Moving Away from Animal Models for Toxicity Testing

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Agency for Toxic Substances and Disease Registry • Consumer Product Safety Commission • Department of Agriculture
Department of Defense • Department of Energy • Department of the Interior • Department of Transportation
Environmental Protection Agency • Food and Drug Administration • National Institute for Occupational Safety and Health
National Institutes of Health • National Cancer Institute • National Institute of Environmental Health Sciences
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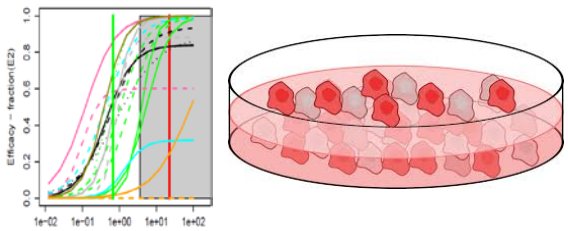
Understanding Human Physiology

A detailed knowledge of human physiology will enable pathways-based approaches to be used for human health assessment.

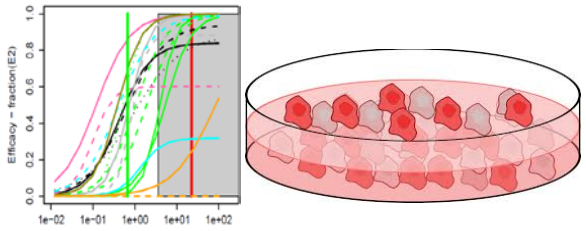
Until human pathways are sufficiently mapped, animal studies will continue to represent the “Gold Standard”.

How do we measure success?

- How do you validate human-based approaches against animal models that are not predictive of human outcomes?
- Should we use rodent-based approaches to predict rodent toxicity in order to establish confidence in new methods / technologies?



Rodent In Vitro



Human In Vitro

Human In Vivo

Rodent In Vivo

Moving away from animal data: near-term

- Concordance between in vitro / computational approaches and animal outcomes is increased by using high quality data (both in vitro and in vivo)
  - Access to high quality animal data are a limiting factor
- Hold animal models to the same standards as alternatives (data quality, variability and reproducibility)
- Characterize the impact of animal model variability on regulatory decisions (retrospective analysis)

Moving away from animal data: near-term

- This approach works best for acute toxicity endpoints

1 Species

LD50

1 Well-Defined Endpoint

Guideline Number	Study Type	Food Use	Non Food Use
870.1100	Acute Oral – Rat	Required	Required
870.1200	Acute Dermal	Required	Required
870.1300	Acute Inhalation – Rat	Required	Required
870.2400	Primary Eye Irritation – Rabbit	Required	Required
870.2500	Primary Dermal Irritation – Rabbit	Required	Required
870.2600	Dermal Sensitization	Required	Required
870.6200	Acute Neurotoxicity – Rat	Required	Required
870.6100	Acute and Delayed Neurotoxicity - Hen	CR	CR
870.3100	90-Day Oral – Rodent (Rat/Mouse)	Required	CR
870.3150	90-Day Oral– Non Rodent (Dog)	Required	CR
870.3200	21/28-Day Dermal	Required	NR
870.3250	90-Day Dermal	CR	Required
870.3465	90-Day Inhalation – Rat	(CR)	CR
870.6200	90-Day Neurotoxicity - Rat	Required	Required
870.4100	Chronic Oral- Rat	Required	CR
870.4200	Carcinogenicity - Mouse	Required	CR
870.4200	Carcinogenicity –Rat	Required	CR
870.3700	Prenatal Developmental – Rat	Required	Required
870.3700	Prenatal Developmental – Rabbit	Required	Required
870.3800	Reproduction & Fertility Effects	Required	Required
870.6300	Developmental Neurotoxicity	CR	CR
870.5100	Bacterial Reverse Mutation Assay	Required	Required
870.5300/ .5375	In Vivo Mammalian cell Assay	Required	Required
870.5385/ .5395	In Vitro Cytogenetics	Required	Required
870.7485	Metabolism & Pharmacokinetics	Required	CR
870.7200	Companion Animal Safety	CR	CR
870.7600	Dermal Penetration	CR	CR
870.7800	Immunotoxicity	Required	Required

Kun Don Yi, Syngenta Crop Protection LLC

Regulatory Guideline Studies

These studies are required by law for the registration of an active ingredient

6K-14K animals per active ingredient*

*informal survey of stakeholders

Moving away from animal data

- Will ultimately will need a comparison to human data
  - Access to large amounts of high quality human toxicological data will be critical but is currently not available

Traditional approaches to validation often rely on comparing data obtained from a new method/strategy with results from an existing animal-based test. This becomes problematic for toxicity tests that have species-specific biases and also precludes any new test from performing "better" than the animal test, as any discordance will be assessed in favor of the existing method. In the absence of sufficient human data, how can new methods be validated as having equivalent (or better) performance than the animal-based test without a direct comparison to data from the animal test intended for replacement?

Is there a place in our current paradigms to begin to apply a fundamental non-animal strategy that allows prospective validation without compromising near term human safety?