The European Commission’s science and knowledge service

Joint Research Centre

PHYSIOLOGICALLY-BASED KINETIC MODELLING IN RISK ASSESSMENT – REACHING A WHOLE NEW LEVEL IN REGULATORY DECISION-MAKING – At a glance*


London, 15th – 16th Feb. 2017

* Contents of this presentation do not necessarily represent the organizational views of the co-authors
The EURL ECVAM Strategy Document on Toxicokinetics* (TK) outlines objectives to enable prediction of systemic toxicity by applying new approach methods (NAM) that consider TK.

The central feature of the strategy focuses on using PBK modelling to integrate data generated by in vitro and in silico methods for ADME in humans and to predict whole-body TK behaviours.

**USE SOLELY IN VITRO and IN SILICO DATA**

(*Bessems et al., 2015)*
Case examples

PBK models built solely on *in vitro* and *in silico*
- Alkenylbenzene (Punt A. & Rietjens I.)
- HT – PBK models (Wetmore B. & Wambaugh J.)
- Ibuprofen (Mielke H. et al., Arch Toxicol. 2016)

Collection of PBK models (Lu et al., 2016).

New concepts new challenges
- AEP & AOPs / IATA
- Solely in vitro
- Solely human
- Challenge IVIVE
- HT - PBK

0. Hypothesis

1. Definition of conceptual model

2. Translation to math. equation

3. Define parameters

4. Solving the equation

5. Evaluation of model performance

6. Model Predictions

7. Model Reporting and Dissemination
In order to facilitate acceptance and use of this new generation of PBK models in the regulatory domain EURLECVAM WS → “PHYSIOLOGICALLY-BASED KINETIC MODELLING IN RISK ASSESSMENT – REACHING A WHOLE NEW LEVEL IN REGULATORY DECISION-MAKING” 16th -17th of November 2016 at the Joint Research Centre (JRC), Ispra, Italy.

With three main objectives of this workshop:
1. The importance of identifying and comparing sources of uncertainty in PBK models;
2. Establish a good kinetic modelling practices workflow as the foundation of a guidance on the generation and use of in vitro and in silico data to construct PBK models which are designed to support regulatory decision making;
3. The need for a longer term strategy to incrementally refine and deploy PBK modelling in parallel with an appropriate evolution of science and regulatory practice.
Three aims – Discussion outputs

1. Regulatory Needs
   • Keep models as simple as possible.
   • Models fit for purpose.
   • Regulators will need to accept the shift to alternative methods!
   • Dialogue between regulators and developers is also very important!
   • Training!
   • Clear documentation/reporting.
   • Different type of users will require different levels of information.
   • More efforts on results analysis evaluation rather than model evaluation.

2. Construction of the Model with No Animal Data
   • Use read across approaches for ADME and TK properties.
   • Use in vitro data [1st screening].
   • High throughput - PBK modelling.
   • Open access modelling platform (like Rvis by UK HSL).
   • Highlight main fate/processes in organism [Knowledge].
   • Increase confidence in PBK models.

3. Assessing Model Credibility
   • Model credibility: biological systems are so complex, we need systems thinking
     and experience based validation.
   • Model Verification vs Validation!
   • Terminology!
The Matrix by Patterson E.

Credibility: the willingness of others to use model predictions to inform decisions.

Validation: The process of determining the degree to which a model is an accurate representation of the real world from the perspective of the intended uses of the model.

[from Patterson EA & Whelan MP, A framework to establish credibility of computational models in biology, Progress in Biophysics & Molecular Biology, 2016].
RECOMMENDATIONS

- **DECISION TREE** for model construct
- **TASK FORCE** for model peer review
- **SCORING SYSTEM** for model evaluation
- **FUNDING** scheme to develop software
- **ADAPT GMP ➔ GUIDANCE**
- **COMMUNICATION**
- **TRAINING**
Actions taken

Proposals submitted to OECD on December 1\textsuperscript{st}, 2016:

- A proposal for the development of an OECD Guidance Document for characterising, validating and reporting Physiologically Based Kinetic (PBK) models intended for regulatory application that are based on data derived from non-animal methods. \rightarrow to be extended.

- A proposal for the development of a Bio-Kinetics Knowledge-Base. \rightarrow Revising the idea internally at JRC.

A JRC Technical Report and a Manuscript are in preparation.

Internal & EU Survey
Applications of Physiologically Based Kinetic (PBK) models in science and regulatory submission.

Scope of the Survey

Welcome to the EURL ECVAM PBK model survey!

Thank you for taking time to take part in this survey!

Today we will ask you 18 questions, 14 with YES/NO or multiple choice answers and 4 in free text format. The YES/NO questions might expand to break-up questions, depending on your reply, and in certain cases also allow you to add comments in free text. In total the survey should take 5 - 10 min.

The aim of this survey is to understand frequency of use and applications of Physiologically Based Kinetic (PBK) models (PBK is a terminology synonymous of PBPK/PBTK/PBBK) in science and regulatory submission.
Take home message

... To achieve all this we will relay on the collective and coordinated contribution of a wide range of stakeholders and international collaboration...
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