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.

Steering Team

Public Steering Team Members

Dr. Rhian Cope (Australian Pesticides and Veterinary Medicines Authority)
Dr. Cecilia Tan (US Environmental Protection Agency)
Dr. Alicia Paini (European Commission, Joint Research Centre)
Dr. Annie Lumen (US Food and Drug Administration)
Dr. Judith Madden (Liverpool John Moores University)
Dr. Hugh Barton (Barton Systems Pharmacology and Toxicology)

Private Steering Team Members

Dr. Jun Abe (Sumitomo Chemical Co.)
Dr. Jean Domoradzki (Corteva Agriscience)
Dr. Hua Qian (ExxonMobil Biomedical Sciences, Inc.)
Dr. Dana Sargent (Bayer CropScience)

HESI Staff

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

2021 Committee Highlights

Participating Organizations

13 government/regulatory agencies, **4** academic/research institute, **8** industry, **1** other, and **6** consulting

Publications

2 published and **5** in progress

Outreach

1 oral presentation

- Presentation by Dr. Michelle Embry (HESI) at the British Toxicology Society Congress 2021 on "Kinetically-Derived Maximum Dose Concept to Refine Risk Assessment: Opportunities and Challenges" (April 2021, virtual, ~200 attendees)

Collaborations

1 external

- MOU for the PBPK project as a whole with US EPA

Geographic Representation

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

Webpage

https://hesiglobal.org/pbpk-models

Working Groups

- **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 **Weight of Evidence to Inform Study Design (Formerly KMD).** This group was initially focused on evaluating the concept of the kinetically-derived maximum dose (KMD). Following a successful 2020 workshop and follow-up publication development, the focus has shifted a broader weight of evidence approach that can be used to inform design and dose selection for repeated dose animal studies, including use of TK data for dose selection.

Areas of Focus for 2022

- **PBPK Framework.** The group will work to refine the drafted flowcharts for various PBPK model applications and submit a manuscript for publication.
- **Weight of Evidence/KMD.** Two sessions will be held in 2022 to highlight the recently published manuscripts; modeling work is ongoing to explore the impact of non-linear kinetics on dose-systemic exposure relationships and additional case studies will be developed. A group focused on incorporating *in vitro* data into a weight of evidence approach to inform dose selection for repeated dose animal studies will convene in 4Q 2021 to develop a manuscript.

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 work products of this committee are intended to increase transparency and appropriate use and interpretation of PBPK information to inform risk assessment – either to refine extrapolation approaches or inform toxicity study design.

Publications

Published

Tan et al. (2021). Opportunities and challenges related to saturation of toxicokinetic processes: implications for risk assessment. *Regulatory Toxicology and Pharmacology*. doi: 10.1016/j.yrtph.2021.105070.

Lowe et al. (2021). Incorporating human exposure information in a weight of evidence approach to inform design of repeated dose animal studies. *Regulatory Toxicology and Pharmacology*. doi: 10.1016/j.yrtph.2021.105073.

In Progress

Authors TBD. Fit-for-purpose physiologically based pharmacokinetic modeling to support extrapolations in chemical risk assessment. In preparation.

Authors TBD. Exploring the non-linear relationship between administered dose and systemic exposure using physiologically based pharmacokinetic modeling analysis. In preparation.

Authors TBD. Development of a generic pharmacokinetic modeling package to analyze non-linear kinetic data. In preparation.

Authors TBD. Interpreting dose-response relationship based on administered dose and systemic exposure using a modeling approach. In preparation.

Authors TBD. Incorporating *in vitro* data in a weight of evidence approach to inform dose selection for repeated dose animal studies. In preparation.

Participating Organizations

Government/Regulatory Agencies

Australian Pesticides and Veterinary Medicines Authority
Brazilian Health Regulatory Agency (ANVISA)
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)
US Centers for Disease Control and Prevention
US Environmental Protection Agency
US Food and Drug Administration
Wright-Patterson Air Force Base

Academic/Research Institutes

Imperial College London
Kansas State University
Liverpool John Moores University
University of Montreal

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

Barton Systems Pharmacology and Toxicology
Exponent, Inc.
Ramboll Environ
ScitoVation
ToxMetrics
ToxStrategies