Agrochemical perspectives on utility of micro physiological systems

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Current Role

General and Genetic Toxicology Leader
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Newark, DE, USA

Education

Veterinary Medicine, ANGRA University, India

PhD in Toxicology, University of Missouri

DABT

1.External Activities

2.Grants reviewer: CEFIC LRI, ARDF, Parkinsons Foundation

3.Editorial member and reviewer for Toxicology and Pharmacology journals

4.BIAC lead for genetic and immune toxicology

5.Expert group for OECD defined approaches for skin sensitization

6.

7.HESI GTTC member

8.CAAT Advocacy Board member

Outline

- Brief overview on global testing requirements in Ag sector
- Current and projected applications of MPS models for advancing safety testing
- Challenges for wider adoption

Toxicity Testing of Agrochemicals

- Pesticides are extensively examined for determination of safety prior to registration to evaluate:
  - Human Health from workers to acute and lifetime dietary exposures in crop
  - Environmental fate in soil, air, water, food chain
  - Ecological safety assessment: Fish, birds, plants, invertebrates, and many other species

Development of Crop Protection Products

Resource intensive:

- It takes 11.8 years and $286 million to research, develop and register a new crop protection product

Tightly regulated:

- Only 1 in 139,000 chemicals successfully progresses through the regulatory process from the laboratory to the field
- A product undergoes >100 rigorous studies to support the health, safety and environmental assessments required for registrations
- From a mammalian toxicology perspective, pesticides have the most comprehensive data requirements of any chemical sector

www.croplifeamerica.org/crop-protection/pesticide-regulation

Development phase - Standard Toxicology Battery

Current global regulatory frameworks require extensive *in vivo* testing. NAMs are being applied whenever qualified procedures are available

• Acute toxicity	Rat, Mouse, *In vitro*
• General toxicity	Rat, Mouse, Dog
• Carcinogenicity	Rat & Mouse
• Developmental toxicity	Rat & Rabbit
• Reproductive toxicity	Rat
• ADME	Rat
• Genetic toxicity	Rat, Mouse, *In vitro*
• Neurotoxicity	Rat
• Immunotoxicity	Rat, Mouse
• Mode of Action	Rat, Mouse, *In vitro*

Required for active ingredient and end-use formulations

Bridging to the Future

Past approaches

Animal intensive

Assume relevance to humans

Descriptive, reactionary

Our committment

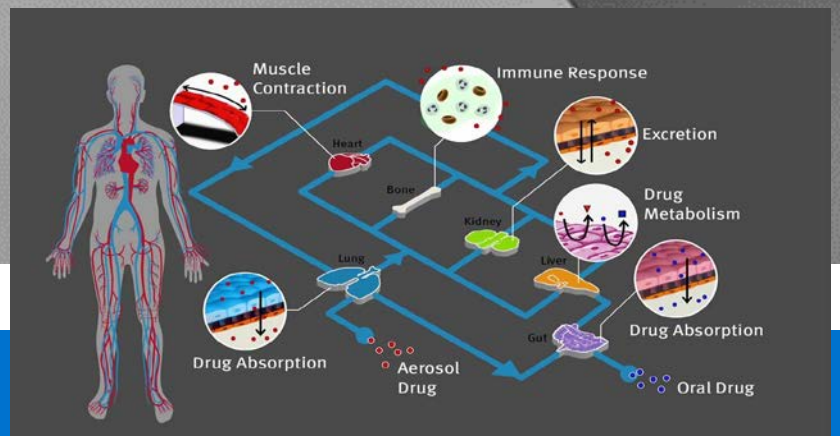
I. Committed to the principles of the 3Rs
II. Exposure-based toxicity testing
III. Integrated testing strategies

Future vision

Elimination of animal testing

Mechanism-focused

Human relevance



MPS models

- Great progress from proof-of-concept studies to actual implementation in:
  - Early discovery screens
  - Mechanistic profiling of molecules
  - Rare disorders and complex diseases
  - Implementation in precision medicine

MPS-based organ/tissue model	Area of use (drug development phase)	MPS-supplier	Reference (if available)
Blood vessel, vasculature	Target identification, validation and compound selection	AIST	Satoh et al., 2016
	Discovery (scleroderma)	Mimetas	–
	Systems toxicology for consumer products	Mimetas	Poussin et al.,2020
	Pharmacokinetics and pharmacology	Mimetas	–
	Target identification and validation	Mimetas	–
Bone marrow	Preclinical safety	TissUse	Sieber et al., 2018
	Preclinical safety	Emulate	Chou et al., 2018
	Preclinical safety	TissUse	–
	Preclinical safety	TissUse	–
Gut epithelium	Discovery (inflammatory bowel disease)	Mimetas	Beaurivage et al., 2019
	Discovery	Mimetas	–
	Clinical development	Mimetas	–
	Preclinical safety	Emulate	–
Lung	Discovery (alveolus)	Wyss	Huh et al., 2012
	Drug efficacy (epithelium)	Wyss	Benam et al., 2016b
	Preclinical safety	Emulate	–
Liver	Pharmacological and toxicological effects	Emulate	Foster et al., 2019
	Preclinical safety – assessment of species (rat, dog & human)	Emulate	Jang et al., 2019
Ocular compartment	Discovery	Fh IGB / EKUT	Achberger et al., 2019
Kidney epithelium	Pharmacokinetics and pharmacology	Mimetas	Vormann et al., 2018
Liver-Pancreas	Target validation / identification	TissUse	Bauer et al., 2017
Liver-Thyroid	Preclinical safety – assessment of species-specificity (rat and human)	TissUse	Kühnlenz et al., 2019
Skin-Tumor	Preclinical safety & efficacy	TissUse	Hübner et al., 2019

Adopted from Marx et al., 2020

Application of MPS models for agrochemical testing

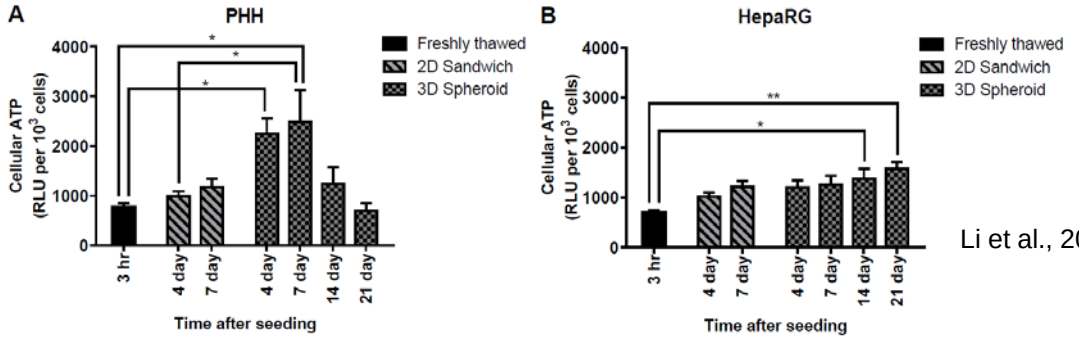
- Micro physiological models of healthy human, rodent or dog models to evaluate
  - Physiological crosstalk of the organ models and
  - Test primary and secondary toxicity of compounds

- Applications:
  - Early-stage screening
  - Hazard assessment
  - Assessment of Mode of Action and Human relevance of effects
  - Toxicokinetic applications

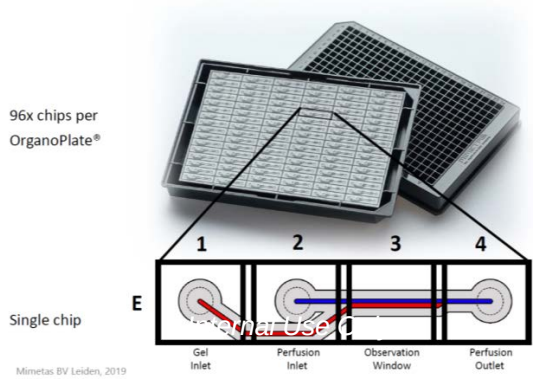
Applications: Early-stage screening

- Early-stage screening to select best candidates from the promising analogs
- Support better informed decisions and may substitute screening *in vivo* studies for some endpoints
- Liver and kidney are primary target organs for agrochemicals
  - Currently validating liver and kidney organ-on-chip models to predict *in vivo* toxicity

Hepatic cultures

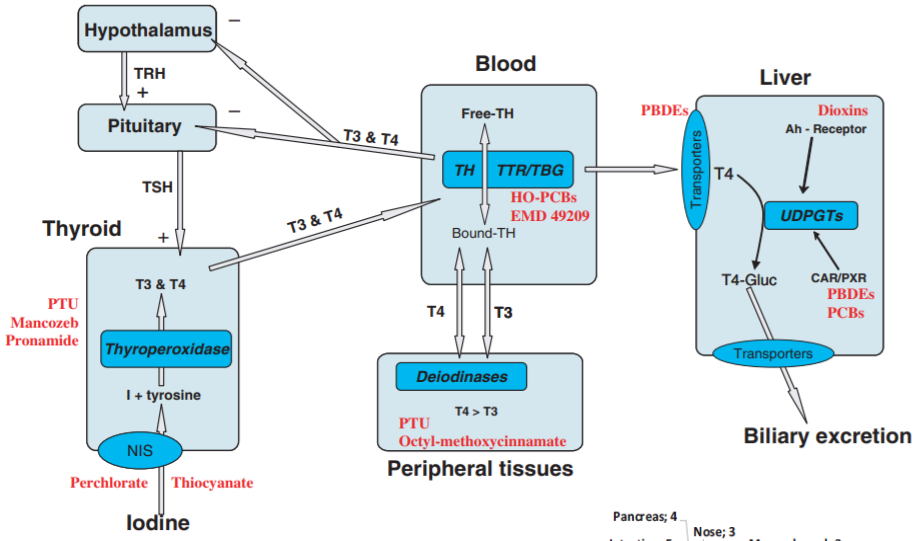


Li et al., 2019



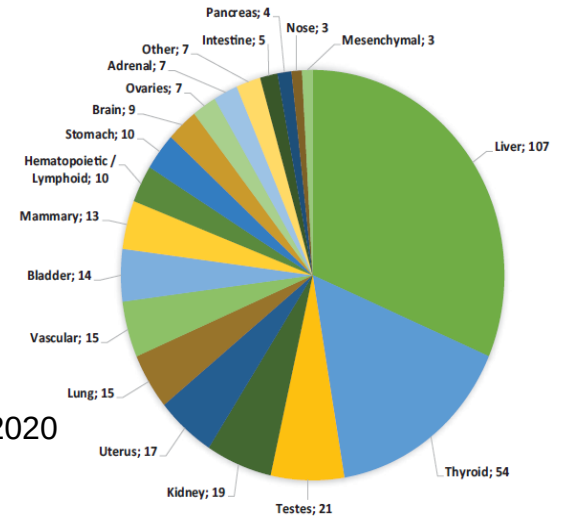
Applications: Hazard assessment

- To better characterize hazard following shorter- or longer-term exposures
  - Evaluate the time course of toxicity responses and recovery
  - Biological read across approaches



- To improve mechanistic understanding
  - Specific target toxicity (e.g. thyroid toxicity)

- Support the transition towards a mechanism-based WoE approach to enhance the prediction of carcinogenic potential
  - Require cross-talk between various organ systems and pathways
  - Complex models to identify various non-genotoxic carcinogenesis mechanisms
  - Integration of PoD assessment via omics, cell painting etc

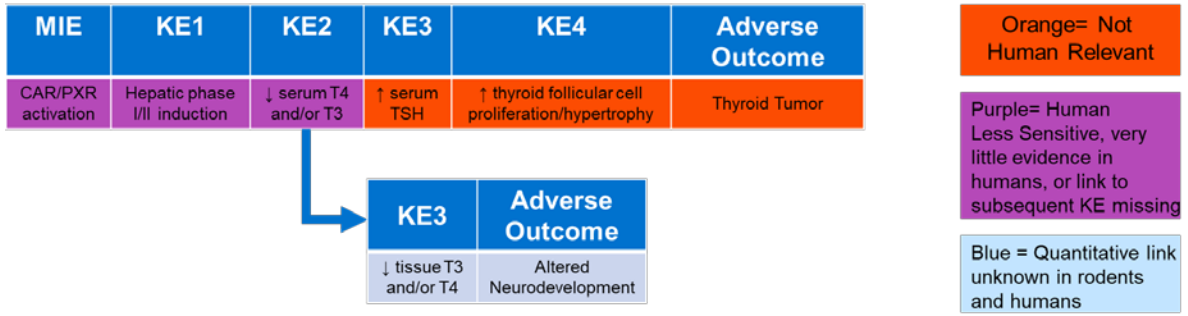


Heusinkveld et al., 2020

Figure 3. Organ distribution of all 340 observed treatment-related tumors with a suspected nongenotoxic MOA. The category "Other" includes bone, skin, eye, and prostate tumors.

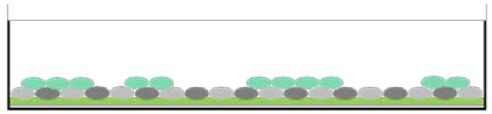
Applications: Assessment of Mode of Action and Human relevance of effects

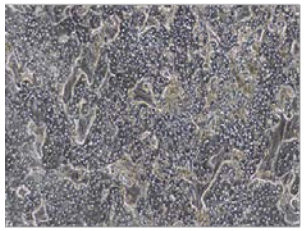
- Toxicological responses could differ between *in vivo* models and humans
  - E.g., Difference in sensitivity to thyroid toxicity between rodents and humans

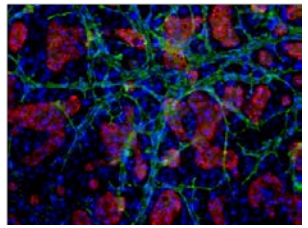


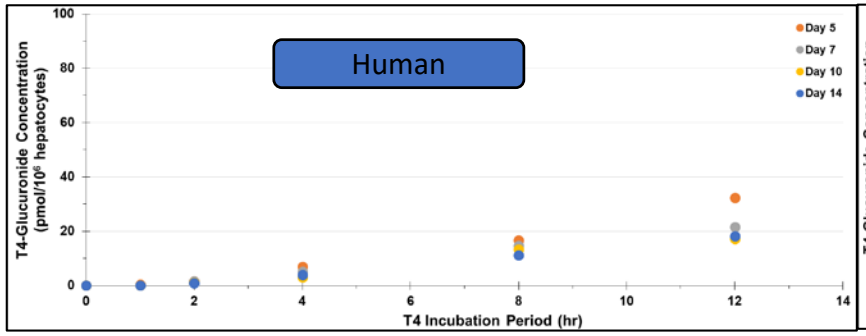
Human relevance purple & blue color-coding based on conclusions from Sauer et al. (2020) Crit. Rev. Toxicol.

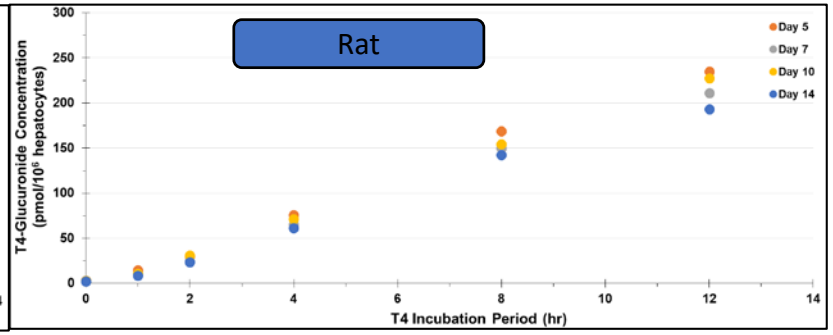
- T4-Glucuronide formation was higher (~5-10-fold) in the rat cultures compared to human cultures











- Development of human and rodent hypothalamus-Pituitary-Thyroid-Liver MPS models could help to further decipher species sensitivities

Applications: Assessment of Mode of Action and Human relevance of effects

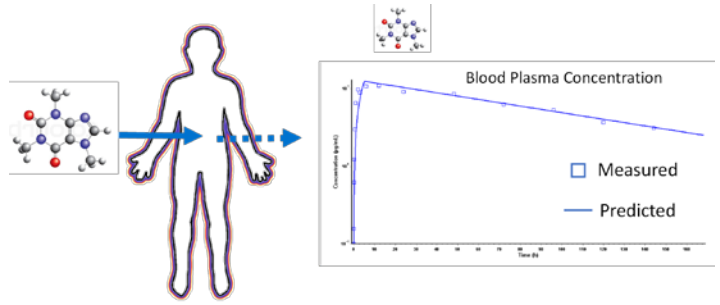
- Selection of appropriate nonrodent species for toxicological testing

  - A cross-species multi-organ MPS models for prediction of organ toxicity and human relevance of effects
    - Valuable when knowledge about the mode of action of the compound is well characterized
    - Characterization of species-specific TK or TD differences to support decisions
    - Could aid in study waivers when they offer little additional scientific information for safety assessment
      - E.g., Waivers for dog testing

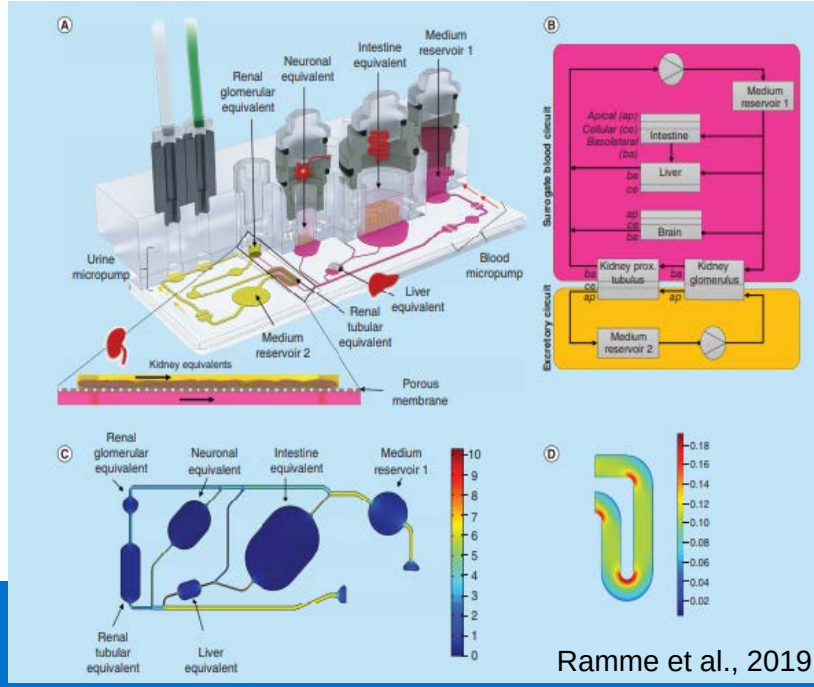
  - Micro physiological liver chip models recapitulated species-specific drug toxicity in a rat, dog and human MPS model (Jang et al., 2019)

Toxicokinetic Applications

- MPS models consisting of
  - Functional absorption barrier (intestine, skin or lung equivalents),
  - Metabolically competent human liver model and
  - Functional excreting kidney equivalent may generate compound-specific ADME profiles



- Potential applications:
  - Improve *in vitro* comparative metabolism assessment via longer-term exposures
  - Earlier or better characterization of species-specific TK or TD differences
  - Metabolite identification in effluent and target tissue
  - Develop route to route extrapolation
    - Better prediction of systemic exposures and to refine the risk assessment



Ramme et al., 2019

Opportunities to increase adoption

- For wider adoption, require
  - Further refinement to recapitulate complex *in vivo* interactions
  - Additional qualification with known controls (with wider potencies)
  - Establish uniform criteria for test systems
    - e.g., level of differentiation of cells, quality and source of cells etc.
  - Develop criteria for testing and data interpretation
  - Reproducibility of results and increase awareness on their utility
  - Partnership between academia, industry and global regulatory bodies

Conclusions

- MPS models could be applied at various stages of molecule development to improve toxicity profiling of agrochemicals
  - Shorter-term: Early-stage screening, Hazard and MoA assessment, Toxicokinetic applications
  - Longer-term: Recapitulate complex *in vivo* systems and support replacing *in vivo* studies

Thank you!