NICEATM, USEPA, HESI

Opportunities and Challenges in Using the Kinetically Derived Maximum Dose Concept to Refine Risk Assessment

FINAL AGENDA

DATE: September 30, 2020

TIME: 8:00 – 13:30 (US Eastern)

CONNECTION: Zoom Webinar; Registration required but open to all.

BACKGROUND: The kinetically-derived maximum dose (KMD) refers to the highest dose at, or slightly above, the departure from dose proportionality or linear pharmacokinetics (PK). Non-linear PK can be caused by saturation or limitation of various factors related to absorption, distribution, metabolism, and excretion (ADME). In the pharmaceutical field, the KMD concept is often described as "the dose level that results in non-linear kinetics" or "the dose level above the inflection point of transition to non-linear kinetics", and it is routinely considered in preclinical studies to provide perspective on the relevance of these studies to human safety assessment. However, consideration of KMD in the design or interpretation of animal toxicity studies for environmental chemicals is rare.

WORKSHOP OBJECTIVES: The purpose of this workshop is to provide an opportunity for impacted stakeholders to 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.

- Discuss 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 (e.g., acute, high-exposure situations)

PARTICIPATION: Open to the public. All talks will be recorded and made available. Register at: https://ntp.niehs.nih.gov/go/kmd-2020.

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8:00 Welcome and introductions
Nicole Kleinstreuer, NICEATM

8:05 Use and evaluation of KMD data at USEPA
Anna Lowit, USEPA

8:15 Overview of OECD discussions on dose selection in chronic toxicity studies
Anne Gourmelon, OECD

8:25 Problem Formulation: Background, motivation and expected outcomes of the workshop
Michelle Embry, HESI

8:30 Maximum tolerated dose (MTD): Concepts and background
Chad Blystone, National Toxicology Program

8:45 Concepts of non-linear pharmacokinetics and KMD
Alan Boobis, Imperial College London

9:15 Implications of non-linear PK in toxicity testing and interpretation of dose-response data
Salil Pendse, Nuventra Pharma Sciences

9:45 Determining an inflection point from external-internal dose data
Philip Villanueva, USEPA

10:15 Estimating human exposures and comparison to doses used in testing
Jeff Dawson, USEPA

10:45 BREAK

11:00 Dose-setting and considerations for the 3Rs
Fiona Sewell, NC3Rs

11:30 Integration of TK into toxicity studies and dose level setting in repeat dose studies
Jeanne Domoradzki, Corteva

12:00 Integrating KMD/PK data with MOA and other information in a weight of evidence approach
Harvey Clewell, Ramboll

12:30 Brief summary
Cecilia Tan, USEPA

12:45 Q&A and additional discussion

13:30 Adjourn