PBPK Models

Our Mission

The committee's mission is to address key needs related to physiologically based pharmacokinetic (PBPK) modeling practices and applications that could facilitate the use of PBPK models more consistently within the risk assessment context.

Chairs

Public Chair
Dr. Anna Lowit (US Environmental Protection Agency)

Private Chair
To be determined

Steering Committee

To be determined

HESI Staff

Dr. Michelle R. Embry (membry@hesiglobal.org)

2020 Committee Highlights

Participating Organizations

12 government/regulatory agencies, **2** academic/research institute, **8** industry, **1** other, and **3** consulting

Publications

1 published

Scientific Meetings and Trainings

1 workshop

- Opportunities and Challenges in Using the Kinetically Derived Maximum Dose Concept to Refine Risk Assessment (virtual; 450 attendees)

Outreach

1 oral presentation

- Presentation by Dr. Cecilia Tan (USEPA) at the 24 June 2020 Science Advisory Board Meeting

Collaborations

2 external

- Workshop co-sponsorship with USEPA and the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICETAM)
- MOU for the project as a whole with USEPA

Geographic Representation

Australia, Canada, Germany, Italy, Japan, United Kingdom, and United States

Working Groups

- **PBPK Template Development.** This work was focused on the development of a general reporting template derived from a consensus among modelers and risk assessors, which expands on an FDA template and will recommend additional elements necessary for submission of PBPK analyses to public health agencies.
- **PBPK Framework Development.** This group is developing a framework to inform the minimum set of *in vivo*, *in vitro*, or *in silico* absorption, distribution, metabolism, or excretion (ADME) data required for various extrapolation applications; manuscript in preparation.

NEW **Kinetically Derived Maximum Dose (KMD).** The purpose of this group is to evaluate and address commonly raised technical and scientific issues related to the use of KMD as an approach to select doses in toxicology testing studies or to interpret dose-response study results. Examples of these issues include the appropriate use of PK data to determine dose non-linearity, the possibility of human exposure levels close to KMD, the determination of KMD from sparse blood or tissue concentration data, the use of *in silico* models to predict systemic dose and key ADME parameters, and the use of KMD to set the top dose in toxicity studies. This group aims to:

- Discuss best practices and lessons learned on the following:
  - Defining KMD
  - Selecting the appropriate PK parameter to examine dose proportionality
  - Estimating the onset of nonlinear PK based on measurements or predictions

    - Conducting statistical analyses to determine a KMD
    - Determining and using a KMD to set the top dose in toxicity studies
  - Discuss if and how KMD can be applied in the context of hazard classification, as well as risk assessment
  - Discuss and identify situations where the use of KMD might be limited or not possible (e.g., acute, high-exposure situations)

Areas of Focus for 2021

- **PBPK Framework.** The group will work to refine the drafted flowcharts for various PBPK model applications and submit a manuscript for publication.
- **KMD.** It is anticipated that the Fall 2020 symposium will lead to the development of several smaller subteams that are focused on KMD-related topics, including, but not limited to, dose proportionality, exposure, dose-setting and 3Rs, and weight of evidence.

Strategic Impact Areas

Enhanced Efficiency and Accuracy in Safety Assessment Practice

This committee is working to develop and articulate best practices and consensus approaches for evaluating PBPK models with different degrees of data availability and data gaps. The framework that will be developed will allow for easier use and interpretation of PBPK model information into chemical risk assessment. The work on the KMD strives to provide clarity on the approaches that can be used when determining the dose-setting for toxicity studies and how to interpret and use those data within a risk assessment context.

Enhancement of the Societal Knowledge Base on Human Biological Processes of Relevance for Protecting Human Health

The attendance and interest in the 2020 KMD Symposium (450 people from 22 countries) underscores the importance of the topic toward improving human health risk assessment and ensuring that testing strategies are appropriate and fit for purpose.

Publications

Published

Tan YM, Chan M, Chukwudebe A, Domoradzki J, Fisher J, Hack CE, Hinderliter P, Hirasawa K, Leonard J, Lumen A, Paini A, Qian H, Ruiz P, Wambaugh J, Zhang F, Embry M (2020) PBPK model reporting template for chemical risk assessment applications. *Regulatory Toxicology and Pharmacology*. 115:104691. doi: 10.1016/j.yrtph.2020.104691.

Participating Organizations

Government/Regulatory Agencies

Australian Pesticides and Veterinary Medicines Authority
European Commission, Joint Research Centre
Food Safety Commission of Japan
Health and Safety Executive (UK)
Health Canada
National Institute of Health Sciences (Japan)
National Institute of Technology and Evaluation (Japan)
NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM)
Public Health England
US Centers for Disease Control and Prevention
US Environmental Protection Agency
US Food and Drug Administration

Academic/Research Institutes

Imperial College London
Kansas State University

Industry

BASF
Bayer
Corteva Agriscience
The Dow Chemical Company
ExxonMobil Biomedical Sciences, Inc.
FMC Corporation
Sumitomo Chemical Co.
Syngenta

Other

National Centre for the Replacement, Refinement, and Reduction of Animals in Research (NC3Rs, UK)

Consulting

Exponent, Inc.
ScitoVation
ToxMetrics