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

Integration of TK into Toxicity Studies and Dose Level Setting

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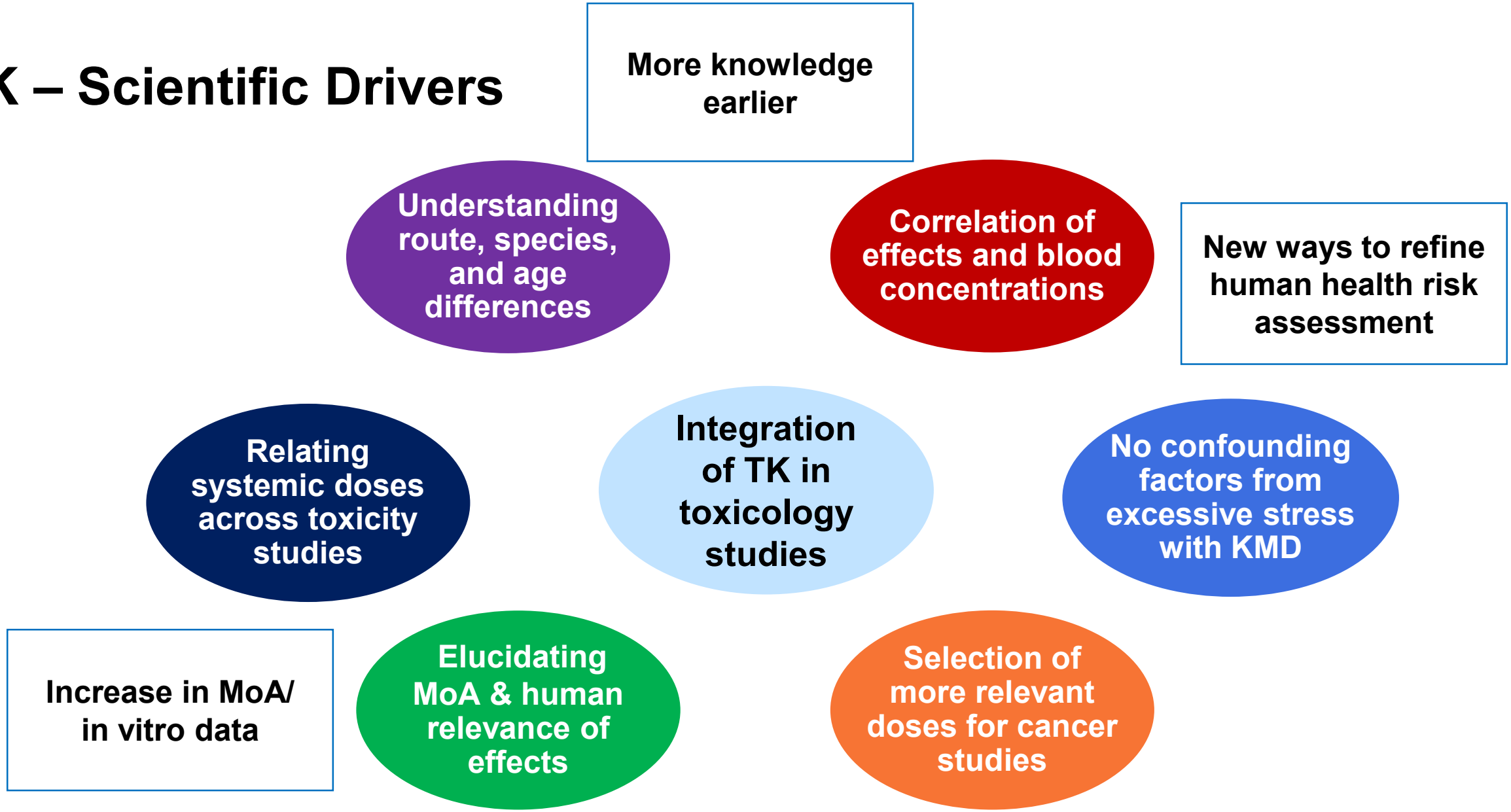
CORTEVA™ agriscience

TK – Scientific Drivers



MoA – Mode of Action
KMD= Kinetically-derived maximum dose

TK: Regulatory Drivers

Region/ Authority	Document Type	Summary of Requirements/Recommendations	Reference
EU	EC 1107/2009	TK required in short-term & long-term studies Dose level selection should take into account saturation of absorption	EC (2009)
	Guidance Chapter R.7c	"Even though toxicokinetics is not a toxicological endpoint and is not specifically required by REACH, the generation of toxicokinetic information can be encouraged as a means to interpret data, assist testing strategy and study design, as well as category development, thus helping to optimise test designs"	ECHA (2012)
	EFSA Scientific Report	Th…rences, human variability. Su…nt purposes.	EFSA (2014)
EPA	OPP HED	Re… "T…	GD #G2003.02
	EPA Guidelines from Risk Assessment Forum	"The high dose in long-term studies is generally selected to provide the maximum ability to detect treatment-related carcinogenic effects while not compromising the outcome of the study through excessive toxicity or inducing inappropriate toxicokinetics (e.g., overwhelming absorption or detoxification mechanisms)".	EPA (2005)
	EPA Framework Document	"…data in evaluating the s…	US EPA (2006)
	Draft Guidelines from Risk Assessment Forum	T…such as lifestage, race, s…ure assessment requirements.	US EPA (2015)
OECD	TG 451	... points to be considered in dose selection include: Known or suspected nonlinearities or inflection points in the dose–response TK…es not occur.	OECD (2018)
	TG 426	"[…and toxicokinetics of the te…Direct dosing of pups s…	OECD (2007)
	TG 443	A…anning of the study design, selection of dose levels and interpretation of results. Of particular utility are data which: 1) verify exposure of developing fetuses and pups to the test compound (or relevant metabolites), 2) provide an estimate of internal dosimetry, and 3) evaluate for potential dose-dependent saturation of kinetic processes. Additional TK data, such as metabolite profiles, concentration-time courses, etc. should also be considered, if they are available. Supplemental TK data may also be collected during the main study, provided that it does not interfere with the collection and interpretation of the main study endpoints. As a general guide, the following TK data set would be useful in planning the Extended One-Generation Reproductive Toxicity Study: • Late pregnancy (e.g. Gestation Day 20) - maternal blood and foetal blood • Mid-lactation (PND 10) - maternal blood, pup blood and/or milk • Early post-weaning (e.g. PND 28) - weanling blood samples	OECD (2018)

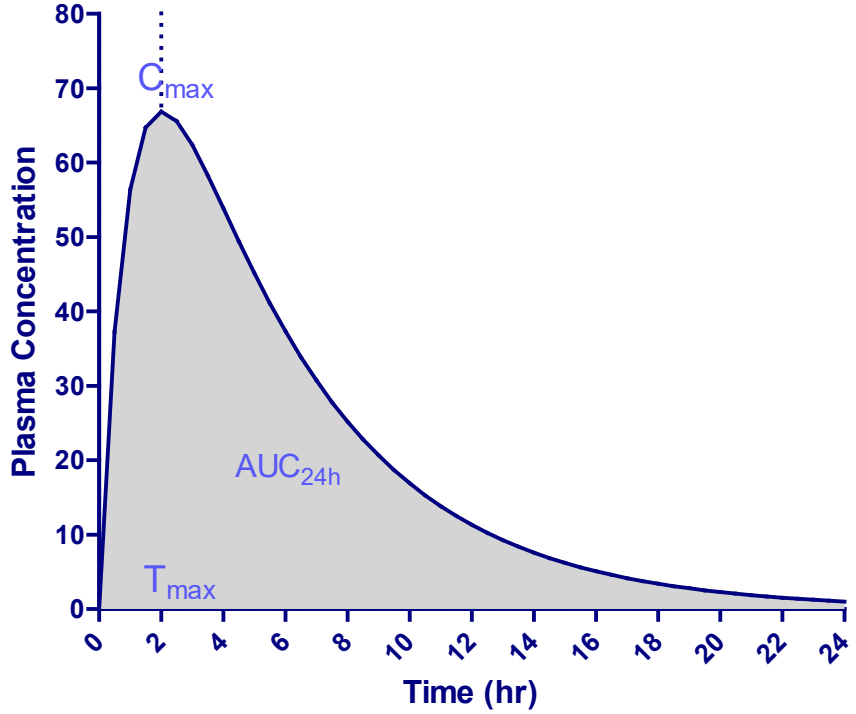
➢**Use TK in dose level selection**

➢**Avoid TK non-linearity in dose level selection**

➢**Highest dose should not be above a dose that results in saturation of absorption & clearance**

Toxicokinetics

Systemic (internal) Exposure vs. Time



AUC – Internal Dose Metric

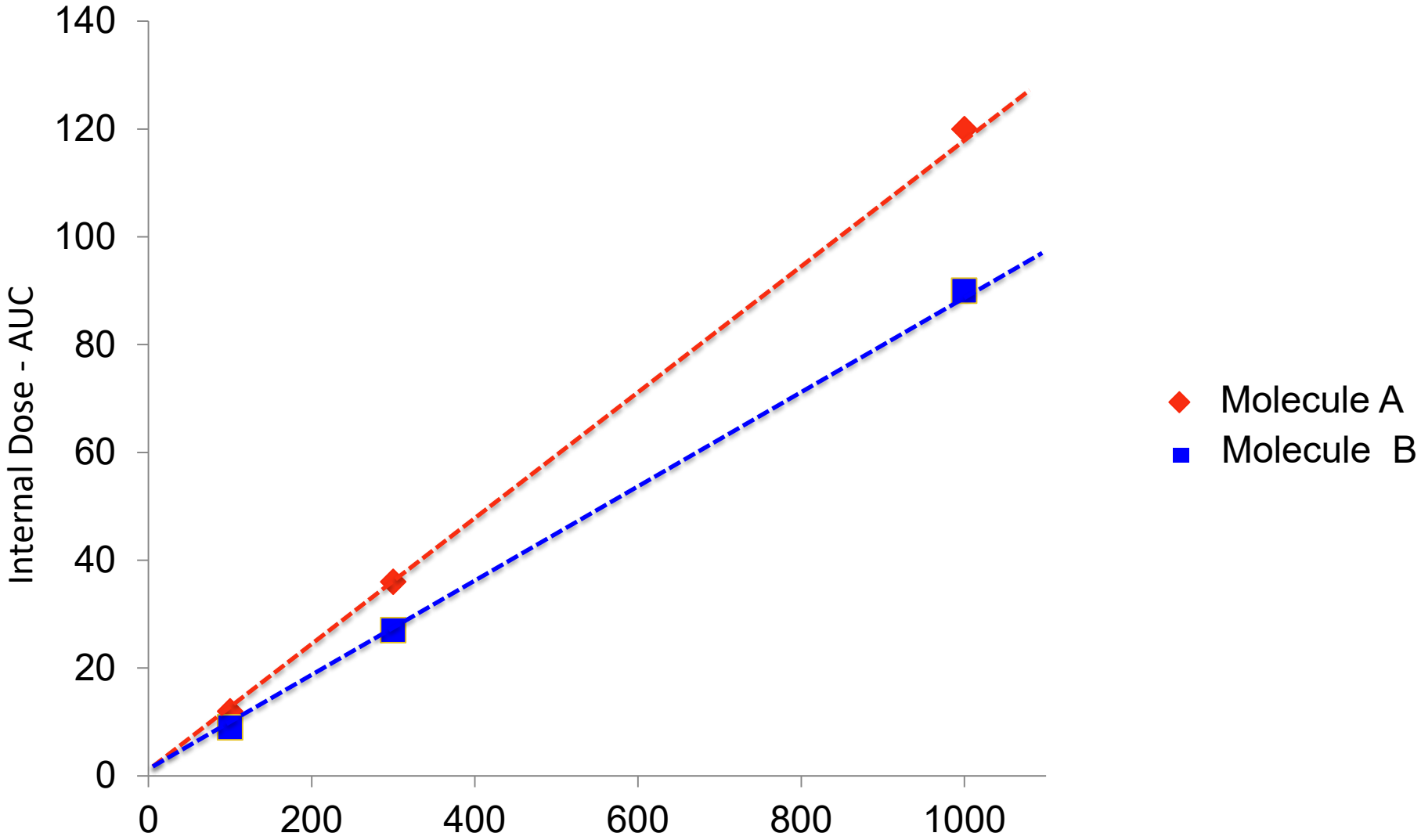
PK not a new concept

Early 1900s accomplishments

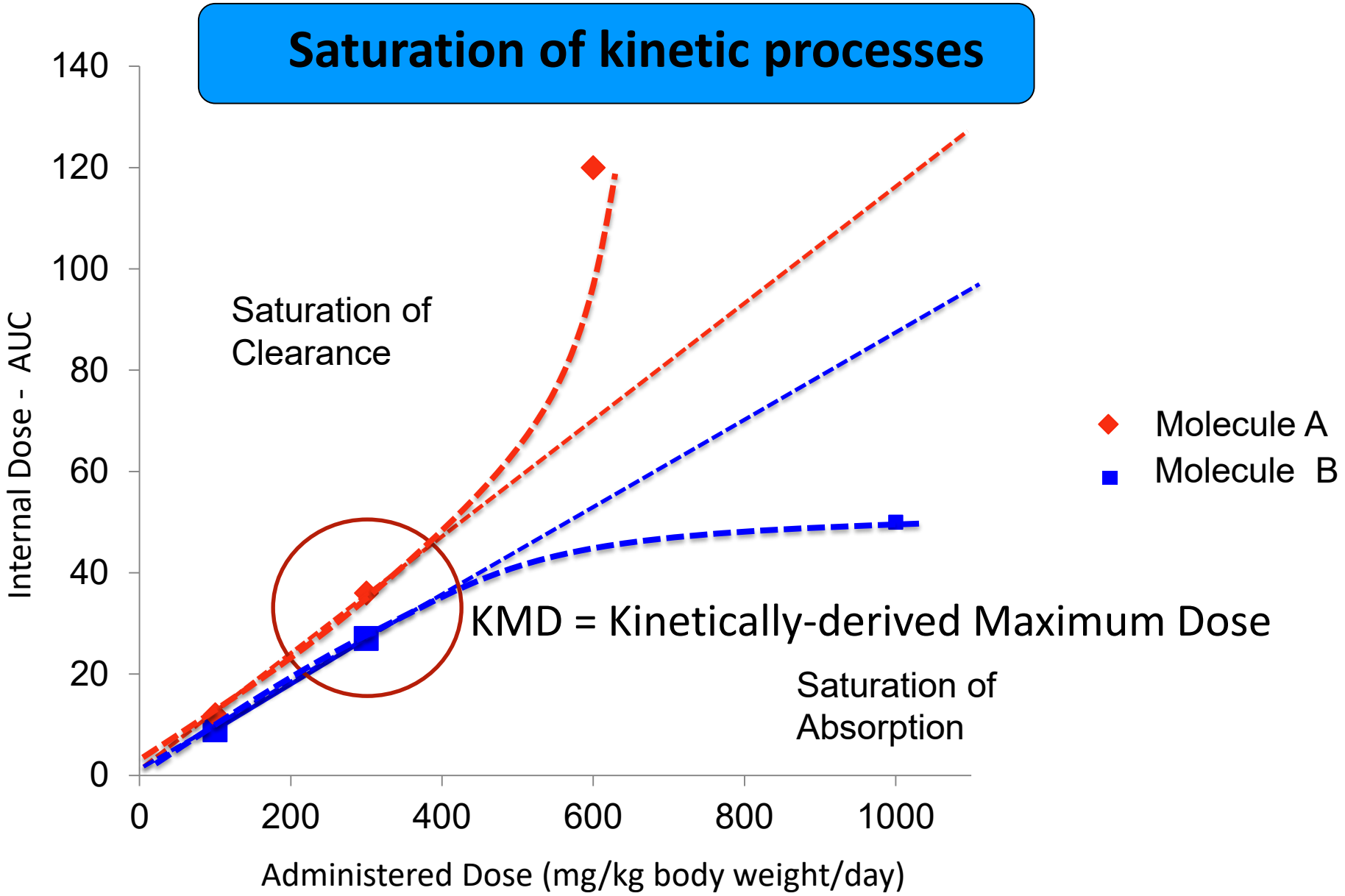
1913- Michaelis and Menten: enzyme kinetics
1924- Widmark and Tandberg: one compartment model
1924- Haggard: uptake distribution and elimination
1939-1950 Dominquez, rate of absorption, volume of distribution
1937- Teorell: first PBPK model

PK - Utilized by Pharma for decades

Toxicokinetics



Toxicokinetics



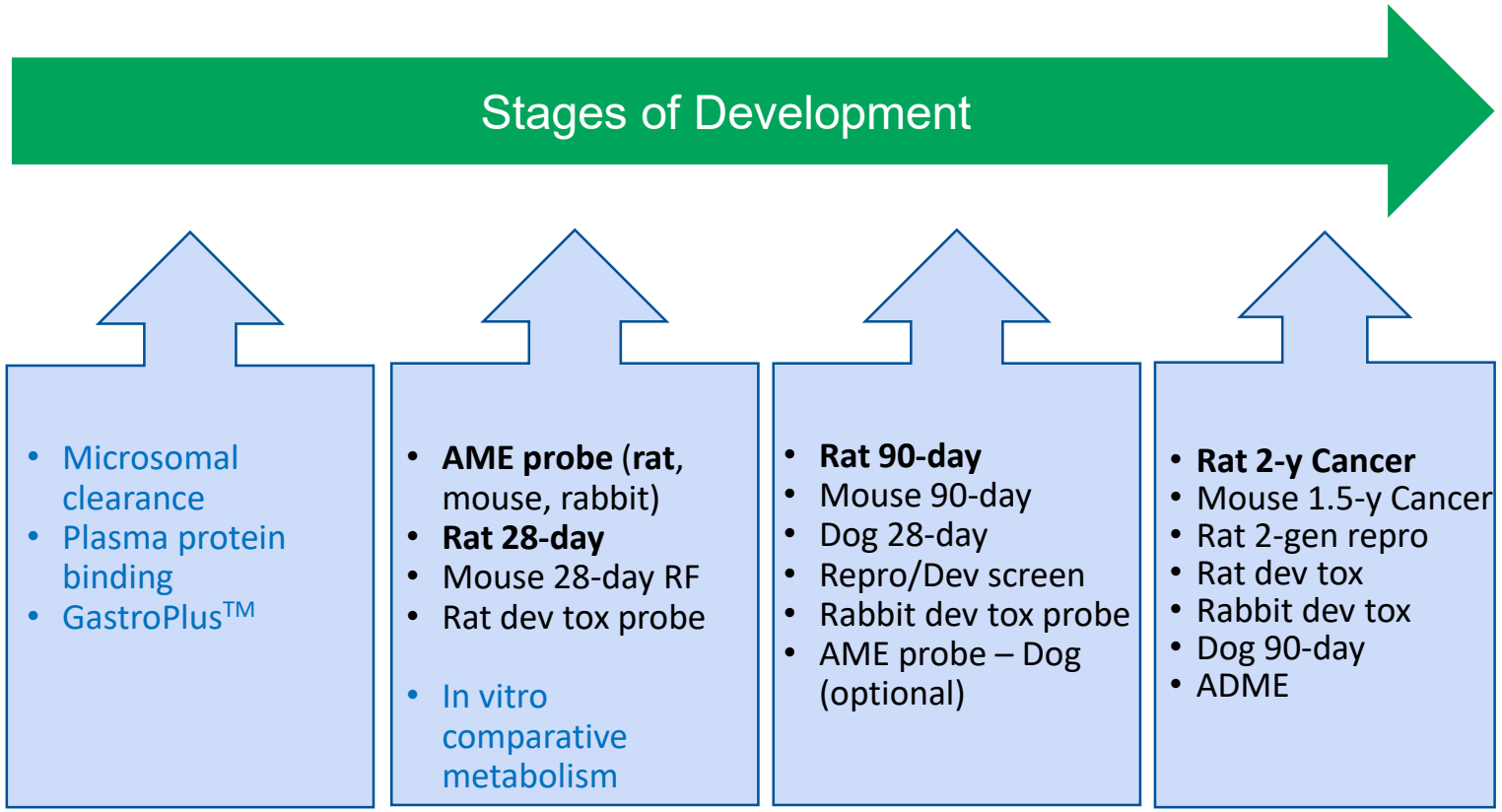
Modern Pesticide Toxicology Programs

- Dose level selection is a scientific WoE approach where both apical toxicity data and kinetic data are used for selection of the high dose.

- There are cases where KMD is the best scientific and 3Rs approach but there are also many examples where the apical endpoint data will drive dose level selection for toxicity studies.

- A clear understanding of measured or predicted human exposures validates the relevance of this approach for use in human health risk assessments.

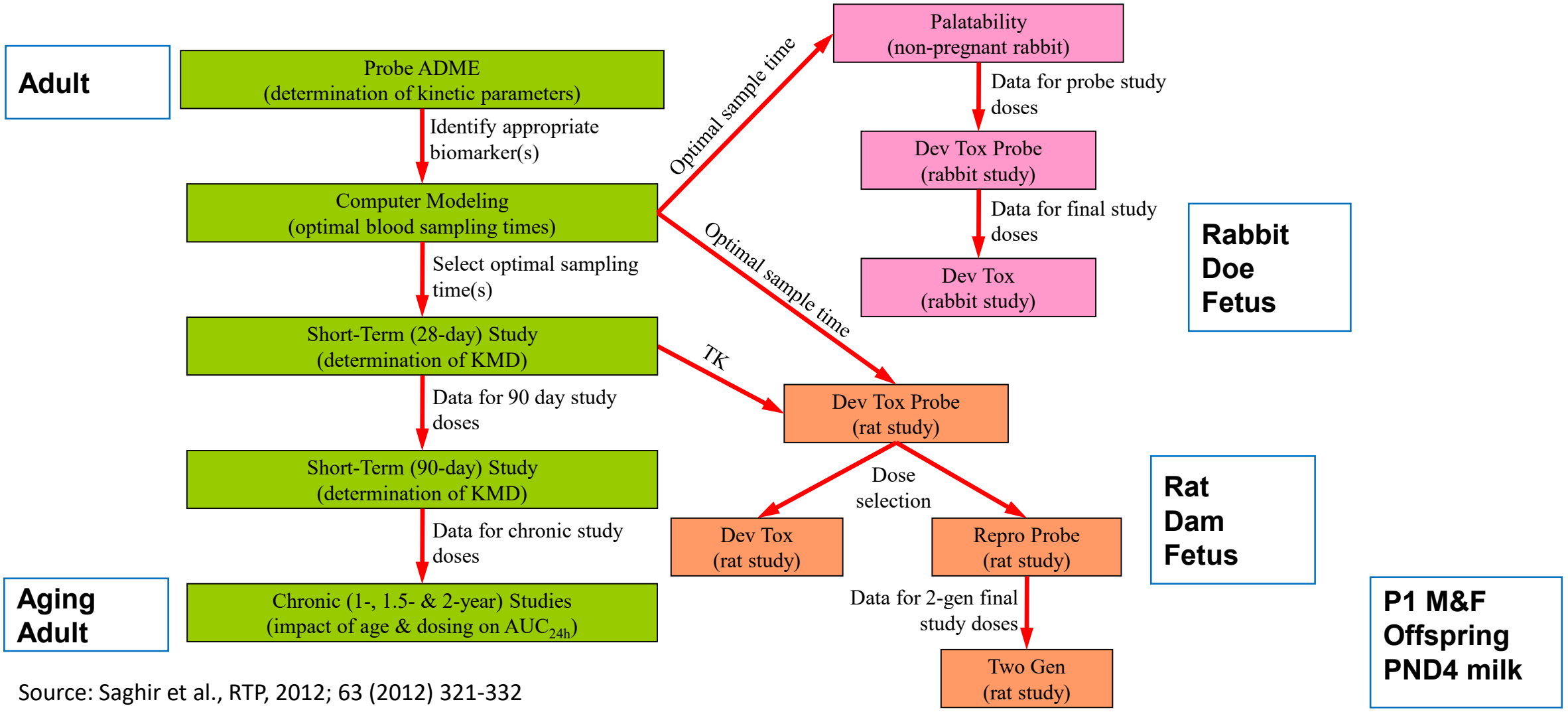
Toxicokinetics in Product Development



GastroPlus™ Software Suite (Simulations Plus)

- Default approach is to generate TK data-rich information for all new active substances by integrating TK into in vivo toxicity studies.
- Extra animals not required for in vivo TK sample collection.
- Measurement of blood concentrations of selected biomarkers.

Common Sequence of Mammalian Toxicity Studies



Source: Saghir et al., RTP, 2012; 63 (2012) 321-332

Probe Studies: Absorption, Metabolism and Excretion

Select TK biomarkers (parent/metabolites) for subsequent toxicology studies

- Obtain AME data following administration of radiolabeled form of a molecule;
  - Single oral bolus gavage administration
  - Dose levels high enough to allow for metabolite identification while not producing apparent toxicity
- Evaluate the PK of ^{14}C-activity in blood (plasma and red blood cells)
- Identify and quantitate metabolites
  - Urine, whole blood, plasma, feces (rat), and selected target tissues
- Initial indication of percent absorption
- Serves as a pilot study for OECD 417 guideline rat ADME study

Roth Metabolism Cage

Selection of Biomarkers

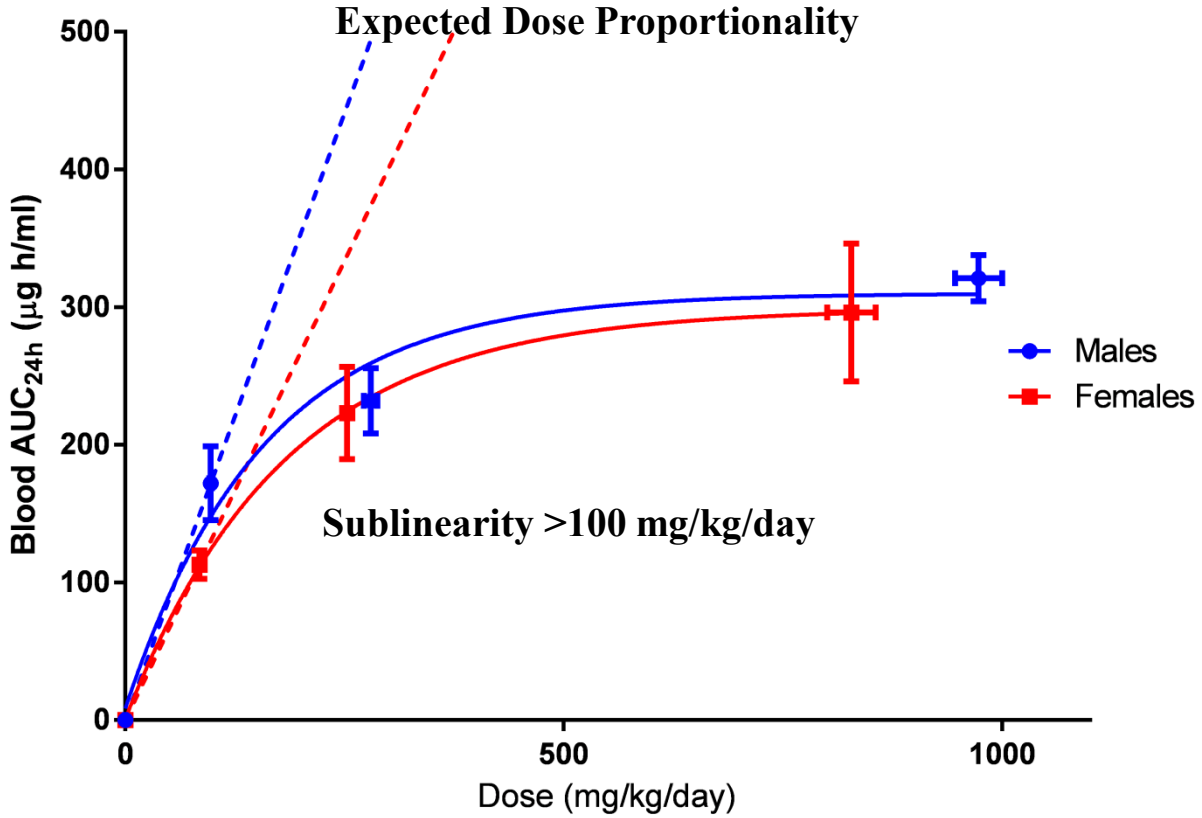
- Based predominately on probe AME data
- Different species may have different biomarkers
- For a given species the same biomarkers will be measured in all biological matrices
- Blood: Metabolites >10% region of interest in plasma or blood
- Urine: Metabolites >5% of the administered dose or metabolites >10% region of interest
- Examples:

Molecule	Sulfoxaflor	Florpyrauxifen-benzyl	Fenpicoxamid
# metabolites	0	1	5
# biomarkers	1 - parent	2 - parent and metabolite	3 metabolites and no parent

High Dose Level Selection for Repeat Dose Toxicity Study

Dose Proportionality	Saturation of Absorption	Saturation of Clearance
No Saturation Toxicity **Base on Toxicity** Halauxifen	Saturation Absorption Toxicity **WoE: KMD +Toxicity** Sulfoxaflor (F) Fenpicoxamid	Saturation Clearance Toxicity **WoE: KMD +Toxicity** Sulfoxaflor (M)
No Saturation No Toxicity	Saturation Absorption No Toxicity **KMD** Florpyrauxifen-benzyl	Saturation Clearance No Toxicity

Florpyrauxifen Benzyl - Saturation of Absorption and No Toxicity



Metabolite of Florpyrauxifen Benzyl

Sub-linear response – saturation of absorption

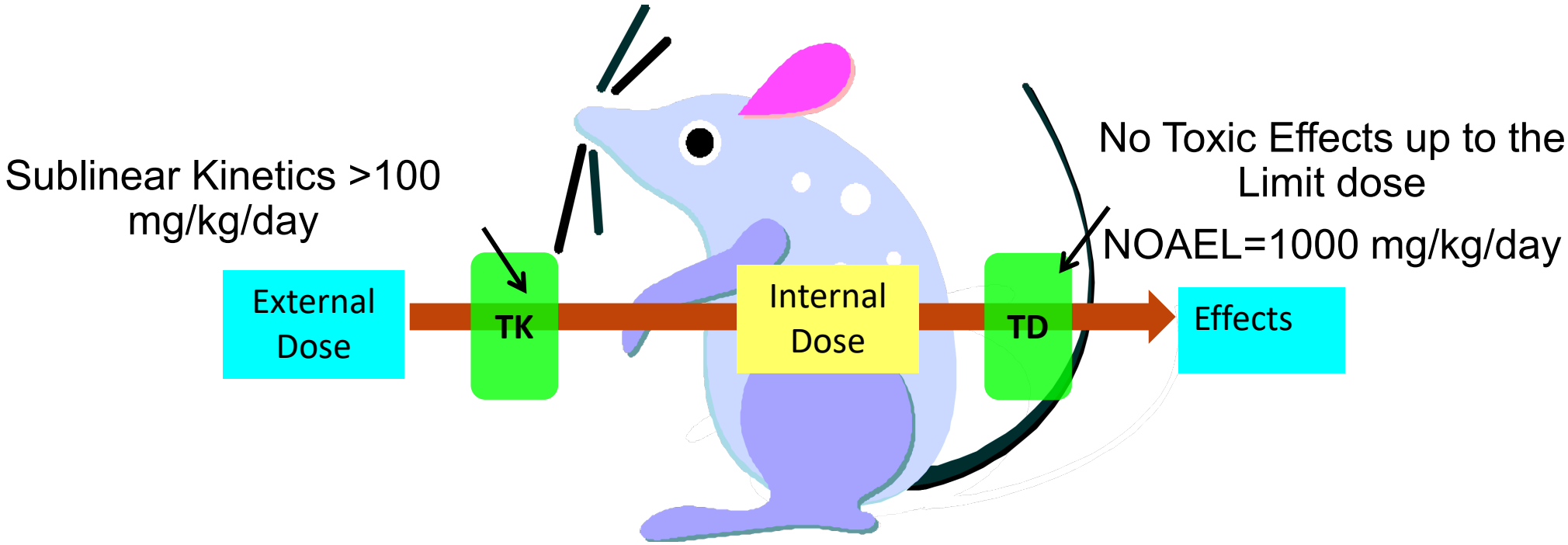
- **No toxicity up to 1000 mg/kg/day**
- **AUC did not increase proportionally to external dose**

Integration of TK was instrumental in selecting the most relevant dose levels for critical Rinskor™ guideline dietary toxicity studies leading to a KMD approach instead of the traditional toxicity testing MTD approach.

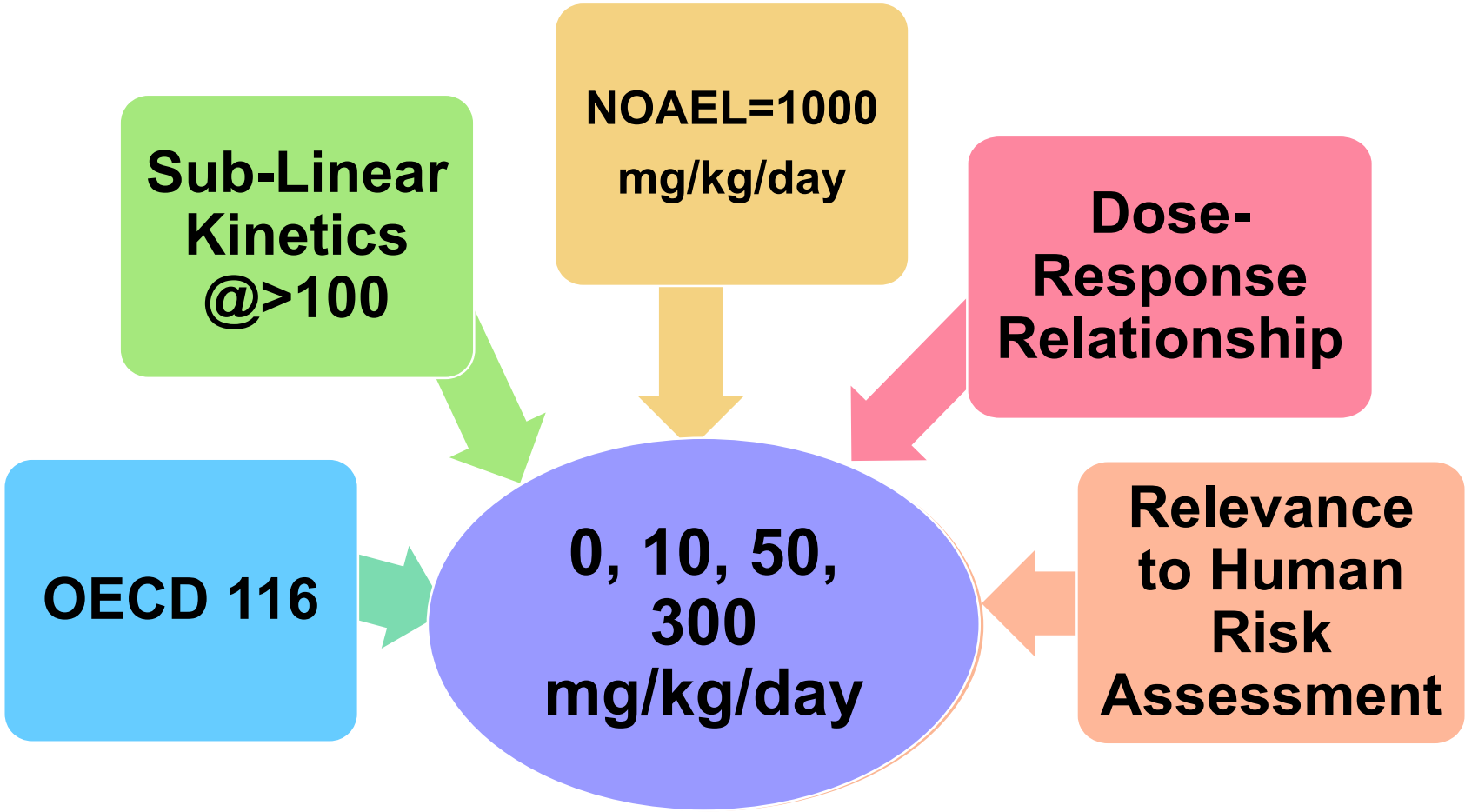
Florpyrauxifen Benzyl - High Dose Level Determination for Chronic Rat Study

MTD

1000 MKD



Florpyrauxifen Benzyl - Weight of Evidence in High Dose Level Selection
KMD - Saturation of Absorption and No Toxicity



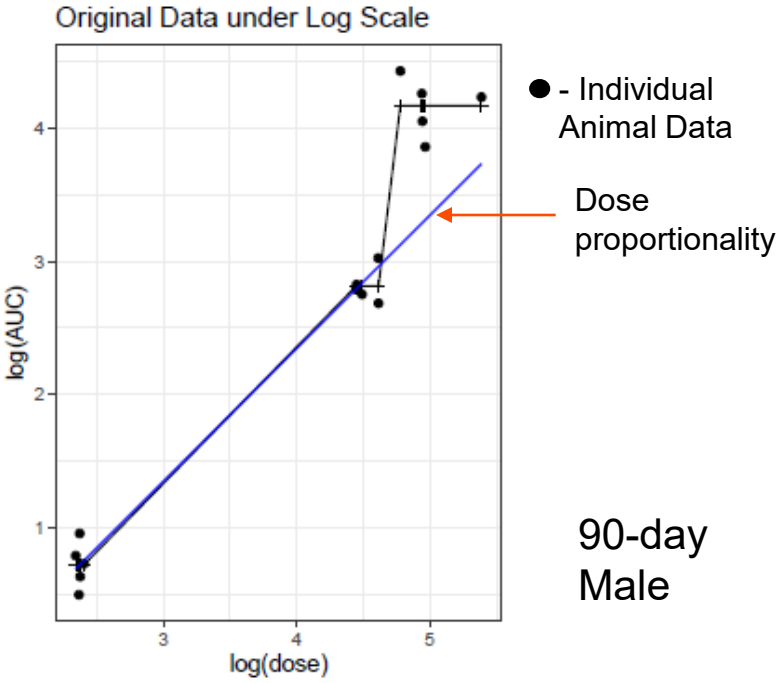
Halauxifen – Dose Proportionality (no saturation of kinetic processes) and Toxicity

- **90-day dietary rat study**, GLP OECD 408
  - N=10/sex/dose
  - Toxicokinetics: Blood collected during last week of treatment
  - 0, 10, 50, 250 and 750 mg/kg/day
  - Kidney effects – 750 mg/kg/day, treatment-related microscopic effects
  - NOAEL: 250 mg/kg/day
  - Dose proportionality - AUC vs external dose
- **2-year rat study**
  - High dose selected based on renal toxicity and no saturation of kinetic processes
  - 0, 20, 100, 400, 625 (M) / 750 (F) mg/kg/day
  - During study systemic exposure proportional to dose
  - No treatment related increase in neoplasms
  - NOAEL: 100 mg/kg/day (M) based on primary effects in kidney,
    400 mg/kg/day (F) based on bladder and kidney effects

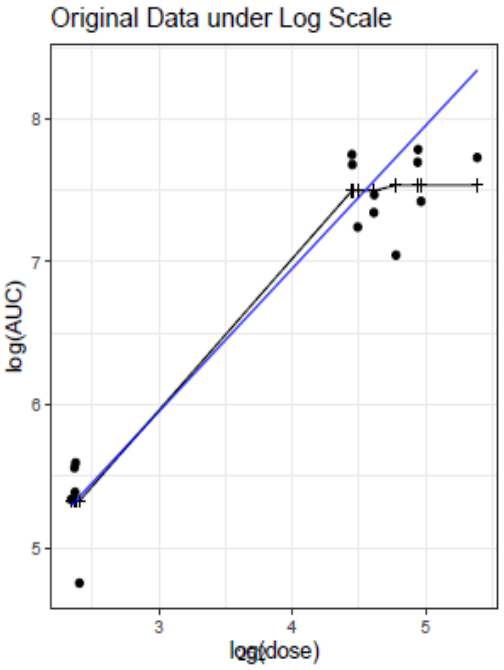
Sulfoxaflor – WoE (Saturation & Toxicity)

- **90-day dietary mouse study** (OECD 408)
  - Males: 0, 100, 750, 1250 ppm
  - Females: 0, 100, 1500, 3000 ppm
  - Liver effects: Hepatocyte hypertrophy (M&F), ↑ in mitotic figures & fatty change (M)
  - NOAEL: 100 ppm (M&F)
  - Saturation of clearance (M): 1250 ppm
  - Saturation of absorption (F): 3000 ppm
  - WoE (KMD and toxicity) used to set high dose in 18-month mouse

- **18-month mouse study**
  - Males: 0, 25, 100, 750 ppm
  - Females: 0, 25, 250, 1250 ppm
  - During study systemic exposure proportional to dose
  - Liver tumors at 750 ppm (M) and 1250 ppm (F)
  - NOEL: 100 ppm (M) and 25 ppm (F)
  - NOAEL: 250 ppm (F), based on slight hepatocellular hypertrophy



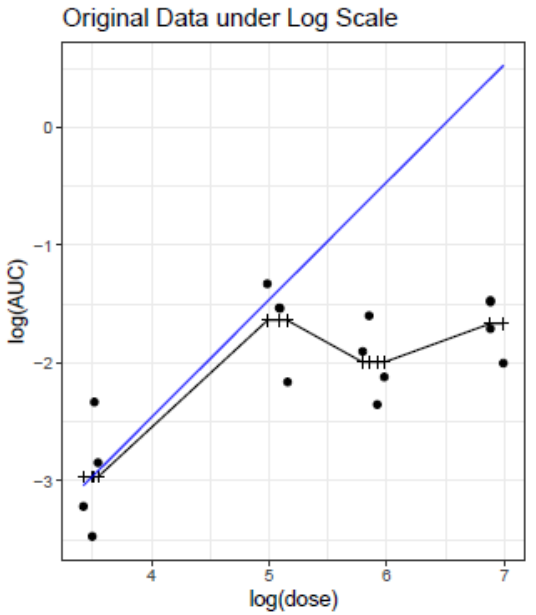
90-day Male



90-day Female

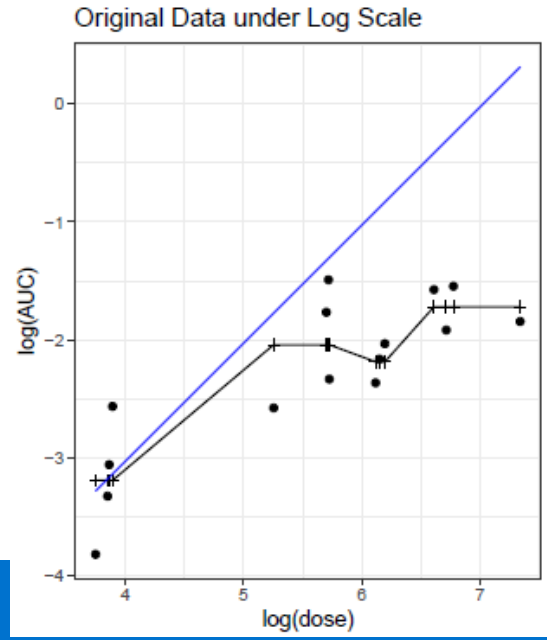
Fenpicoxamid – WoE (Saturation of Absorption and Toxicity)

- **90-day dietary mouse study** (OECD 408)
  - Males and Females: 0, 300, 1500, 3000, 6000 ppm
  - Liver effects:
    - Males, 1500 ppm; ↑ in rlw, hepatocellular hypertrophy, v. slight necrosis
    - Females, 3000 ppm; similar ↑ in rlw as males, slight hepatocellular hypertrophy
  - NOAEL: 300 ppm (M&F)
  - Saturation of Absorption (metabolite): 3000 ppm
  - WoE (KMD and Toxicity) used to set high dose in 18-month mouse



90-day Male

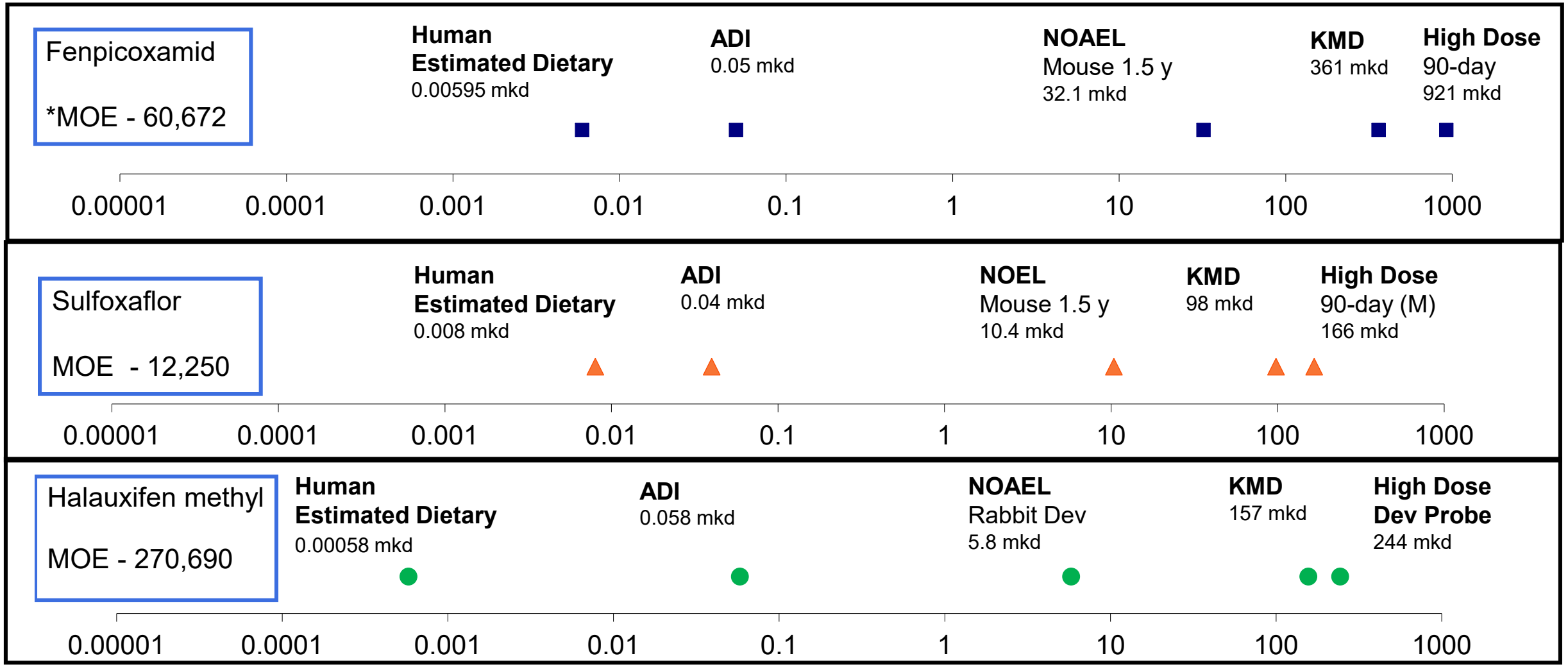
- **18-month mouse study**
  - Males: 0, 50, 300, 1500 ppm
  - Females: 0, 50, 300, 3000 ppm
  - Metabolites exhibited sublinear kinetics at the middle and high doses.
  - No treatment-related increases in neoplasms
  - Treatment-related, adverse liver effects in males at 1500 ppm and females at 3000 ppm,
  - NOAEL: 300 ppm (M&F)



90-day Female

rlw – relative liver weight

MOE - KMD and Estimated Dietary Exposure



Summary

- ✓ **There are important scientific and regulatory drivers for obtaining kinetic data in conjunction with standard toxicity studies**
- ✓ **TK can be integrated into studies with no additional animals**
- ✓ **High dose level selection is a WoE approach**
- ✓ **Integration of TK can provide valuable insight**
  - Instrumental in dose level selection - KMD approaches can be more relevant for human health risk assessments
  - Cross species/routes of exposure/life-stages comparison
  - Better interpretation of the data in the context of human exposure
- ✓ **Human dietary exposures are orders of magnitude below the KMD**
- ✓ **Understanding systemic exposure to animals moves us closer to exposure-based dose setting ≡ relevance to humans**

Acknowledgements

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