Use and evaluation of KMD data at USEPA's Office of Pesticide Programs

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Workshop on Kinetically Derived Maximum Dose Concept to Refine Risk Assessment

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Kinetics in Risk Assessment: Dose Makes the Poison

- Risk assessment is the characterization of the potential adverse effects of human **exposures** to environmental **hazards** (NRC, 1983)

- Kinetics determines the movement of a chemical into, through, and out of the body; the time course of a chemical's absorption, distribution, metabolism, and excretion

- The internal target tissue dose determines the initiation and degree of toxicological responses

- Kinetics connects exposures to hazards

Value of Kinetic Data/Models

- Support smarter testing strategies
  - Reduce & Replace: eliminate duplicative testing or unnecessary studies
  - Refine: lessen animal suffering by not testing at doses that cause overt toxicity
- Quantify and reduce uncertainty in risk assessment
- Evaluate consistency with mode of action hypothesis
- Extrapolate points of departure across species, routes, life-stages, etc.

Examples of risk assessment applications in OPP

- Using physiologically based pharmacokinetic (PBPK) models to replace the use of default uncertainty factors for inter-species extrapolation, route-to-route extrapolation, and age-specific extrapolation
- Using PBPK models to estimate scenario-specific points of departure
- Using *in vitro* and *in vivo* dermal absorption measurement to adjust route-specific points of departure
- Using *in vitro* metabolism data to understand dose-response difference across species or life-stages
- Using kinetic data to interpret dose-response data or select doses in animal toxicity studies – kinetically-derived maximum dose (KMD) approach

KMD Concept

- KMD is the intended to be the highest dose at, or slightly above, the point of departure from linear kinetics

- Non-linear kinetics can arise from various factors, such as saturation of absorption, metabolism, protein binding, excretion, resulting in chemical concentrations in the body to be disproportionally high or low relative to the change in external dose

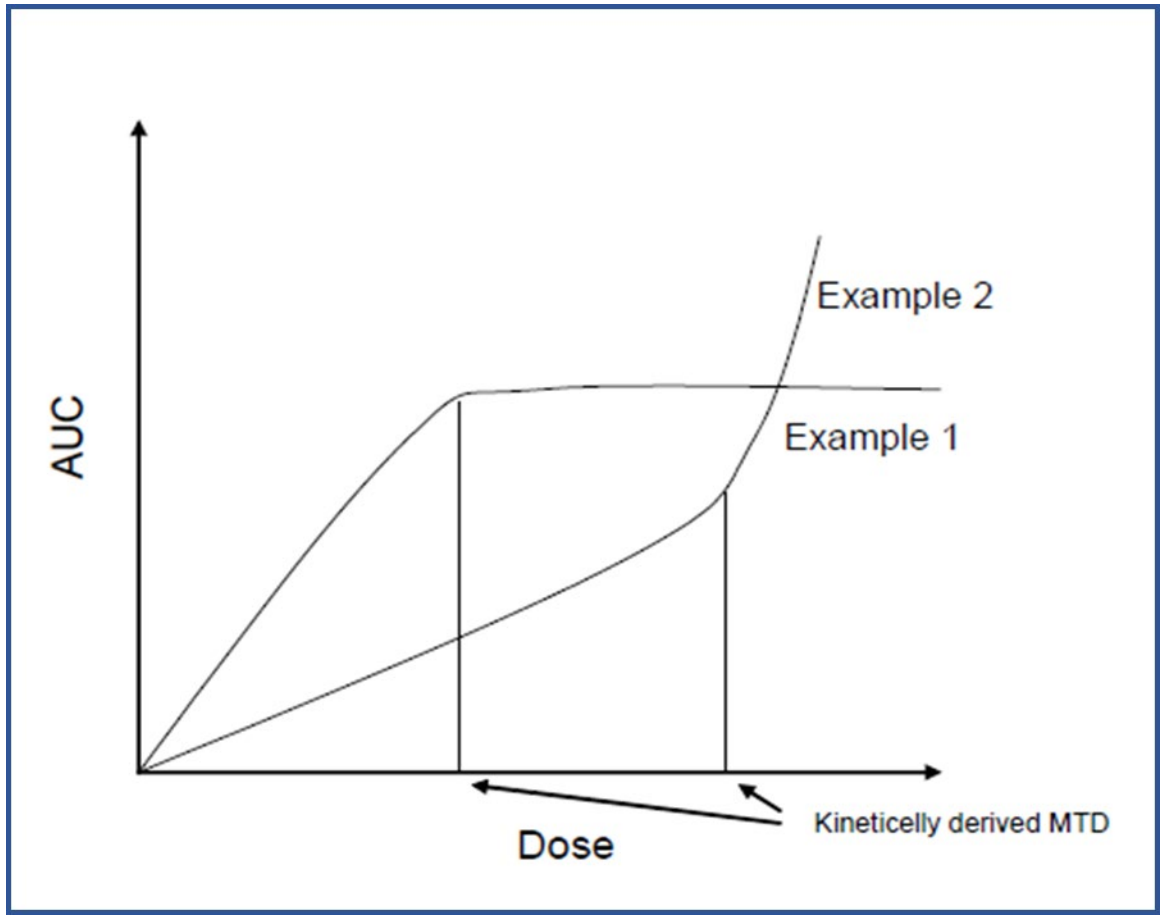

Figure adopted from 2008 REACH Guidance, Figure R.7.12-2

KMD Implications

- When internal dose becomes disproportionally low relative to the change in external dose, “there is little point in increasing administered dosage if it does not result in increased plasma or tissue concentration” (ICH S5)

- When internal dose becomes disproportionally high relative to the change in external dose, “exposures in rodents, greatly in excess of the intended human exposure, might not be relevant to human risk; because they so greatly alter the physiology of the test species” (ICH S1A, S1B, S1C)

Impact of KMDs on the Determination of Hazard

OECD 116: *"Although top dose selection based on identification of inflection points in toxicokinetic nonlinearity may result in study designs that fail to identify traditional target organ or body weight effects, it must be appreciated that metabolic saturation in fact represents an equivalent indicator of biological stress.* In this case, the stress is evidenced by appearance of non-linear toxicokinetics rather than appearance of histological damage, adverse changes in clinical chemistry, haematology parameters or decrease in body weight gain."

Support & Challenges KMD Approach

- EPA's Office of Pesticide Programs (EPA-OPP) supports use of TK data to determine KMD, but <10 received

- Some challenges & observations:
  - Lack of standard approach
  - Lack of harmonized guidance on determining adequacy of dose selection based on dose proportionality
  - Quality of the analytical measurements has varied

Case Study – Weight of Evidence Approach

- Study purpose: Understand if lung tumors observed in male mice at high dose (60 ppm) of telone are due to saturation of metabolic clearance
- Multiple lines of evidence suggest that systemic exposures in mice become non-linear at 30 ppm or above
  - Both a hockey-stick model and a power model conclude that area under the curve (AUC) of blood concentrations become non-proportional to external dose between 30-40 ppm
  - The cis- and trans-isomers of telone changes from 0.13 to 0.2 between the external concentrations of 40-60 ppm
  - The glutathione(GSH)-dependent metabolism of telone results in significant depletion of GSH at external dose 30 ppm and above