variability of the input parameter estimates		
		High	Medium	Low
SENSITIVITY	High		Parameter 1	Parameter 3 Parameter 4 Parameter 7
	Medium		Parameter 2	Parameter 10
	Low			Parameter 12 Parameter 13

3. Overall Evaluation Matrix (adapted from WHO 2010)

LEVEL OF CONFIDENCE ← NONE → HIGH

	NONE		HIGH
Biological basis	The model parameters, structure or assumptions are consistent with neither the biology nor the current state of knowledge regarding the kinetics of the chemical.		The model parameters and structure have reasonable biological basis and are consistent with available kinetic data in several experiments using a single set of input parameters.
Model simulations of data	Model is unable to reproduce the shape (i.e. bumps, valleys) of the kinetic time course curves, neither for the chemical of interest nor for a suitable analogue.		Model reproduces consistently all kinetic data, including the shape of time course profiles for chemical of interest.
Uncertainty in input parameters and model output; Sensitivity of model output to	No uncertainty and sensitivity analyses were performed		Global Sensitivity Analysis supports the robustness of the model.

2. Evaluation Checklist

Picture source: OECD PBK model GD in preparation. Icons from ppt

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PBK Model Evaluation Tool Box

PBK Model Reporting Template sections	
A. Name of model	
B. Model developer and contact details	
C. Summary of model characterisation, development, validation, and regulatory applicability	
D. Model characterisation	
E. Modelling workflow	Step 1 – Problem formulation and model conceptualisation Step 2 – Model parameterisation Step 3 – Solving the equations Step 4 – Model Validation Step 5 – Model reporting and dissemination
F. Identification of uncertainties	<ul style="list-style-type: none"> model structure input parameters model output other uncertainties (e.g. model developed for different substance and/or purpose)
G. Model implementation details	<ul style="list-style-type: none"> software (version no) availability of code software verification / qualification
H. Peer engagement (input/review)	
I. Parameter tables	
J. References and background information	<ul style="list-style-type: none"> publications links to other resources

PBK Model Evaluation Checklist	Checklist assessment	Comments
Name of the PBK model (as in the reporting template)		
Model developer and contact details		
Name of person reviewing and contact details		
Date of checklist assessment		
A. Context/Implementation		
A.1. Regulatory Purpose		
A.2. Documentation		
A.3 Software Implementation and Verification		
A.4 Peer engagement (input/review)		
B. Assessment of Model Validity		
B.1 Biological Basis (Model Structure and Parameters)		
B.3. Reliability of input parameters		
B.4. Uncertainty and Sensitivity Analysis		
B.5. Goodness-of-Fit and Predictivity		

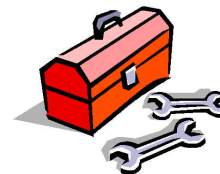
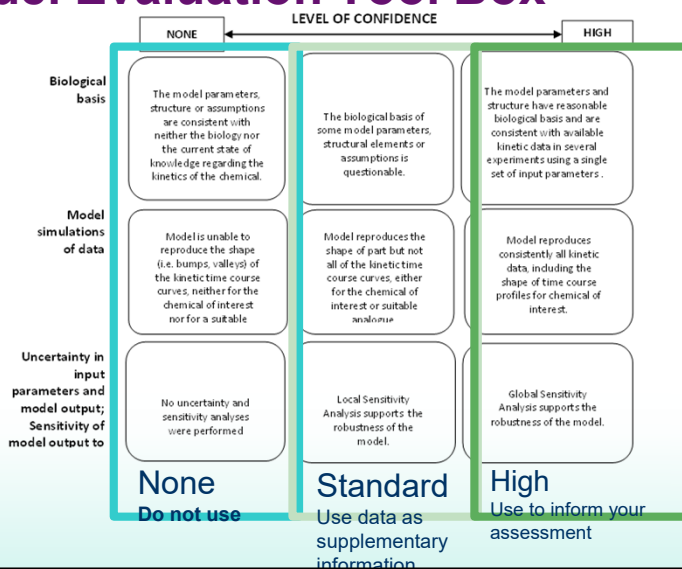
Comprising 19 questions to be answered

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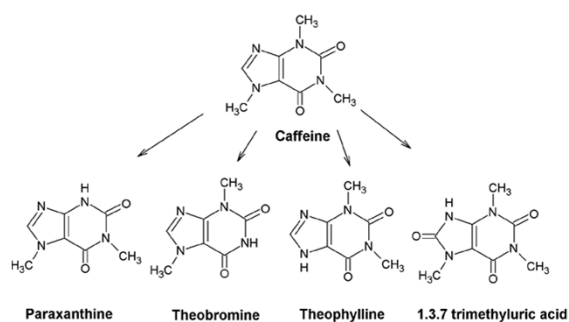
PBK Model Evaluation Tool Box



Picture source: OECD PBK model GD in preparation.
Icons from ppt

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Caffeine Case Study



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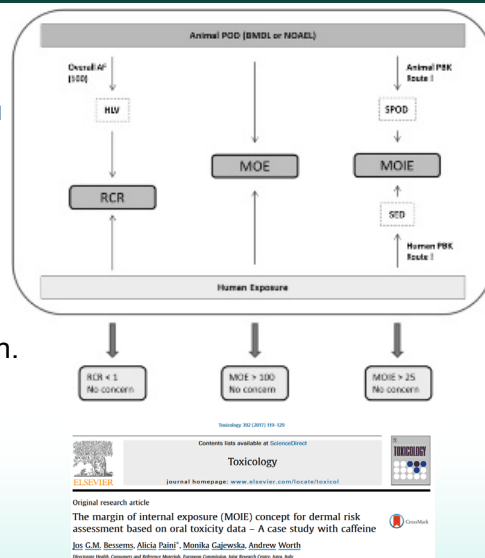
PBK Model for Caffeine

Human health risk of exposure to a chemical can be characterized.

- RCR = Risk characterisation ratio approach
human exposure level compared to human limit value (HLV), based on an animal point of departure (POD) divided by relevant assessment factors.
- MOE = [POD]/SED
POD point of departure : i.e. NOAEL or BMDL
SED systemic exposure dose (SED)

A shortcoming in both approaches is the apparent lack of attention for species- and route-dependent ADME information.

- MOIE = [SPOD]/SED
 - SPOD Systemic point of departure by PBK modelling
 - SED Systemic exposure dose (SED) by PBK modelling

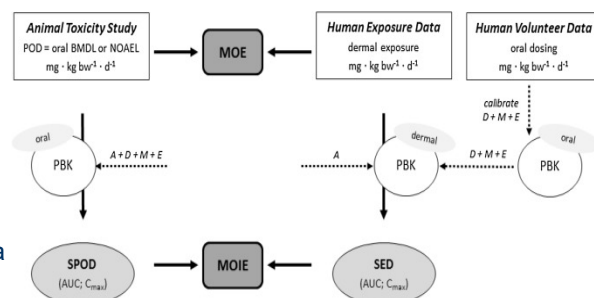


Pictures source: Bessems et al., 2017

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PBK Model for Caffeine

- Caffeine in cosmetics, in food products.
- PBK model for rat (oral)
 - Define the toxicity using fetotoxicity
 - LOAEL 10 mg/kgbw/d
 - NOAEL < 10 mg/kgmg/kgbw/d
- PBK model for human (dermal & oral)
 - Calibration using oral human *in vivo* data
 - Model validation using oral and dermal *in vivo* data



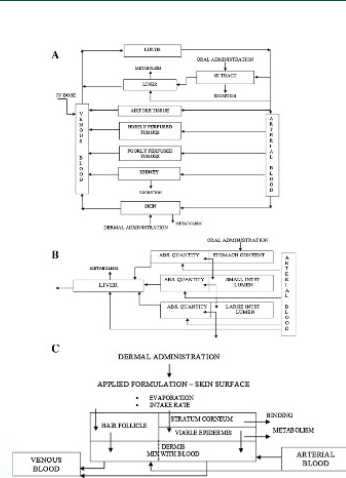
Original research article
The margin of internal exposure (MOIE) concept for dermal risk assessment based on oral toxicity data – A case study with caffeine
Jos G.M. Bessems, Alicia Pardini, Monika Gajewska, Andrew Worth
Eurocentric Health, Consumers and Reference Materials, European Commission, Joint Research Centre, Ispra, Italy

- Developed in R (<http://cran.r-project.org>)
- Model equation reported in the appendix
- Model assumptions reported
- Literature data and *in silico* data as input
- Historical *in vivo* data to calibrate and validate the model

Pictures source: Bessems et al., 2017

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PBK Model for Caffeine



Pictures source: Bessems et al., 2017

The PBK modelling approach was based on the following **assumptions**:

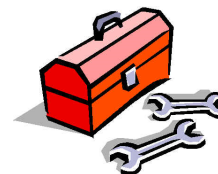
- In the human models, skin and GI tract are represented by sub-compartments, the rat PBK model the GI tract is represented by a single compartment.
- It is assumed that the test compound is applied onto the skin surface in a pure solvent (vehicle) to account for a simple formulation (i.e., in ethanol, acetone). → No mixture effects was considered.
- Metabolism is assumed to occur only in the liver. (Michaelis–Menten kinetics)
- Excretion via urine is described by a first order rate constant.
- Tissues are assumed to be homogenised compartments with respect to the concentration of a chemical.
- Transport between blood and tissues is assumed to be flow-limited and equilibrium between free and bound fractions in blood and tissue is instantaneous.
- Inter-individual differences in metabolism and excretion are not considered. To partially account for such variations, the metabolic rates are corrected by the subject's body weight.

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PBK Model Evaluation Tool Box

Overall Evaluation Matrix



Standard Confidence

	LEVEL OF CONFIDENCE		
	NONE		HIGH
Biological basis		The biological basis of some model parameters, structural elements or assumptions is questionable.	
Model Structure simulations of data; predictivity		Model reproduces partially all kinetic data, including the shape of time course profiles for chemical of interest.	
Variability/ Uncertainty in Parameter Analysis; Global Sensitivity Analysis		Local Sensitivity Analysis supports the robustness of the model.	

Picture source: Icons from ppt

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Cosmetic Europe—OECD IATA CS—Case Study on the Use of Integrated Approaches for Testing and Assessment for Systemic Toxicity Arising from Cosmetic Exposure to Caffeine

Extensive revision—simplification
recoded in Berkeley Madonna
New data to parametrize the model

	NONE	← LEVEL OF CONFIDENCE →	HIGH
Biological basis			The model parameters and structure have reasonable biological basis and are consistent with available kinetic data in several experiments using a single set of input parameters.
Model simulations of data; predictivity			Model reproduces consistently all kinetic data, including the shape of time course profiles for chemical of interest.
Variability/Uncertainty in Parameter Analysis; Global Sensitivity Analysis		Local Sensitivity Analysis supports the robustness of the model.	

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Reasonable Confidence

Integrated Approach to Testing and Assessment

Pictures source: Cosmetic Europe OECD IATA CS and EC, 2016

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Take Home Message

System biologist	Toxicologist	Risk assessor	Risk manager

Slide courtesy of Luigi Margiotta-Casaluci

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M. Sachana, A. Worth, C. Tan, B. Meek, G. Loizou, M. Evans, J.L. Dorne, I. Gardner, C. Ellison, T. Barton-maclaren, S. Kulkarni, K. Goss, I. Sorrell, C Brochot, L. Rousselberlier, H. Clewell, A. Nong, C.A. Gomes, J. Stadnicka, J. Dibella, J. Arnot, T. Preuss, M. Embry, M. Gwinn, T. Russel, G. Ouedraogo, E. Fabian, S. Kulkarni, P. Bos, J. Wambaugh, M. Zeilmaker, J. Chan, Ishida, Kanda, M. Yoon, P. Hinderliter, J. West, K. Tabata, W Drost, J. Melbourne, M.M. Mumtaz, SC Gehen, K. Tabata, Y Dancik, R. D. Clark, M. Bolger, H Kojimaa, P. Chuan, Kuwa-shino, H. Yamazaki, H. Yoon.

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