Ruolo dei NAMs nel Progetto HESI TEA

(Transforming the Evaluation of Agrochemicals).

(Role of NAMs in the HESI TEA project)

22 FEBRUARY 2023

ITALIAN SOCIETY OF TOXICOLOGY MEETING (SITOX)

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& Marco Corvaro, PhD, ERT (Corteva)

Outline

- Project Background
- Transforming the Evaluation of Agrochemicals (TEA)
  - Project vision, structure and objectives
  - Science integration
  - Problem formulation and exploration
  - Ongoing work
  - Industry case examples collection
  - Expected project output
- Q&A

Health and Environmental Sciences Institute

International non-profit building science for a safer, more sustainable world.

108 Academic Institutions, NGOs and Research Institutes

56 Government & Regulatory Agencies

75 Corporate Sponsors

>100 Distinct Projects

17 Scientific Committees (+1 consortium)

Meetings and Workshops

13 Countries, 5 Continents

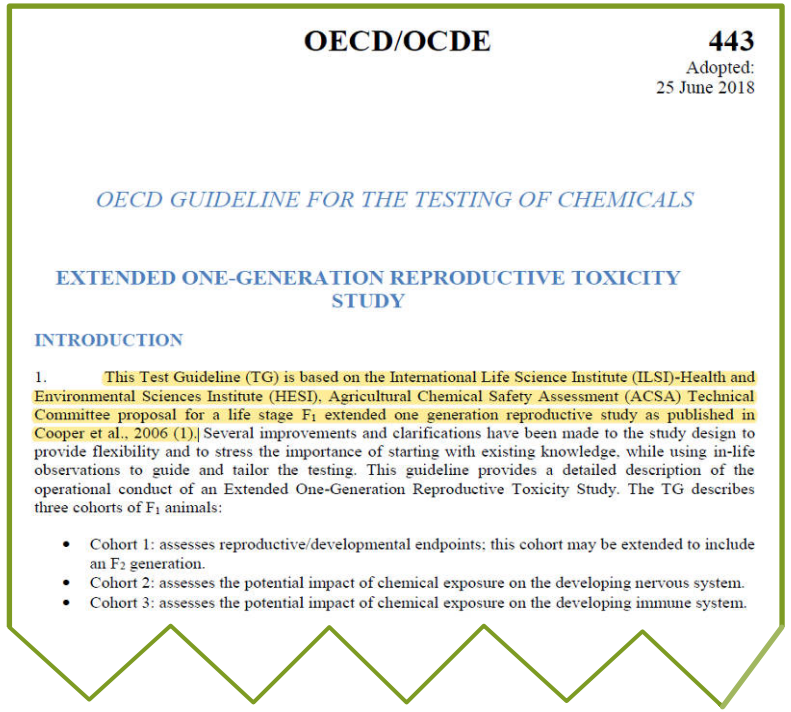
>1000 Scientists
at HESI events in 2019

www. https://hesiglobal.org/

Project Background: Agricultural Chemicals Safety Assessment (ACSA, 2000-2004)

- Recommended
  - A tiered testing approach
  - An increased use of toxicokinetics and NAMs
    - Carmichael et al Crit Rev Toxicol 36:1-7, 2006
    - Barton et al Crit Rev Toxicol 36:9-35, 2006
    - Doe et al Crit Rev Toxicol 36:37-68, 2006
    - Cooper et al Crit Rev Toxicol 36:69-98, 2006
- Resulted in
  - The elimination of the 1-yr dog study
  - OECD GL 443: Extended one-generation reproductive study

- General impact:
  - Modernization of assessment guidelines
  - Integration of more relevant hazard characterization approaches
  - More efficient human health risk assessments
  - Some decrease in animal use
  - More effective use of resources to inform human health risk assessment.



OECD/OCDE **443**

Adopted:
25 June 2018

OECD GUIDELINE FOR THE TESTING OF CHEMICALS

EXTENDED ONE-GENERATION REPRODUCTIVE TOXICITY STUDY

INTRODUCTION

1. This Test Guideline (TG) is based on the International Life Science Institute (ILSI)-Health and Environmental Sciences Institute (HESI), Agricultural Chemical Safety Assessment (ACSA) Technical Committee proposal for a life stage F_1 extended one generation reproductive study as published in Cooper et al., 2006 (1). Several improvements and clarifications have been made to the study design to provide flexibility and to stress the importance of starting with existing knowledge, while using in-life observations to guide and tailor the testing. This guideline provides a detailed description of the operational conduct of an Extended One-Generation Reproductive Toxicity Study. The TG describes three cohorts of F_1 animals:

- Cohort 1: assesses reproductive/developmental endpoints; this cohort may be extended to include an F_2 generation.
- Cohort 2: assesses the potential impact of chemical exposure on the developing nervous system.
- Cohort 3: assesses the potential impact of chemical exposure on the developing immune system.

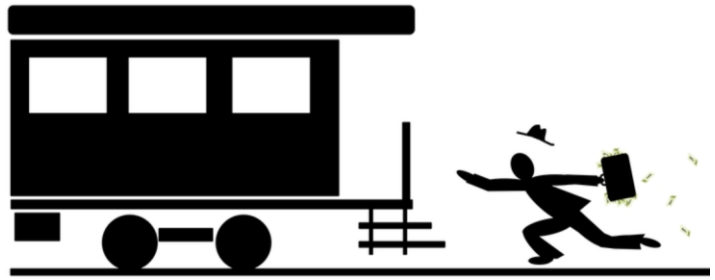
Two Decades Later…

Need to develop and expand sustainable agriculture

- The world (and needs) keeps evolving
  - Rapidly growing, and unevenly distributed population
  - Decrease in arable land
  - Decrease in adequate water supplies
  - New pest pressures

Science keeps evolving

- New technologies
  - AI
  - Bayesian approaches
  - AOPs
  - NAMs
  - …
- New constraints
  - Decrease animal use
  - Fewer resources

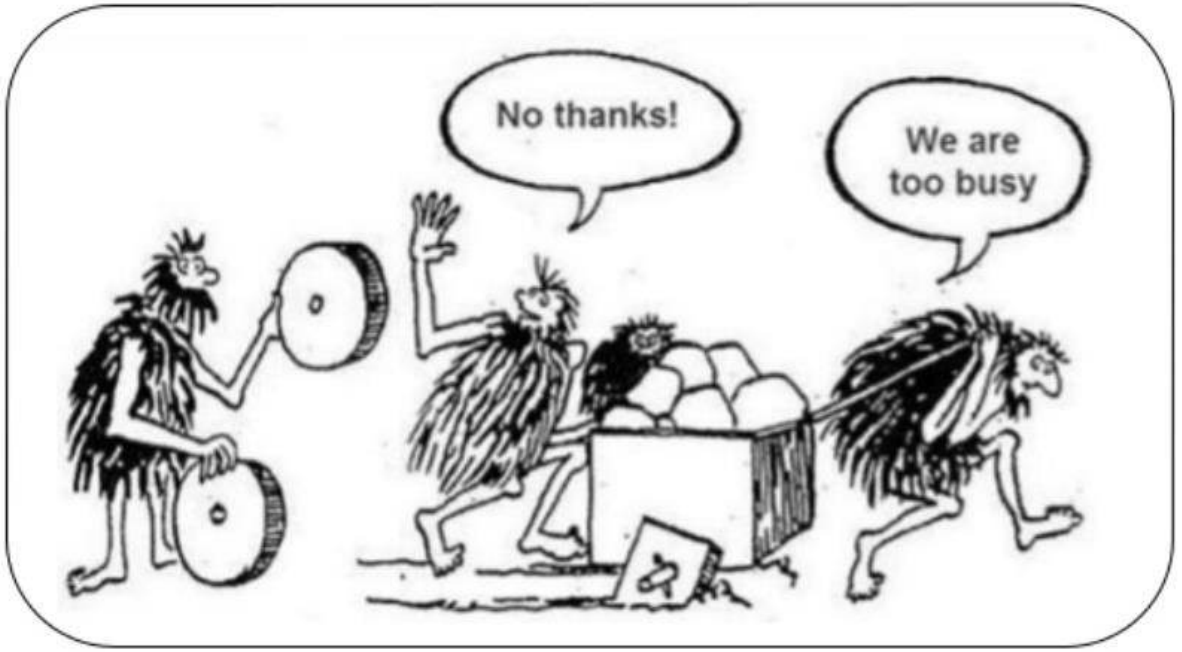


AgChem RA

Two Decades Later…

The current system:

- Fails to flexibly incorporate the most current methods/science to assess the risks of agrochemical uses
- Will not meet the demand for a developing and expanding sustainable agriculture

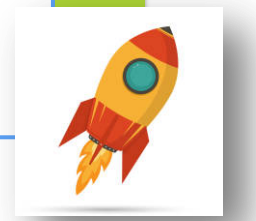


Transforming the Evaluation of AgroChemicals

IT'S TEATIME!
(JAN 2021)

Project Vision, Structure, Mission and Objectives

Transformed evaluation of agrochemicals for globally sustainable agriculture



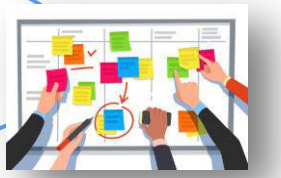
Harmonized, integrated, and sustainable fit-for-safety testing of agrochemicals to inform hazard and risk assessment

Create a roadmap that

- ⇨ Transforms the evaluation of agrochemicals
- ⇨ Better reflects current and emerging science
- ⇨ Accounts for current and emerging evidence requirements for agrochemicals

HESI Collaborative effort

- Multisectoral
- Multidisciplinary
- International



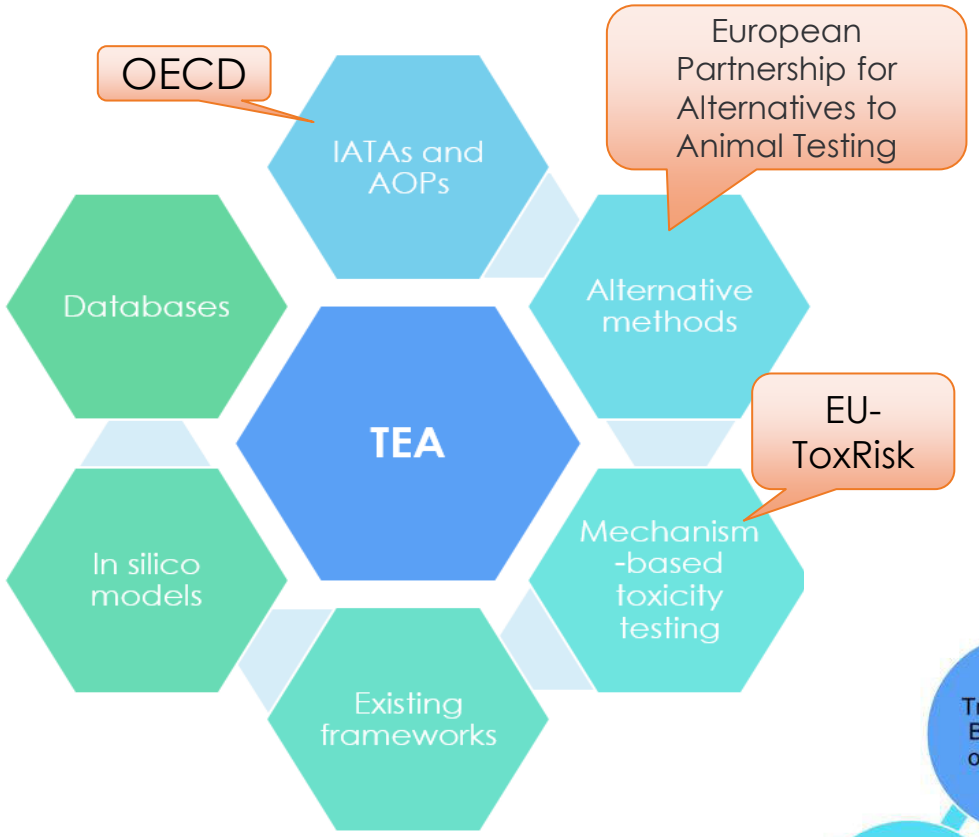
Participating Organizations

Private Sector Organization
Adama
BASF-US
Bayer Crop Science
Corteva
FMC
Sumitomo
Syngenta

Public Sector Organization (*confirmed participation)		
ANVISA (Brazil)	University of Sao Paulo (UNESP)	JRC (Europe)
APVMA (Australia)	Univ of Buenos Aires	NC3Rs (UK)
PMRA (Canada)	Univ. CA Riverside	NIH/NIEHS
RIVM	Univ. Milan	PCRM
US EPA	Univ. of Nebraska	PETA-ISC (UK/Intl)
IBAMA* (Brazil)	EFSA	

Other Partners
Exponent
Juberg Consulting
Penman Consulting
Planitox

*Not yet confirmed



A Work of "Integration"

Problem Statement

"Establish the landscape/map supporting the development of fit-for-purpose safety evaluation for Agrochemicals, that is applicable to changing global as well as local needs for evaluation and regulatory decisions that can incorporate relevant evolving science inputs."

Manuscript 1: D.C. Wolf et al. Pest Manag Sci. 2022 Dec;78(12):5049-5056.

The Big Idea

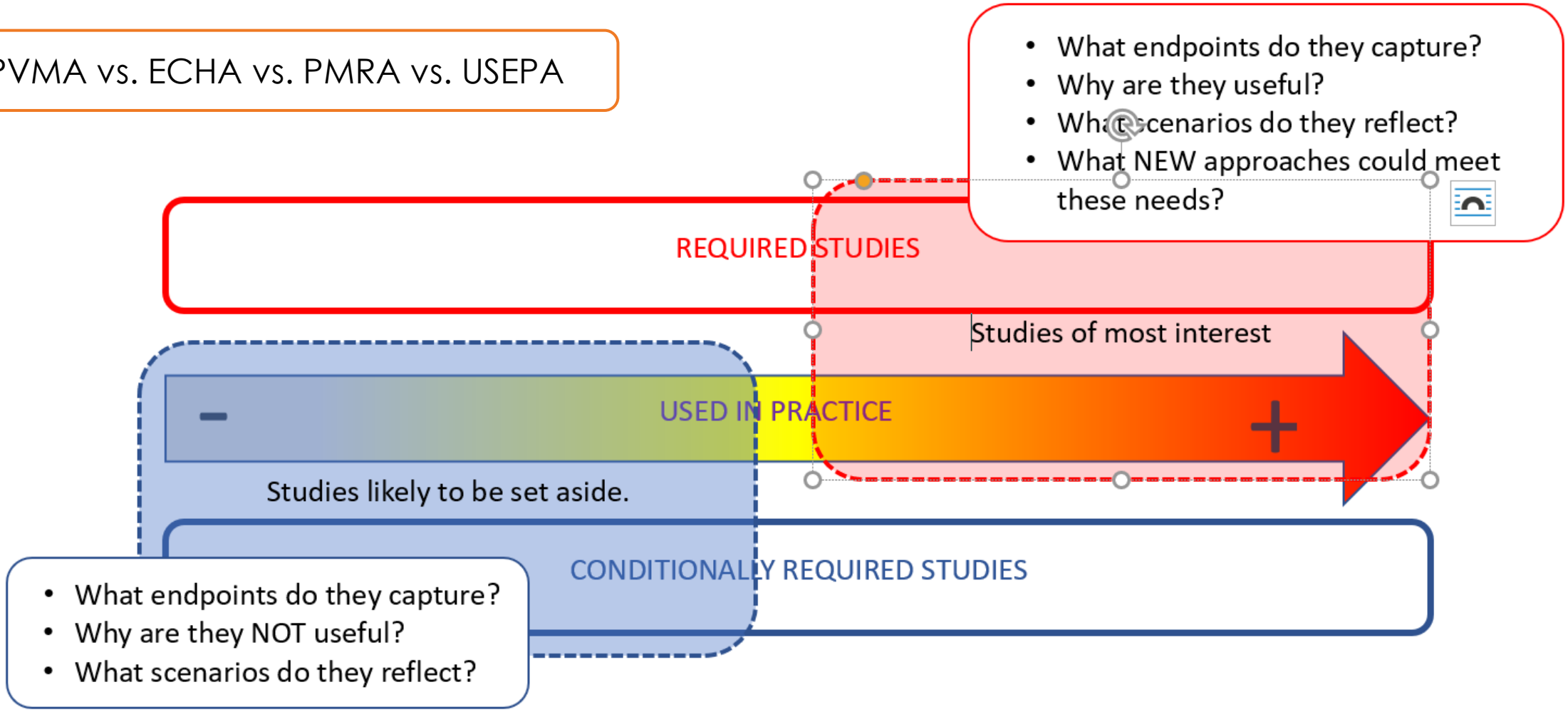
By the end of this decade, we will be able to make a **confident regulatory decision** on a new pesticide **within 12 months** of dossier submission **without** needing chemical specific **vertebrate animal testing**.

Ongoing Work

- Collect information on what test guidelines are currently used or not
- Problem exploration & Conceptual model development
- Manuscripts
- NAM Survey
- Outreach

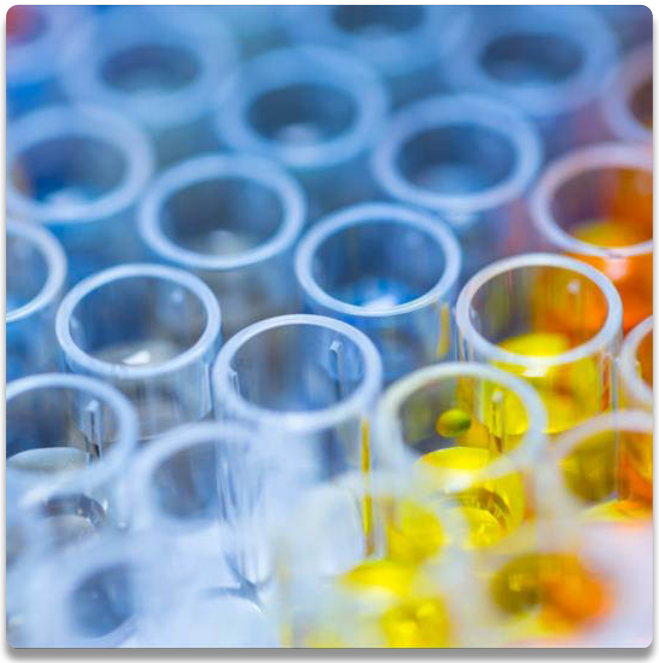
Test GL Information Collection

APVMA vs. ECHA vs. PMRA vs. USEPA



NAMs Survey

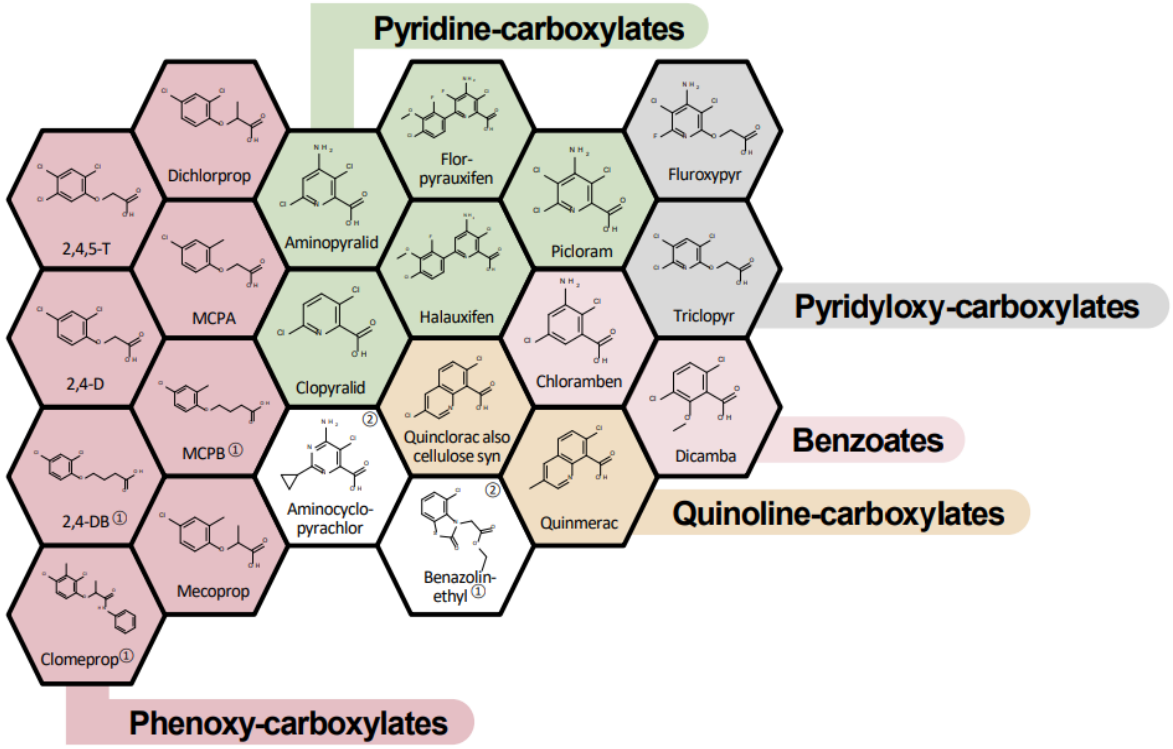
- To better understand the use of new approach methods by the agrochemical industry for both data submissions and R&D
  - What NAMs do they use?
  - With what frequency?
- Develop OECD IATA case studies



Industry Case example 1
NAM-supported read-across

Auxin mimic herbicides

- Compound X in well studies Class (HRAC Gp 4):



- Short term-toxicity with transcriptomic
- Comparative in vitro toxicokinetics

- Assess possible read-across/NAMs- based waivers – for example
  - Waive a Cancer Rodent Bioassay using the ReCAAP project criteria and NAMs
  - Waive a Sub-chronic Dog program

• Figure from: HRAC – mode of action poster 2022

Is Dog testing necessary for Auxines?

Reviewed in Bartels *et al.*, 2020. RTP

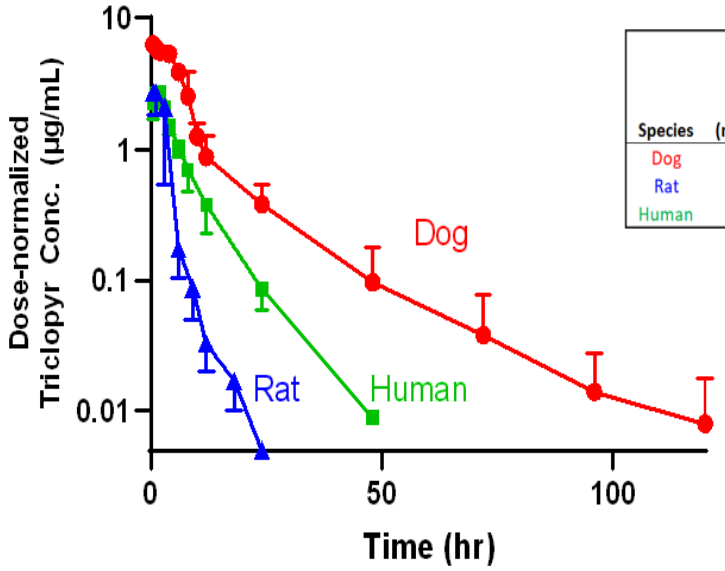
Triclopry case example

- Key Target organ:
  - Kidney, in all species
  - Dog have “apparent” lower NOAELs
- Key TK profile characteristics:
  - Slow renal clearance in dogs, similar for various phenoxyacetic acids
  - Mediated by species-specific effects on Organic Acid Transporter OAT1/3

DOES THE DOG CONTRIBUTE TO RISK ASSESSMENT?

- **The rat NOAELs are used globally as PoD/RfD**
- **The dog is an outlier for kidney clearance/toxicity and findings are therefore not considered human relevant**

Comparative plasma kinetics in rat, dog, human (all doses normalized to 1 mg/kg)



Species	Dose (mg/kg)	Dose-normalized AUC (ug-hr/mL)	Dose-normalized Cmax (µg/mL)	Elim. $T_{1/2}$ (hr)
Dog	5	58.7	6.3	18.7
Rat	3	11.0	2.7	2.3
Human	0.53	19.0	2.7	5.1

Longer half-life in dog correlates with slower renal clearance in this species vs. rat/human - Similar trends seen for a variety of related phenoxyacetic acids

	DOG	HUMAN	RAT
In vivo/in vitro absorption	+++	+++	+++
in vitro metabolism	-	-	-
in vitro plasma protein binding (+ = Saturable)	+++	++	++
in vitro transporter assay	Resorption	Active Secretion	Active Secretion

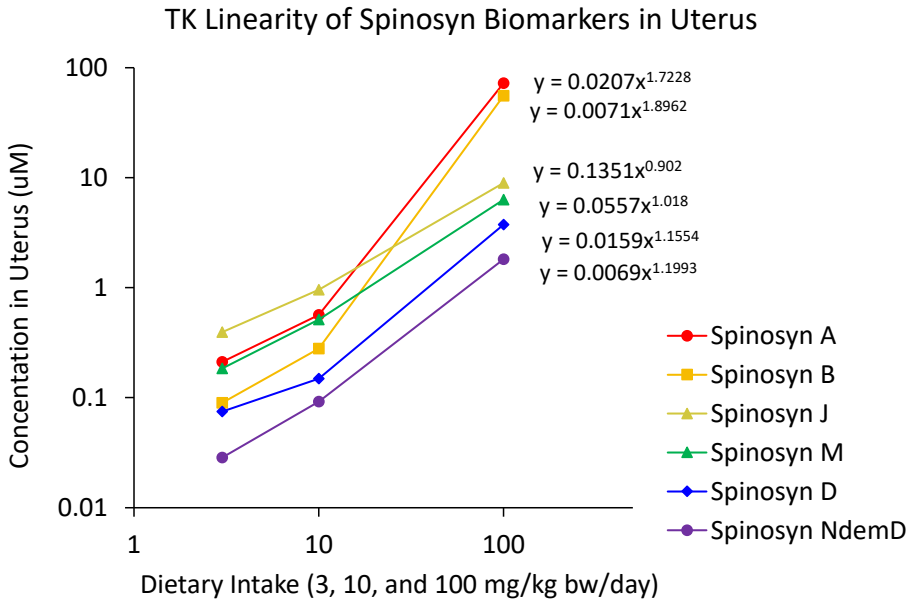
Industry Case example 2
NAMs supported Classification and Labeling and Risk assessment

Spinosad example

Dystocia observed in rats 2-generation study at high dose = 100 mg/kg bw/day

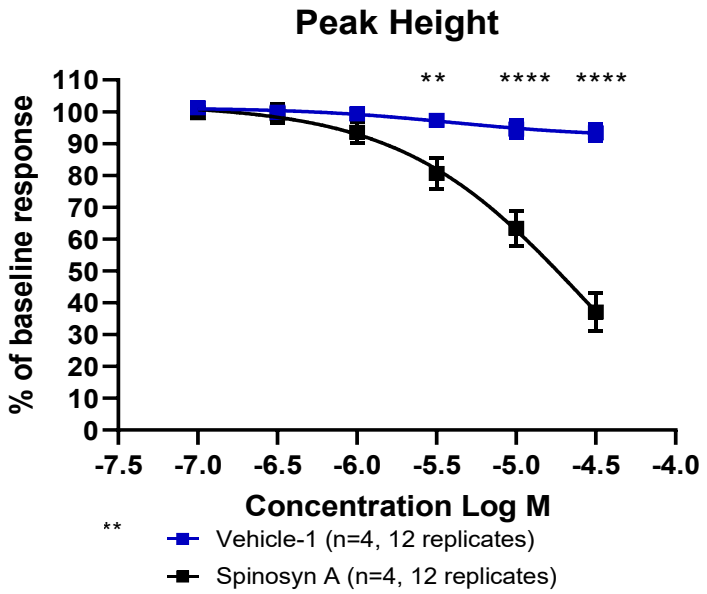
Plasma and tissue exposure in GD21 rats

- Non dose-proportional kinetics at 100 mg/kg bw/day
- Saturation of GSH conjugation (similar to macrolide antibiotics)
- Rat dystocia at uterine concentrations = ca. 70 µM



Ex-vivo rat uterine contractility

- Direct uterine contractility inhibition, receptor mediated (TSPO benzodiazepine receptor)
- Clear effect threshold (parent Spinosyn A):
  - EC50 = 3 µM; full inhibition = 10 µM



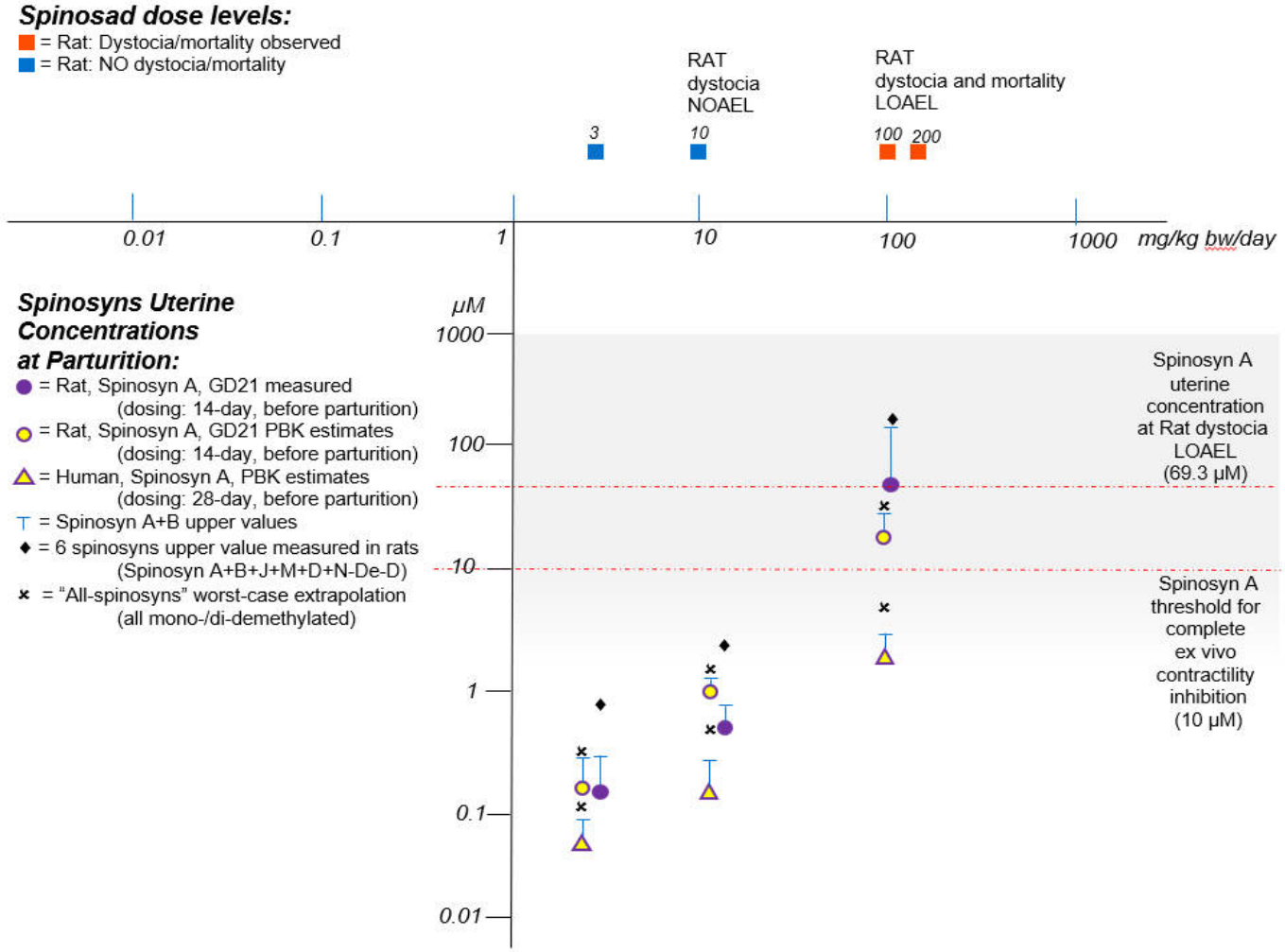
CORTEVA™ agriscience

Eurotox/ICT 2022 Poster P06-13 – Corvaro et al .
4 Manuscripts in preparation.

Bringing Higher Tier Kinetics and Exposure Information into Human Hazard Characterization and Risk Assessment

Rat (○) and human (△) PBK model, based on OECD 331, allow qIVIVE

- Rat experimental data (●)

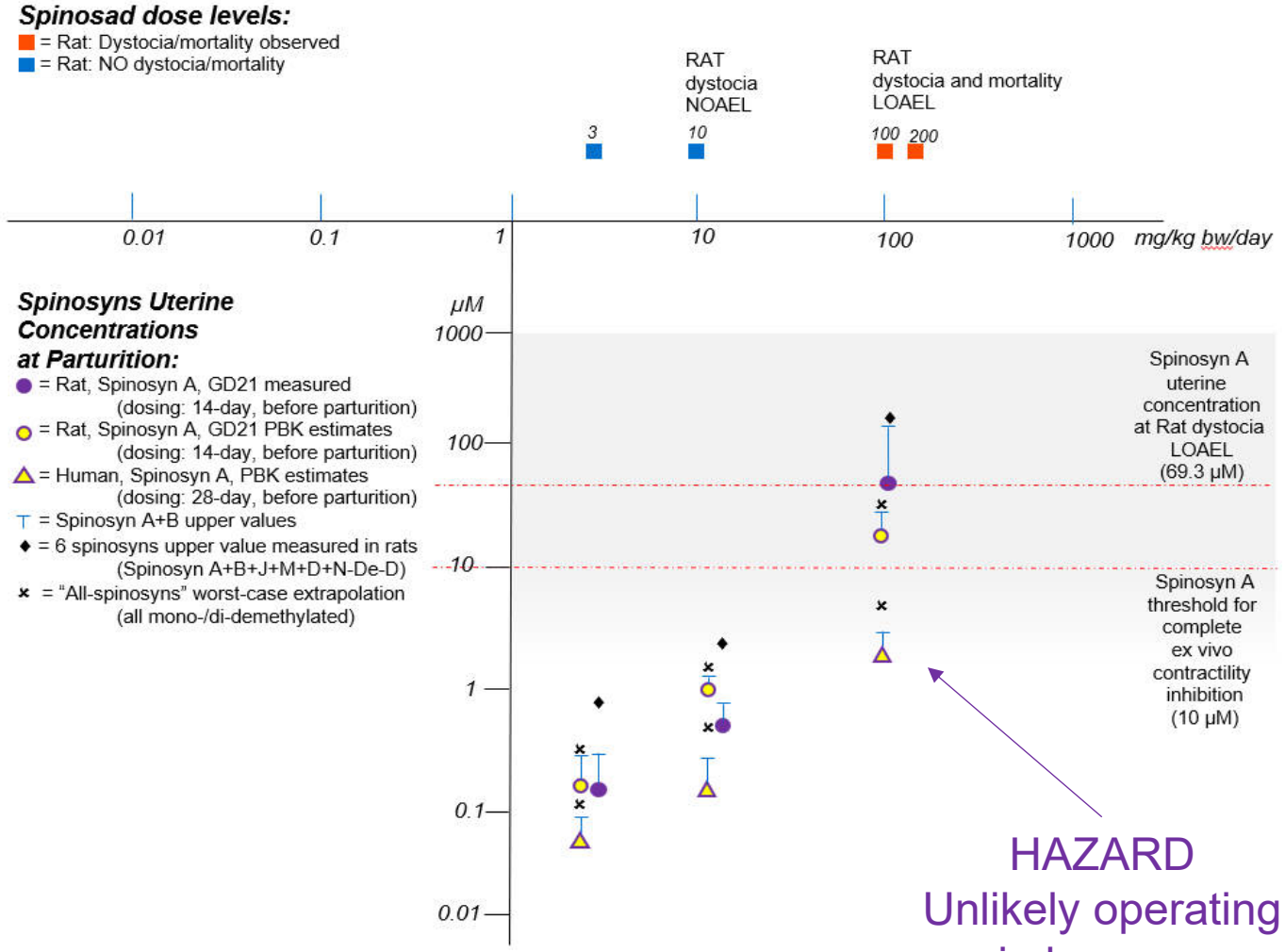


Bringing Higher Tier Kinetics and Exposure Information into Human Hazard Characterization and Risk Assessment

Rat (⬭) and human (△) PBK model, based on OECD 331, allow qIVIVE

- Rat experimental data (⬭)

- Human hazard characterized

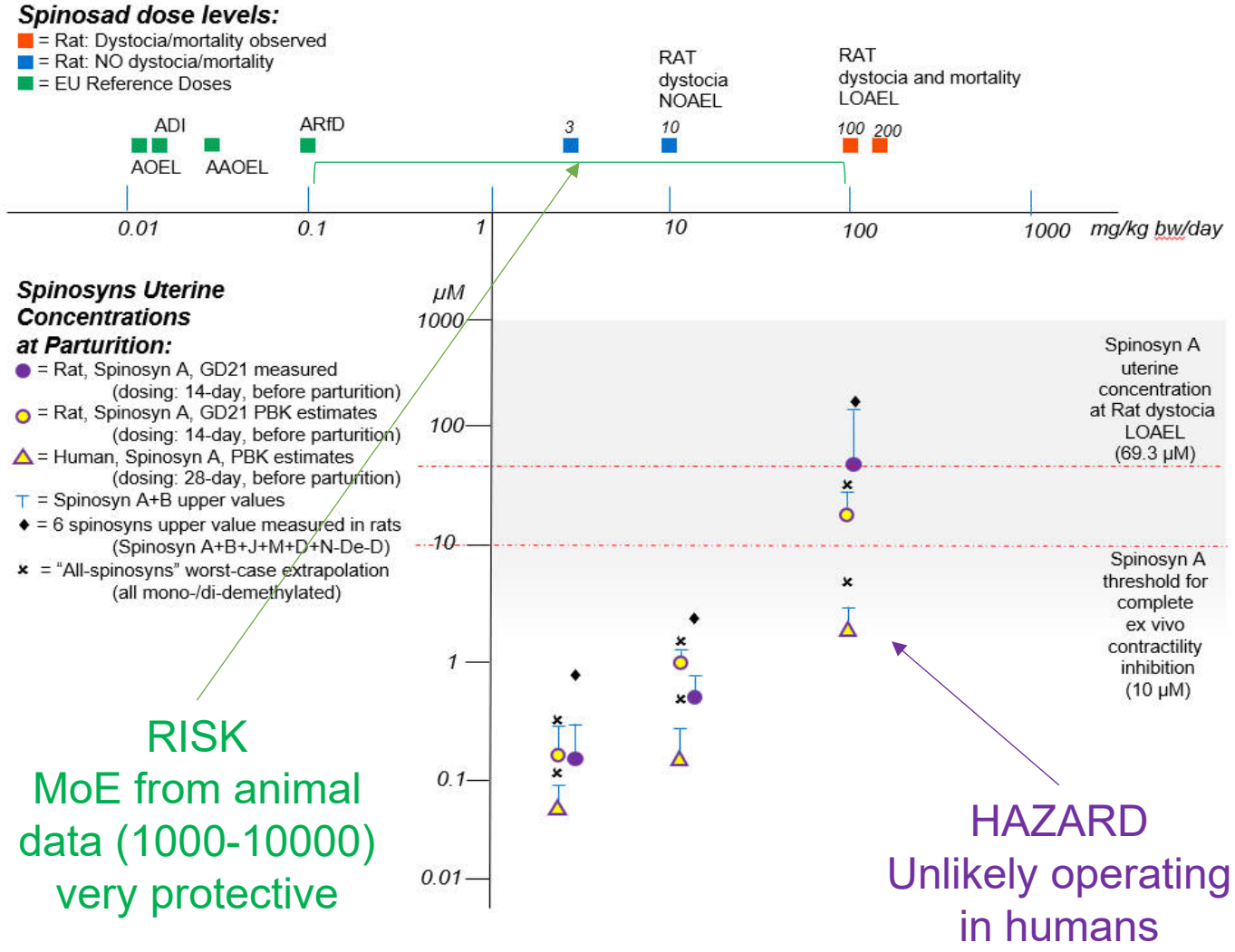


Bridging Higher Tier Kinetics and Exposure Information into Human Hazard Characterization and Risk Assessment

Rat (○) and human (△) PBK model, based on OECD 331, allow qIVIVE

- Rat experimental data (●)

- Human hazard characterized
- Human risk characterized (led by other endpoints)



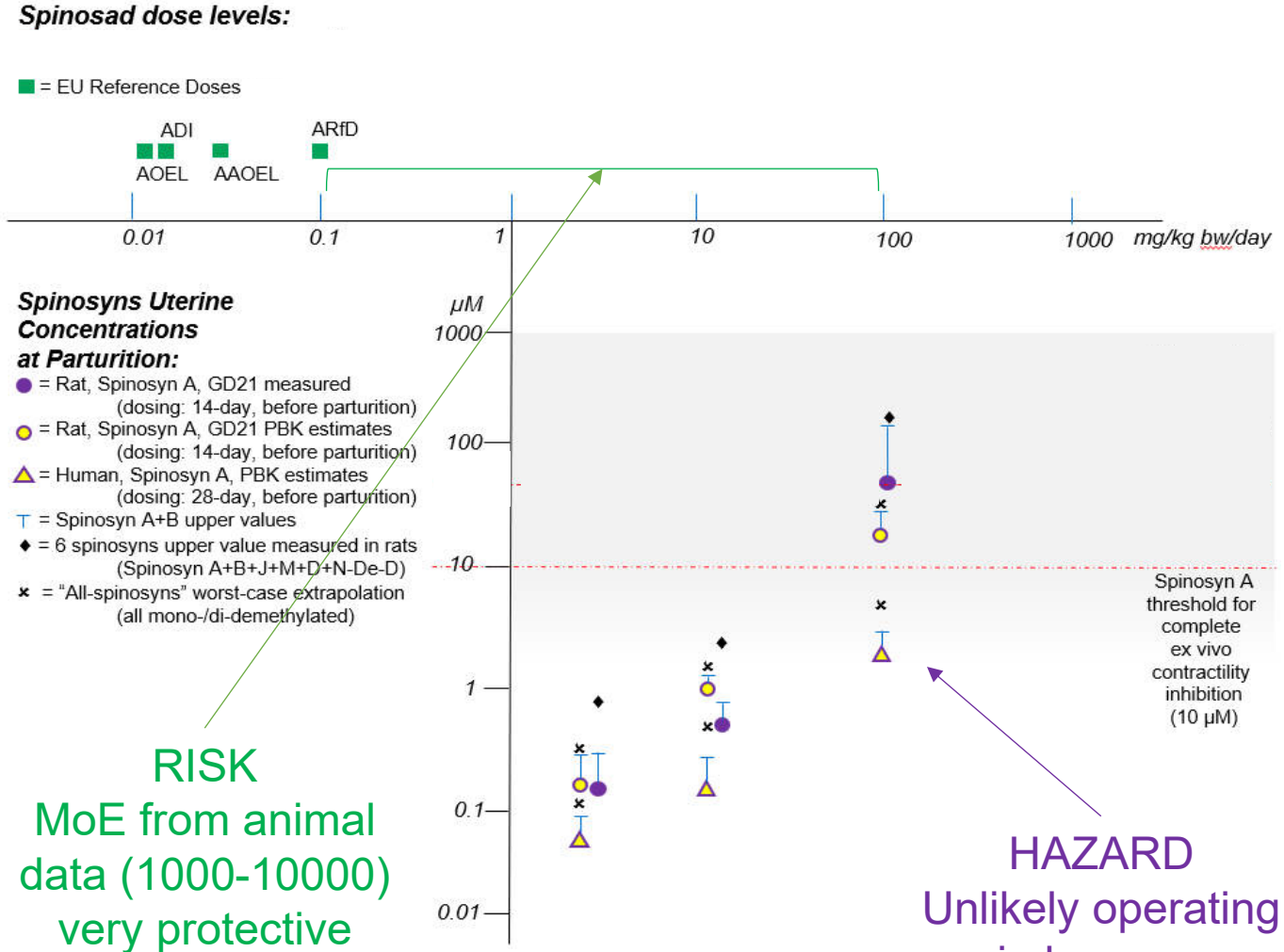
Bridging Higher Tier Kinetics and Exposure Information into Human Hazard Characterization and Risk Assessment

Rat (●) and human (△) PBK model, based on OECD 331, allow qIVIVE

- Rat experimental data (●)

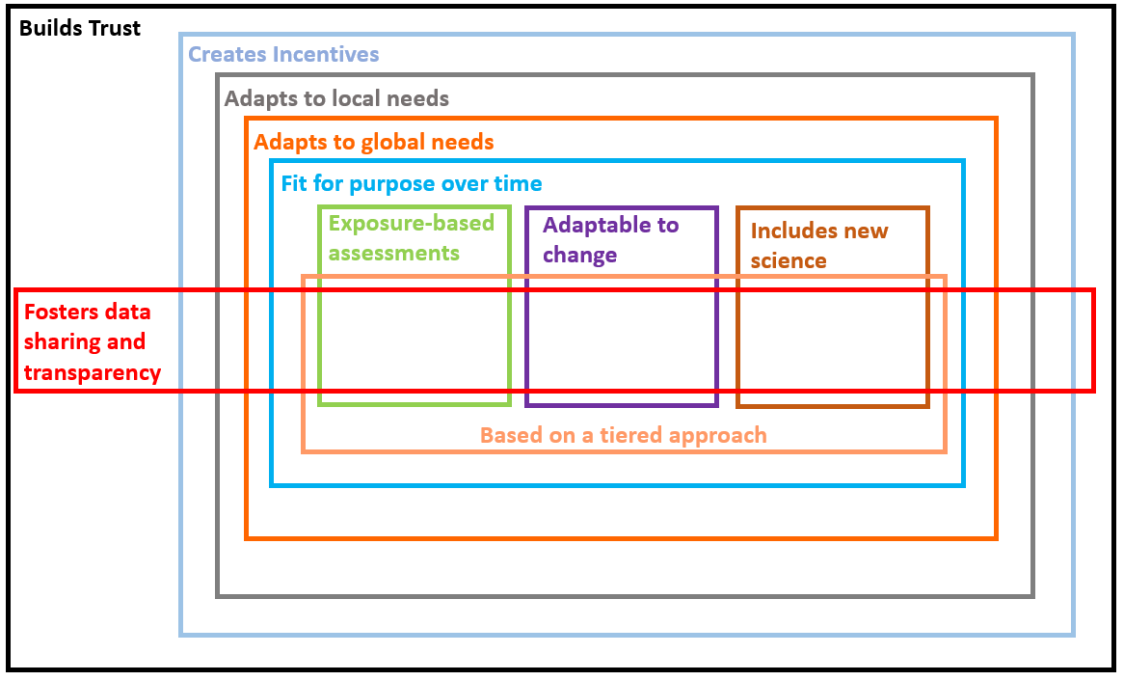
- Human hazard characterized
- Human risk characterized (led by other endpoints)

- if we did not have the animal data (NOAELs)
  - ***Would hazard and risk for humans be still characterized?***
  - ***Would we still be able to classify without observing "The adverse effect"?***



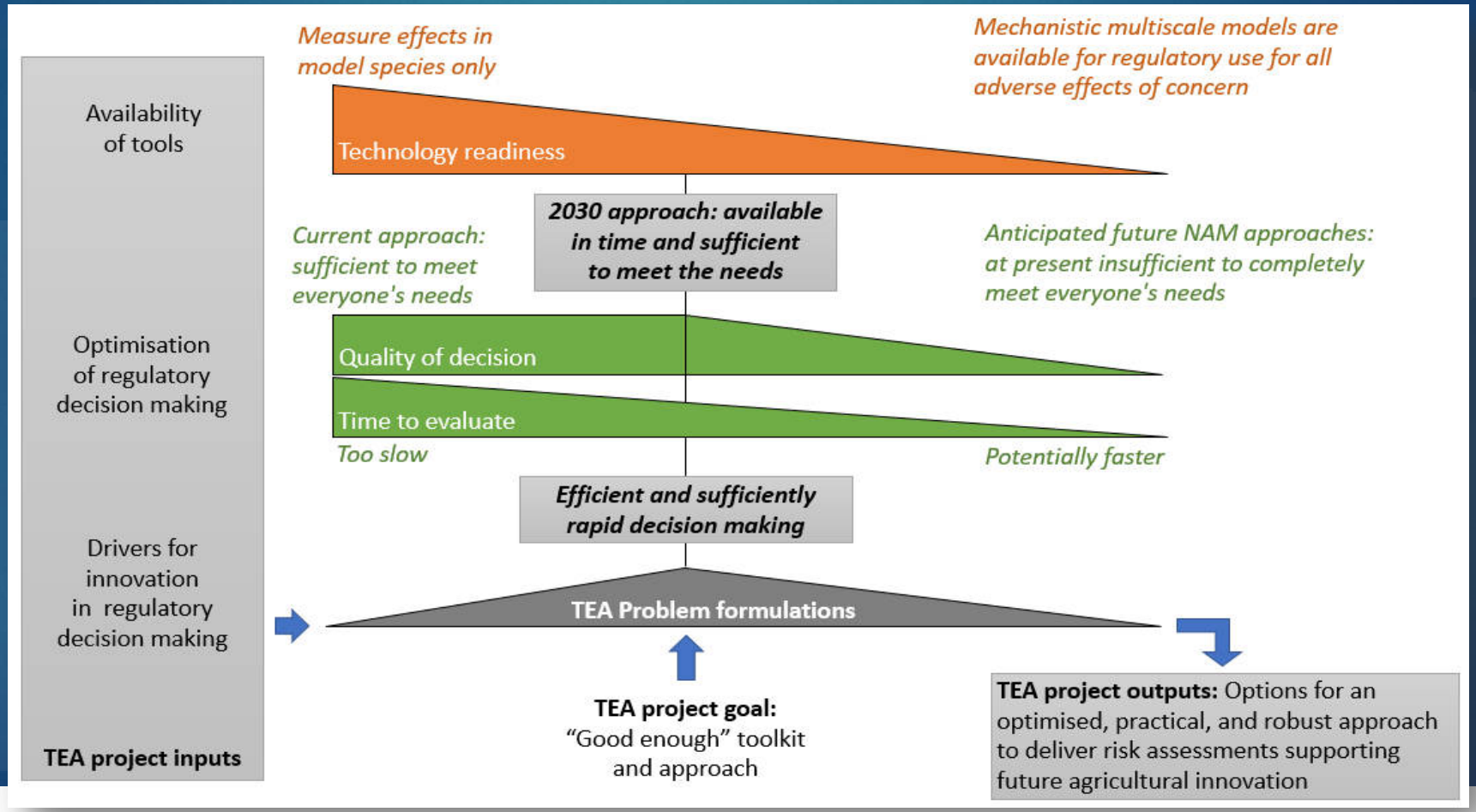
Manuscript #2

- Focused on:
  - The conceptual model
  - Commonalities among different jurisdictions regarding the safety evaluation of agrochemicals
- In progress



Expected Output

A "Good enough toolkit" leading to the efficient implementation of a robust and rapid decision-making process.



Thank You!

- The entire TEA Committee and all our sponsors
- **Special thanks to the TEA Committee Steering Team**
  - Yad Bhueller (PMRA)
  - Rhian Cope (APVMA)
  - Marco Corvaro (Corteva)
  - Richard Currie (Syngenta)
  - John Doe (Liverpool John Moores University)
  - Gina Hilton (PIS Inc.)
  - Tina Mehta (ADAMA)
  - Maria Trainer (APVMA)
  - Doug Wolf (Syngenta)

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