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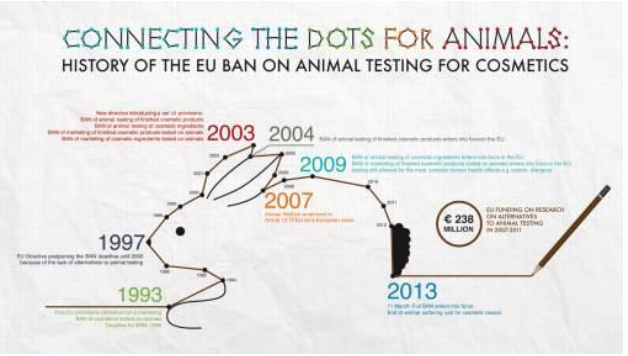
Guidance for increasing confidence in Physiologically Based Kinetic models … are we ready for a regulatory change?

ASCCT- ESTIV Webinar - Alicia Paini, PhD, ERT

Premise

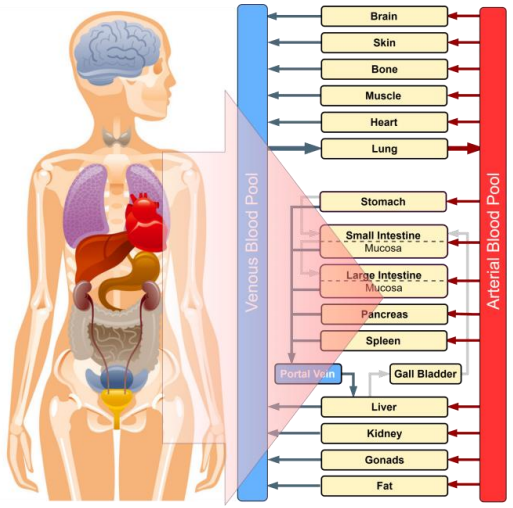
- Chemical Risk Assessment can and should be based on non-animal data
- This implies the need to use alternatives such as in vitro and in silico methods (New approach methodologies, NAMs)
- Especially to interpret and use *in vitro* toxicity data in combination with biokinetic data
- Biokinetic (ADME) data can be generated by *in silico* and *in vitro* models
- Mathematical modelling is the way to accurately integrate and use in vitro data for the design of experiments and extrapolate in vitro to in vivo for safety assessment
- Robust and reliable mathematical models are available



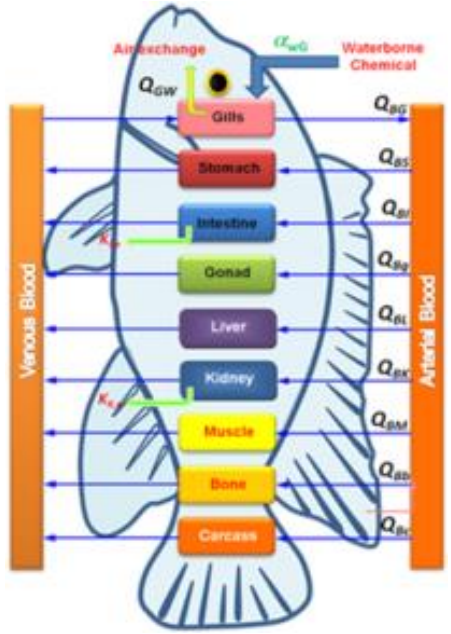
Pictures source: https://ec.europa.eu/growth/sectors/cosmetics/animal-testing_en
https://www.sciencemag.org/news/2019/09/us-epa-eliminate-all-mammal-testing-2035

What kinds of models are in scope?

Physiologically based kinetic (PBK) model



Mathematical description of the body, simulating the xenobiotic distribution into the different organs.



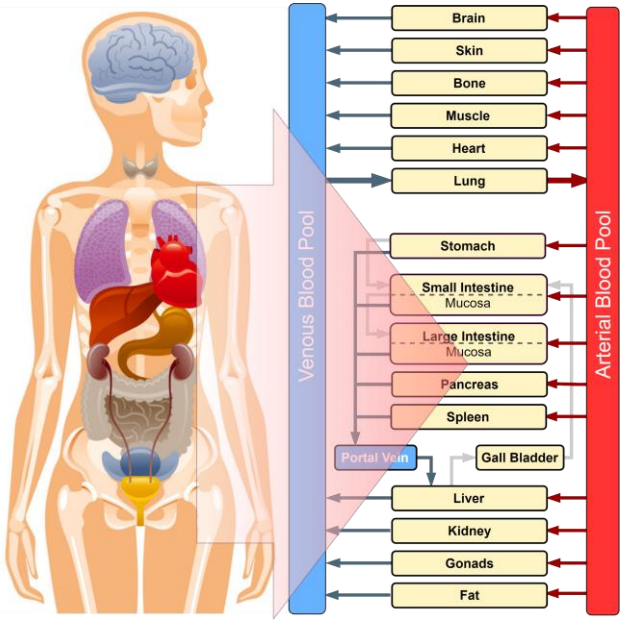
Throughout this presentation the more general term PBK will be used.
Noting that PBK, PBPK, PBBK and PBTK are synonyms.

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 (Clewell & Clewell, 2008). ***More general terms, such as physiologically based biokinetic (PBBK) or physiologically based kinetic (PBK), are thus more appropriate.***

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)

The needs & challenges….

- With current progress in science & NAMs → growing interest in developing and applying NAMs and PBK models due to the increase demanded from risk assessment.
- To increase the acceptance and use of these PBK models there is a need to demonstrate their validity.
- This is challenging in the case of data-poor chemicals that are lacking in kinetic data and for which predictive capacity cannot, therefore, be assessed.
- Need to promote the use of PBK models in regulatory risk assessment and facilitate dialogue between model developers and users



OECD GUIDANCE ON PHYSIOLOGICALLY BASED KINETIC (PBK) MODELING

BETTER POLICIES FOR BETTER LIVES

OECD PBK model document

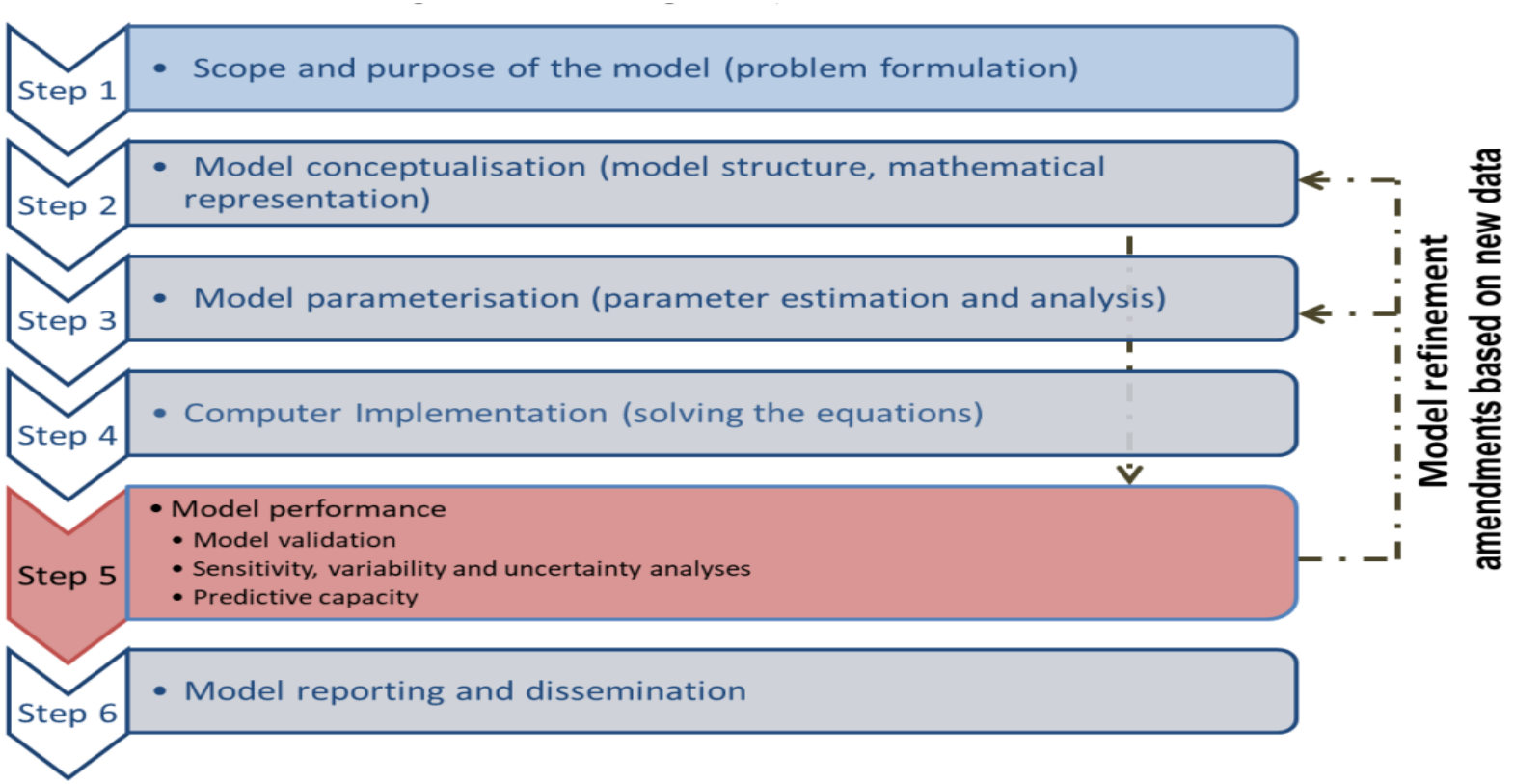
- Focus mainly on PBK models parameterised with *in vitro* or *in silico* input data with respect to the chemical and biochemical information.
  - “data poor” situations – *ab-initio.*
  - Little or no *in vivo* data for model verification.
  - Bottom up PBK model parameterisation rather than top down (fitting) approaches.
- Provide a model assessment framework for facilitating dialogue between PBK model developers and regulators
  - “data poor” situations
  - Uncertainties underlying the model input data, model structure and model predictions
- Provides guidance on characterisation and reporting of PBK models used in the regulatory assessment of chemicals
- Considerations for using human *in vitro* test systems to characterise the pharmacological/toxicological hazard, but applicable to other species, laboratory animals, farm animals, species of ecological importance.
- Document **is not**
  - A technical guidance on PBK model development or best practise
    - This is covered elsewhere (EPA 2006, WHO 2010)

Specific aims

1. A scientific workflow for characterizing and validating PBK models, with emphasis on models that are constructed using *in vitro and in silico data*.
2. Knowledge sources on *in vitro* and *in silico* methods that can be used to generate model parameters.
3. An assessment framework for evaluating PBK models for intended purposes.
4. A template for documenting PBK models.
5. Provide a checklist to support the evaluation of PBK model applicability according to context of use.

Contents of OECD Guidance Document

1. PBK 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

Step 5 - Assessment of model predictive capacity by using a read-across approach

Schematic workflow to identify and use analogues in PBK model development and validation.

PBK model database – to inform PBK models for data poor chemicals – LJMU & EPAA (PI. Judith Madden)

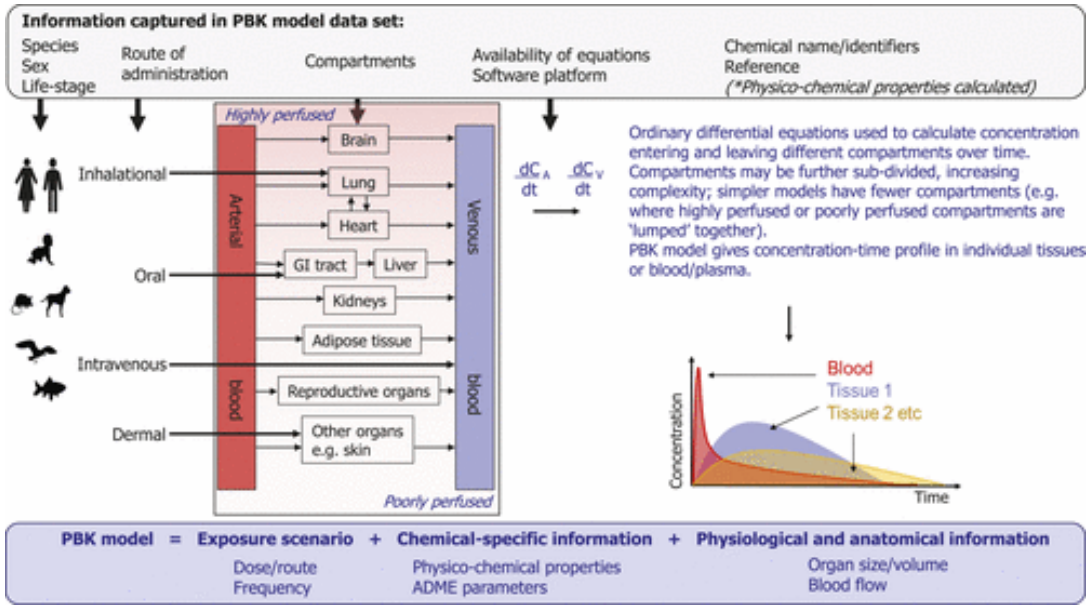
Papers found in database search: 14,803

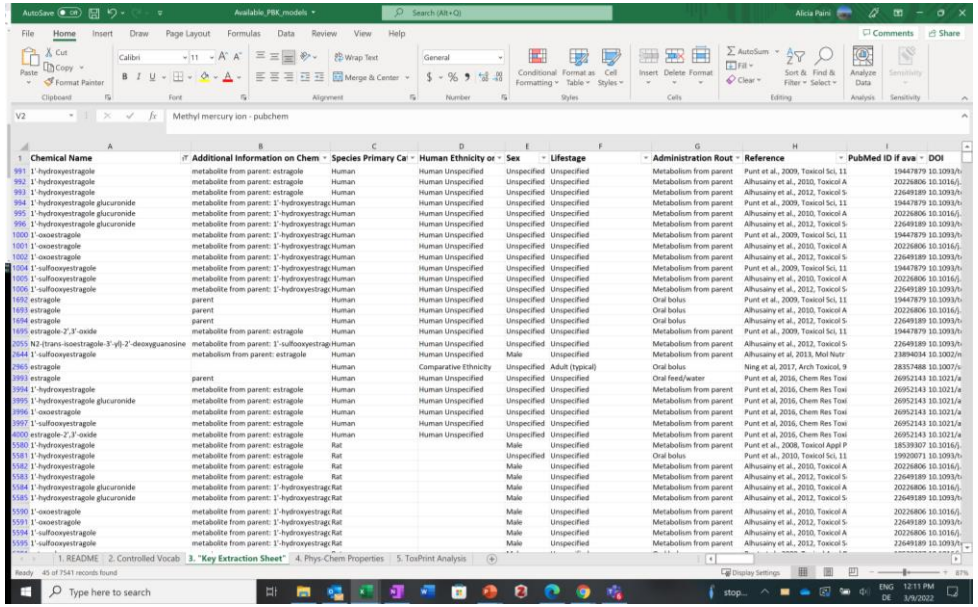
Papers remaining after duplicates removed: 6771

Papers remaining after abstract screening: 3120

Papers remaining after full text screening: 1649

Total models extracted from the papers: 7541





1150 unique chemicals

Review Article

A Systematic Review of Published Physiologically-based Kinetic Models and an Assessment of their Chemical Space Coverage

Courtney V. Thompson[1], James W. Firman[1], Michael R. Goldsmith[2], Christopher M. Grulke[2], Yu-Mei Tan[3], Alicia Paini[4], Peter E. Penson[1], Risa R. Sayre[2], Steven Webb[5] and Judith C. Madden[1]

Alternatives to Laboratory Animals 2021, Vol. 49(5) 187–208
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The European Partnership for Alternative Approaches to Animal Testing

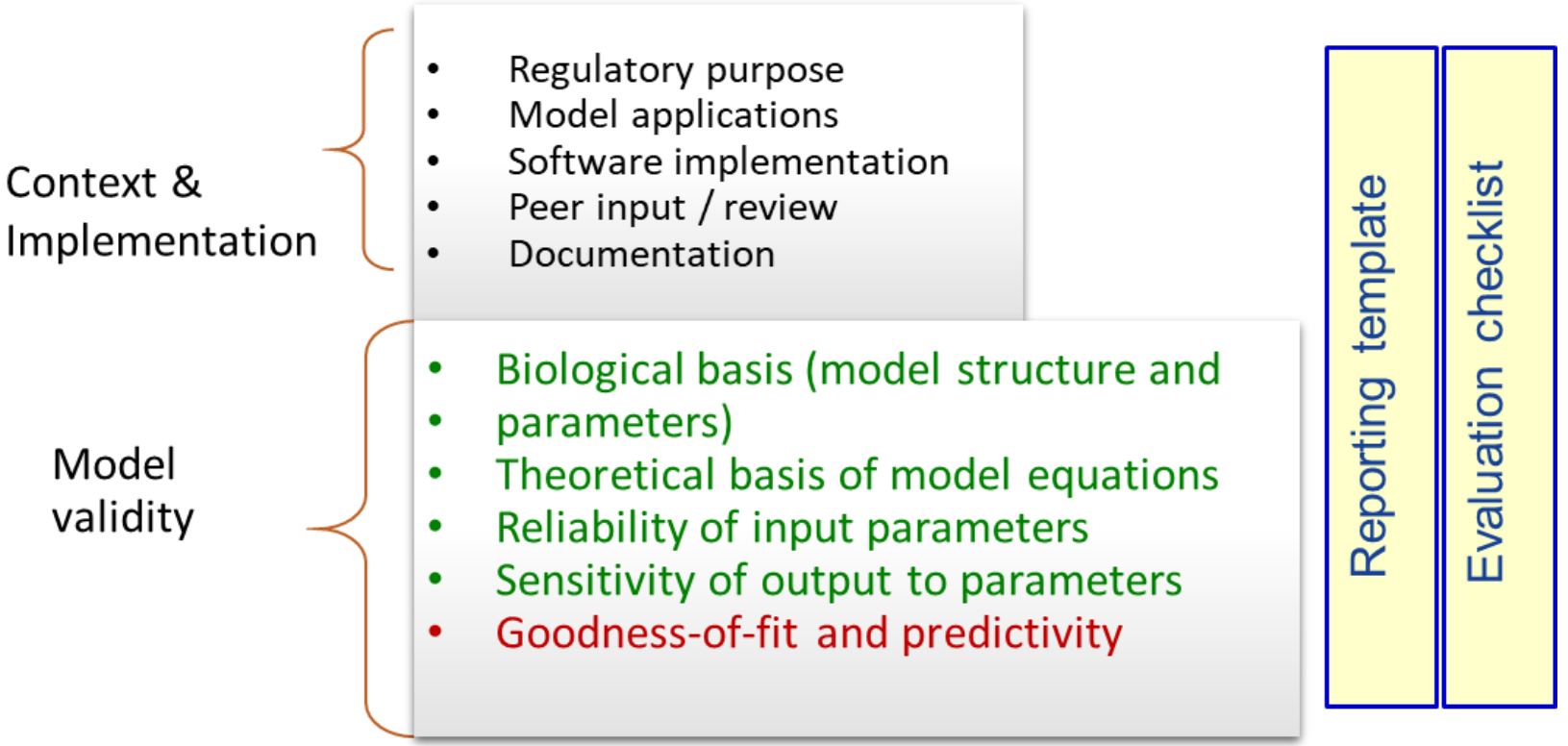
LIVERPOOL JOHN MOORES UNIVERSITY

Interested in the PBK model database:

It can be downloaded from https://data.jrc.ec.europa.eu/dataset/f98e9abf-8435-4578-acd6-3c35b5d1e50c

Contents of OECD Guidance Document

2. Regulatory assessment framework of PBK models



Reports an assessment framework for evaluating PBK models, with emphasis on the major uncertainties underlying the model predictions.

Contents of OECD Guidance Document

3. 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 • model structure • input parameters • model output • other uncertainties (e.g. model developed for different substance and/or purpose)
G. Model implementation details • software (version no) • availability of code • software verification / qualification
H. Peer engagement (input/review)
I. Parameter tables
J. References and background information • publications • links to other resources

1. Model Reporting Template

2. Evaluation Checklist

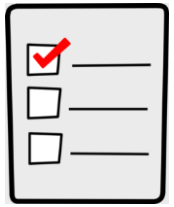
PBK Model Evaluation Checklist	Checklist assessment	Comments
Name of the PBK model (as in the reporting template)		
Model developer and contact details		
Name of person reviewing and contact details		
Date of checklist assessment		
A. Context/Implementation		
A.1. Regulatory Purpose		
A.2. Documentation		
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		

Contents of OECD Guidance Document

3. PBK model Evaluation tool box

1. Model Reporting Template

2. Evaluation Checklist



3. Overall Evaluation Matrix (adapted from WHO 2010)

	NONE ← LEVEL OF CONFIDENCE → 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 biological basis of some model parameters, structural elements or assumptions is questionable.	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	Model reproduces the shape of part but not all of the kinetic time course curves, either for the chemical of interest or 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	Local Sensitivity Analysis supports the robustness of the model.	Global Sensitivity Analysis supports the robustness of the model.

PUBLICATIONS ON TESTING AND ASSESSMENT

No. 331 Guidance Document on the Characterisation, Validation and Reporting of PBK Models for Regulatory Purposes (Glossy - Mono - Annex IV)

Thirteen case studies (listed in Annex 4)

Case Study I: Generic PBK model for farm animal species: Cattle (*Bos taurus*), Swine (*Sus scrofa*), Sheep (*Ovis aries*) and Chicken (*Gallus gallus domesticus*)

Lautz et al. (2019 a,b; 2020 a,b)

Case Study II: Generic PBK models for four fish species

Grech et al. (2017, 2018 a,b; 2019)

Case Study XIII: Generic Human one compartment and QIVIVE PB-K models

Wiecek et al. (2019 a,b)

Case Study VIII

PBK model application in species and route to route extrapolation

Bessems et al., 2017

Case study IX

Caffeine PBBK model to predict MoIE for risk assessment

IATA caffeine CS

Case study X

IVIVE-PBPK model for phenyl-1,4-dihydropyridine calcium channel antagonists

Gardner et al.

Case XI

Using high-throughput pharmacokinetic simulation and in silico property predictions to predict herbicide absorption and bioavailability

Clark Robert D

Case Study XII

Application of physiologically based kinetic (PBK) modelling in the next generation risk assessment of dermally applied consumer products

Moxon et al. 2020

https://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

Case Study III

In vitro-to In vivo extrapolation (IVIVE) by PBTK modelling

Fabian et al. 2019

Case Study IV

PBK model predictions using data from analogues

Paini et al., 2021

Case Study V

Physiologically based pharmacokinetic (PBK) model for acrylonitrile in humans

Takano et al 2010

Case Study VI

PBK model predictions for monoisononyl phthalate

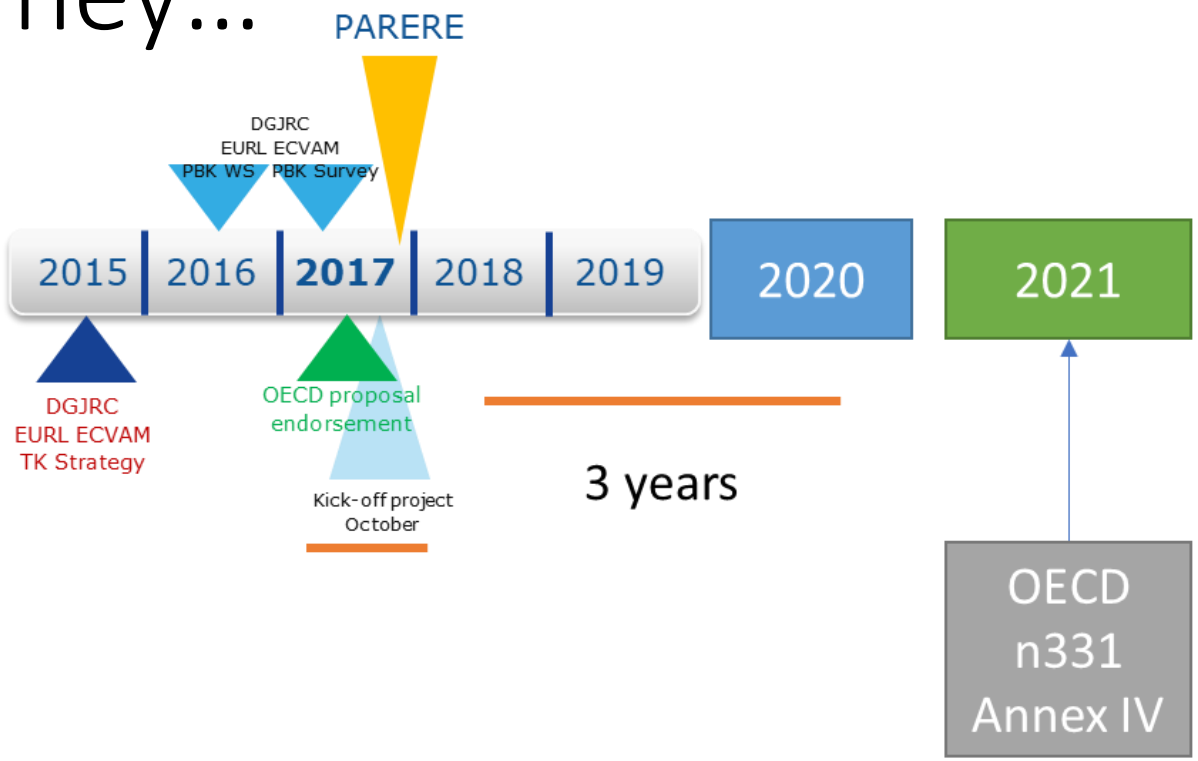
Miura et al.,2019

Case Study VII

Quantitative Proteomics-based Bottom-up PBK Modeling to Predict Chemical Exposure in Humans

Chan et al. 2019

The journey…



The experts' of the OECD PBK model WG

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

Take home message

- Provide guidance on characterising, reporting, and evaluating PBK models used in regulatory assessment of chemicals
- Address challenges associated with developing and evaluating PBK models for chemicals without *in vivo* kinetic data
- Promote the use of PBK models in regulatory risk assessment and facilitate dialogue between model developers and users

Facts

If you submit an IATA → you are encouraged to follow these templates when using and reporting PBK models.

- In evaluation of chemicals in RA, confidential docs.
- In peer reviewed publications; example,
  - Najjar et a., 2022 https://pubmed.ncbi.nlm.nih.gov/35058784/

Source

OECD PBK model GD (n 331 + ANNEXIV)

https://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

OECD PBK model GD webinar

https://www.youtube.com/watch?v=PT7w6PB97Ag&t=4252s

(webinar 10/05/2021)

https://www.youtube.com/watch?v=3u_ghfQsH58

(webinar 06/04/2022)

*SOT2023 **CEC** course on OECD PBK GD – tentative accepted. Hands on experience*
*EUROTOX2023 **CEC** course on OECD PBK GD – tentative accepted. Hands on experience*

Acknowledgments
Magda Sachana (OECD)
Cecilia Tan (US EPA)
Andrew Worth (EC-JRC)

EPAA-LJMU PK model DB
Judith Madden (LJMU)

All the expert scientists that contributed!

Thank you for your attention!

Alicia.paini@esqlabs.com