

Problem Formulation:

Background, motivation, and expected outcomes

Michelle Embry, PhD

Associate Director

Health and Environmental Sciences Institute (HESI)

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Problem Statements

- Toxicology studies that utilize KMD are often submitted for the purpose of interpreting dose-response data from repeated dose animal studies to assess human health risks of occupational and environmental chemical exposures. However, there is **no agreed upon scientific guidance** that clearly specifies what data are necessary and sufficient, in a fit-for-purpose context, to evaluate such studies.
- There are no **specific criteria** on how to incorporate/integrate all available data streams, including, but not limited to toxicokinetic and exposure information, to use KMD approach as an option for top-dose selection in repeated dose animal studies for occupational and environmental chemical exposures.

Symposium Objectives

- Highlight best practices and lessons learned on the following:
 - Defining KMD
 - Selecting the appropriate PK parameter to examine dose proportionality
 - Estimating the onset of non-linear 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

Out of scope....

- While the information from these sources could be used to further inform the discussion on KMD, the following topics are **out of the scope:**
 - Regulatory frameworks and study/data requirements of individual countries or regulatory agencies
 - Proposed and final regulatory decisions made by individual countries or regulatory agencies
 - Interpretation and design of pre-clinical studies for pharmaceutical drugs, biologics and natural health products
 - Risk management and risk mitigation activities (including off-label uses)
 - Exposure scenarios related to acute toxicity (e.g., accidents, intentional misuse)

Expected Outcomes

- This is the **start** of the discussions; we intend that there will be additional follow-up via various activities
- HESI PBPK Technical Committee working group
 - Memorandum of Understanding (MOU) with USEPA
 - Will develop a short meeting report
 - Follow-up work will occur in smaller focus groups
 - Topics will be determined based on output from this meeting and follow-up discussions

Contact information

Michelle Embry

membry@hesiglobal.org

www.hesiglobal.org