Application of the RISK21 framework as a decision and communication support tool to inform project risk and business decisions

Dr David Cowie - SOT Symposium Presentation - March 2020

Crop protection products are among the most highly regulated of all man-made chemicals

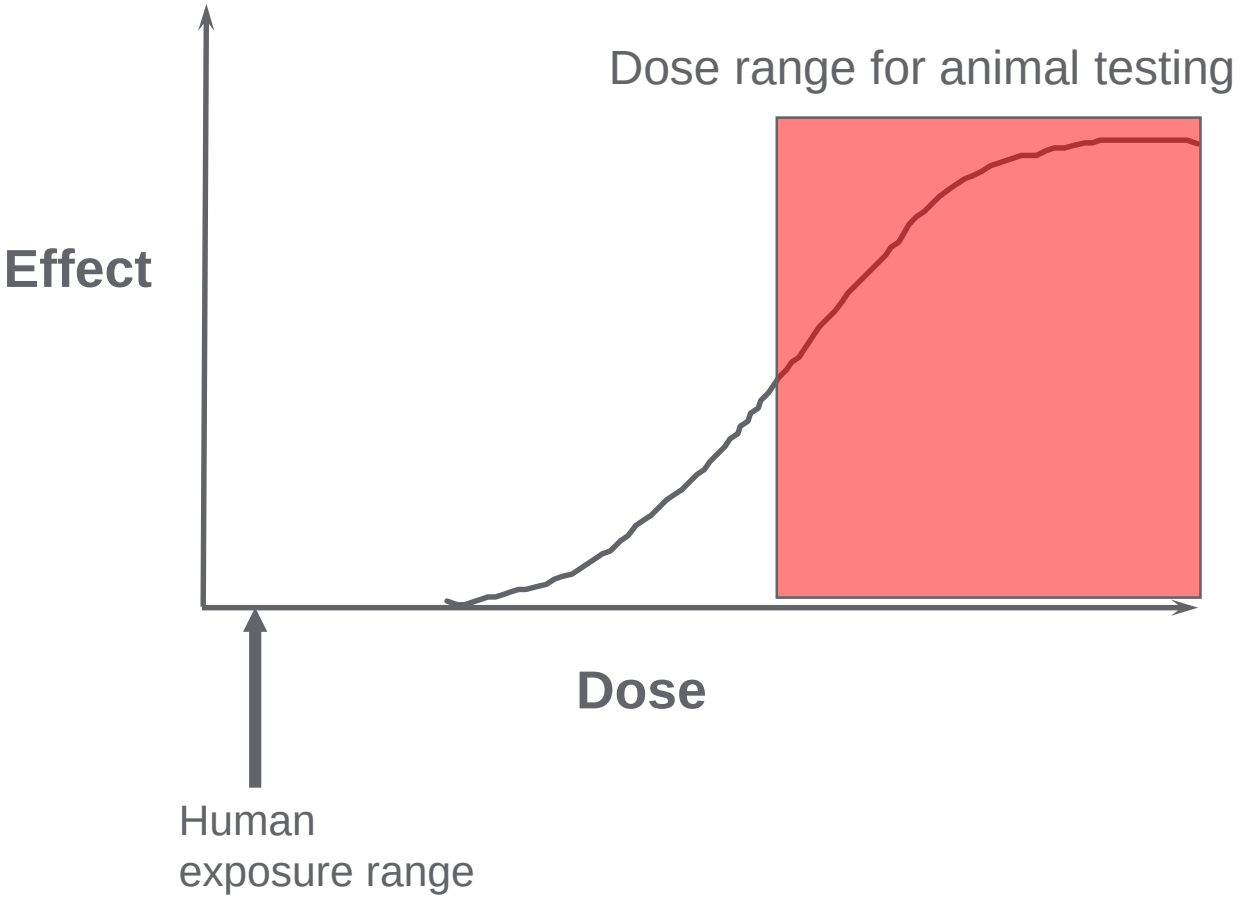
- The primary focus of the Regulators is ensuring operator, worker, bystander, consumer and environmental protection
  - The assumption is that all population groups have the potential for exposure

- Regulations include assessments of all aspects of human health, environmental and dietary exposure.

- Regulators check and verify both
  - the calculated acceptable doses (risk)
  - the predicted amounts of pesticide exposure
  - the hazard profile

- Every regulatory submission is fully reviewed by each relevant governing body and permission to market in a country is ONLY given following full regulatory clearance

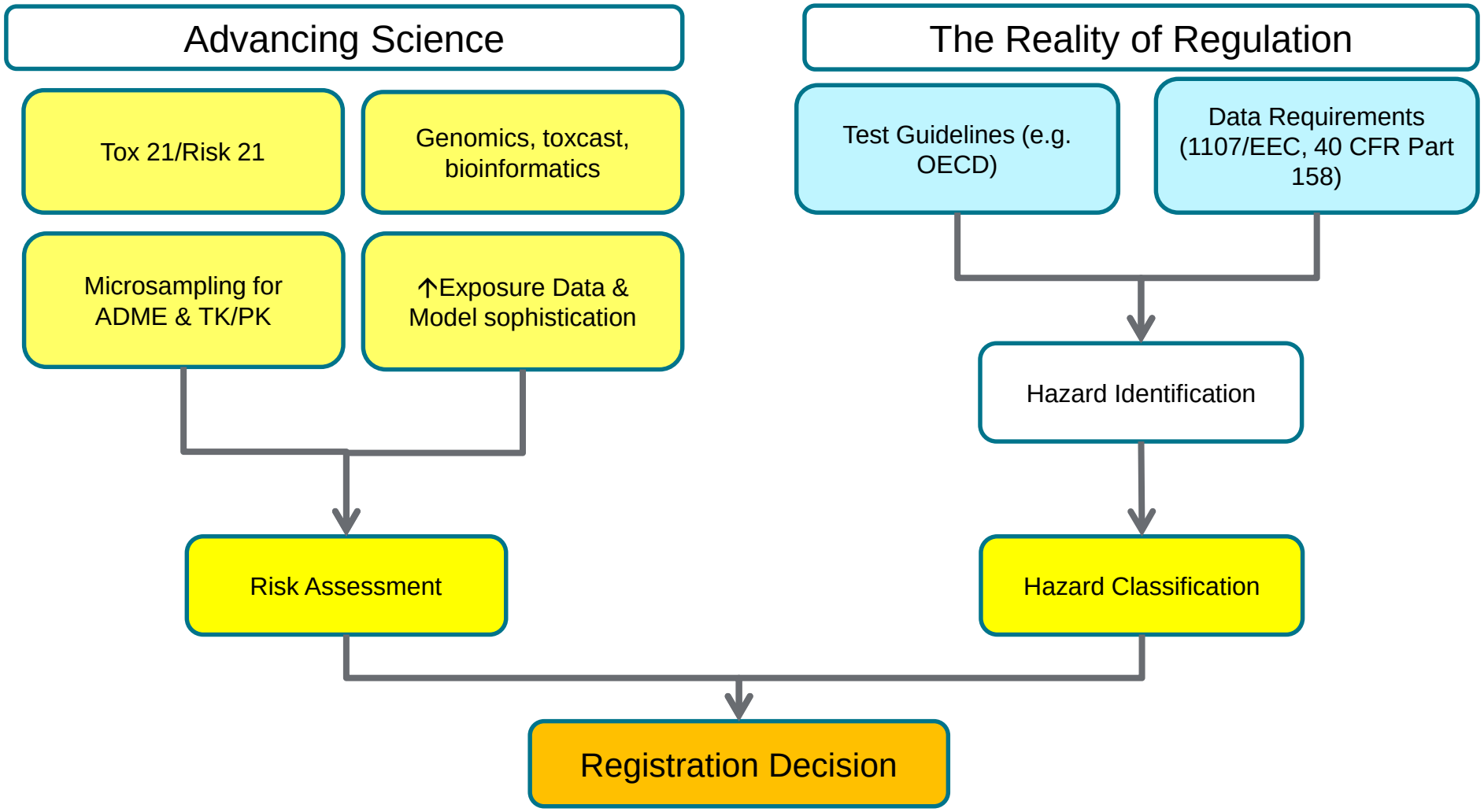
A Question of Relevance - the Testing Paradigm for Pesticides



Test Guideline Philosophy

- Generally, guidelines aim to maximise the ability to detect hazard
  - Guidelines are universal - applicable to all chemicals.
  - For a non-toxic chemical, the top dose should be the limit dose for that particular study guideline
    - Usually a 1000 mg/kg bw/day for repeat dose studies
    - Paradoxically – if in development you aim to design an intrinsically safer AI *eg by identifying target-specific modes of action resulting in compounds of low mammalian toxicity* – they then can be dosed up to limit doses.
  - For compounds causing toxicity, the top dose used in studies should be based on evidence of dose limiting target organ toxicity or demonstrable deficits in body weight gain compared to concurrent controls – the “MTD approach”

This Leads to a Fundamental Disconnect Between What is Required and What Modern Science Can Deliver:

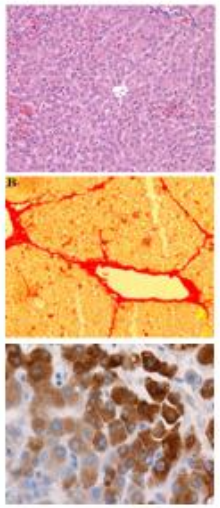


This Leads to a Fundamental Disconnect Between What is Required and What Modern Science Can Deliver:

Example: Some Methodologies for MoA Assessment

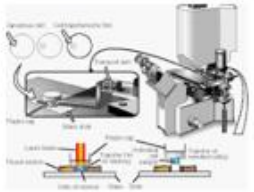
Many types of technology developed:

Histopathology / IHC

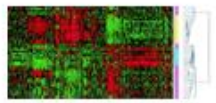


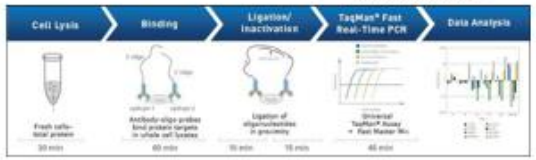
Tissue Fixation

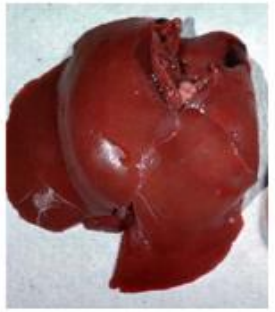
LCMD



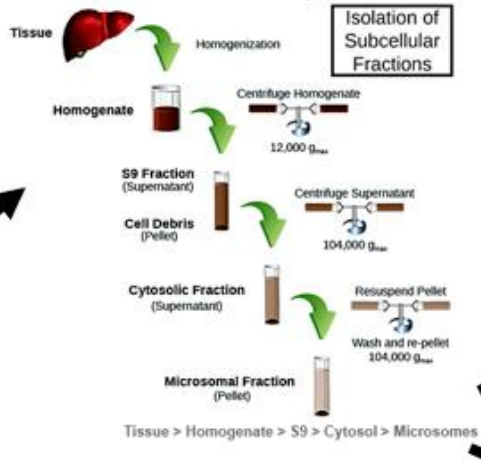
RT-PCR / Microarray / RNASeq



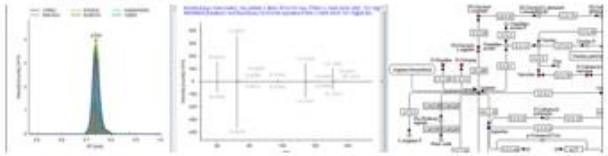




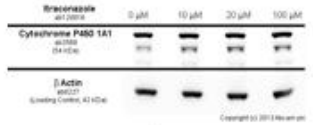
Microsomal Preparations



'omics Analysis

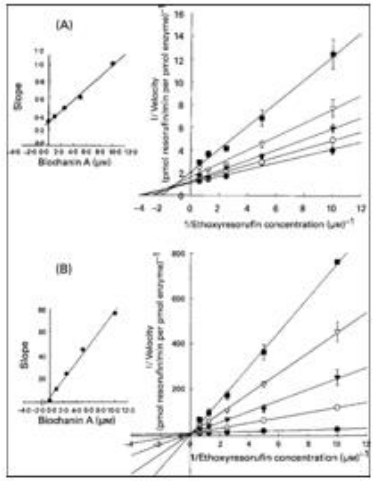


Western Blot



Total Protein

Enzymatic Assays (P450)



syngenta

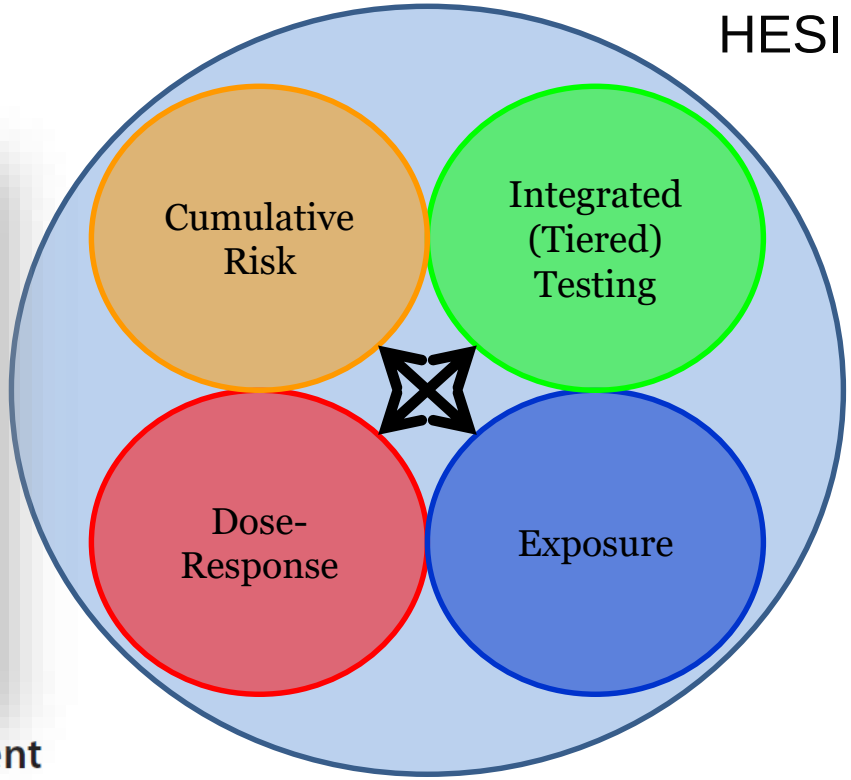
The RISK21 Project

www.risk21.org

www.hesiglobal.org

HESI

MISSION:
Bring applicable, accurate, and resource appropriate approaches to the evolving world of human health risk assessment



A 21st century roadmap for human health risk assessment

Timothy P. Pastoor[1], Ammie N. Bachman[2], David R. Bell[3], Samuel M. Cohen[4], Michael Dellarco[5], Ian C. Dewhurst[6], John E. Doe[7], Nancy G. Doerrer[8], Michelle R. Embry[8], Ronald N. Hines[9], Angelo Moretto[10], Richard D. Phillips[2], J. Craig Rowlands[11], Jennifer Y. Tanir[8], Douglas C. Wolf[9]*, and Alan R. Boobis[12]

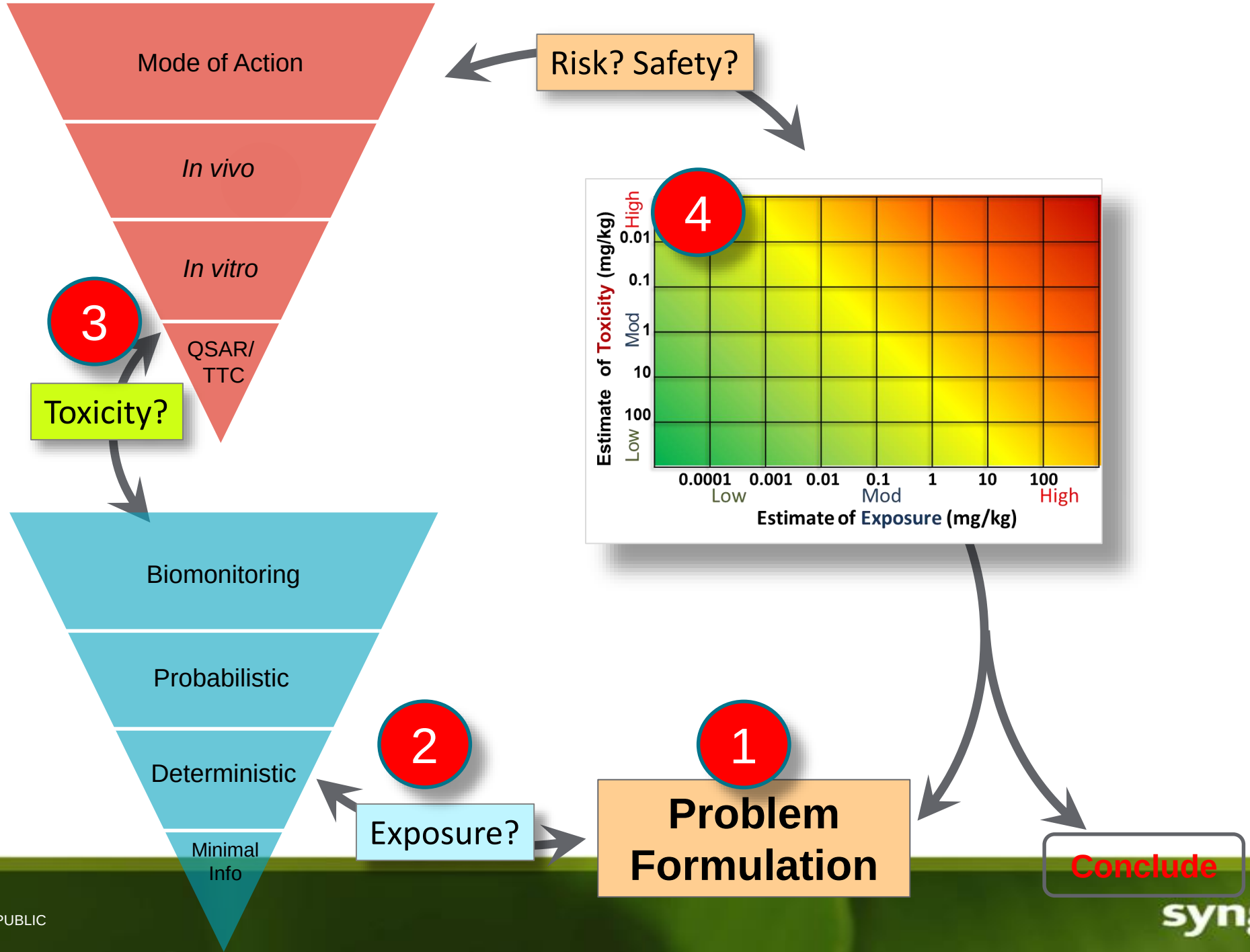
Crit Rev Toxicol, 2014; 44(S3): 1–5

Risk assessment in the 21st century: Roadmap and matrix

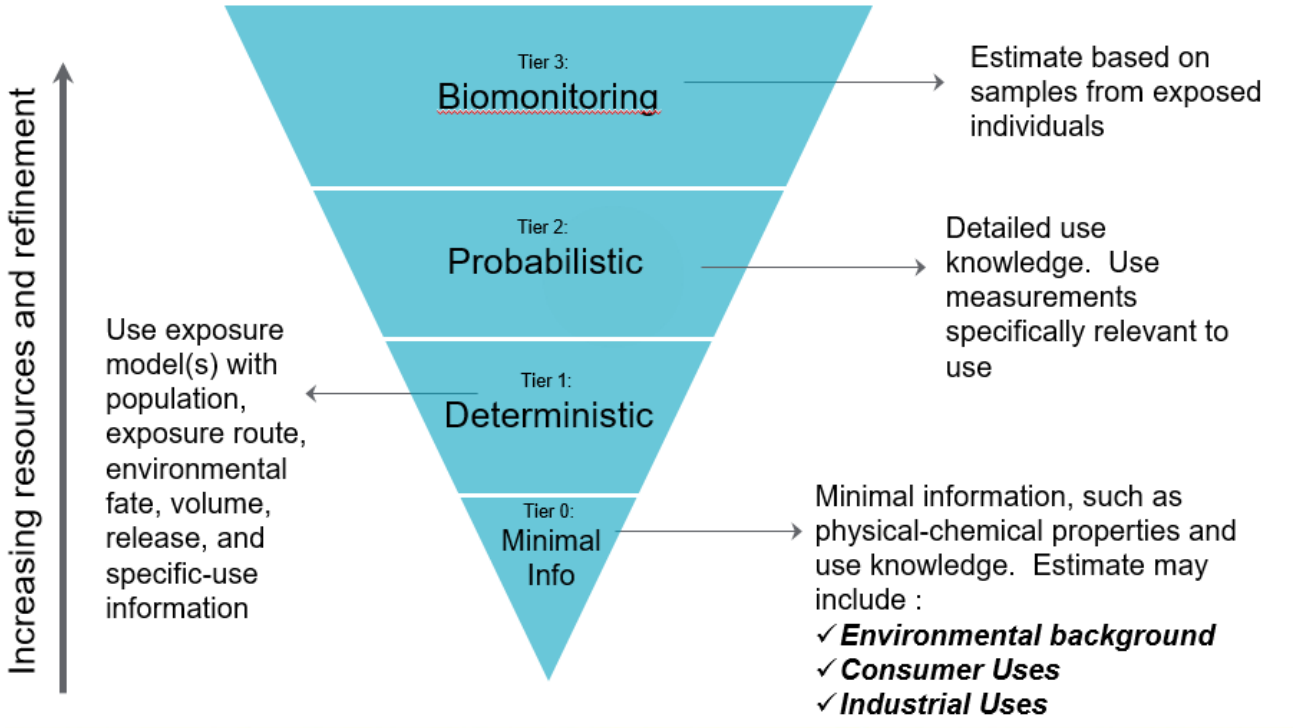
Michelle R. Embry[1], Ammie N. Bachman[2], David R. Bell[3], Alan R. Boobis[4], Samuel M. Cohen[5], Michael Dellarco[6], Ian C. Dewhurst[7], Nancy G. Doerrer[1], Ronald N. Hines[8], Angelo Moretto[9], Timothy P. Pastoor[10], Richard D. Phillips[2], J. Craig Rowlands[11], Jennifer Y. Tanir[1], Douglas C. Wolf[8]*, and John E. Doe[12]

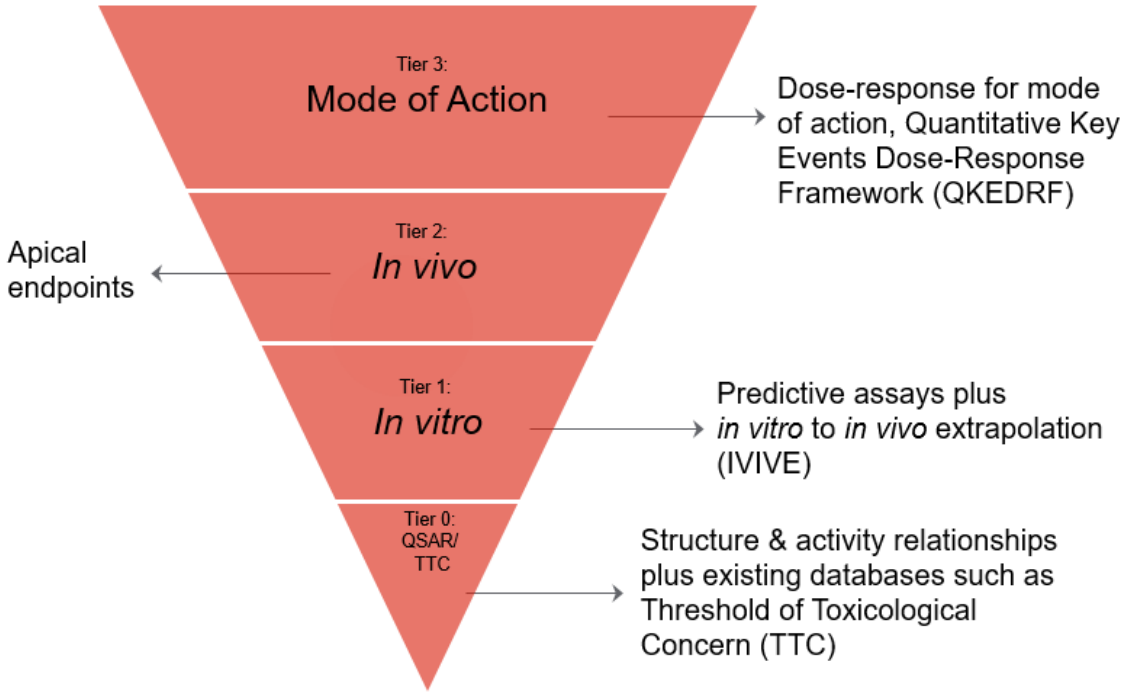
Crit Rev Toxicol, 2014; 44(S3): 6–16

syngenta



Enough Precision for Exposure & Toxicity Estimation





Chemical Research R&D Involves Many Different Activities and Phases

Depending on the project question:

- Type of decision to make.
- Level of precision required.
- Speed with which to make decisions.

Profile
~5000 compounds

Evaluate
~30

Differentiate Chemical Series With Best Chance of Success

Optimise
~5

Select Candidates with Optimal Safety Profile

Develop
1

PredictSafety and Registrability

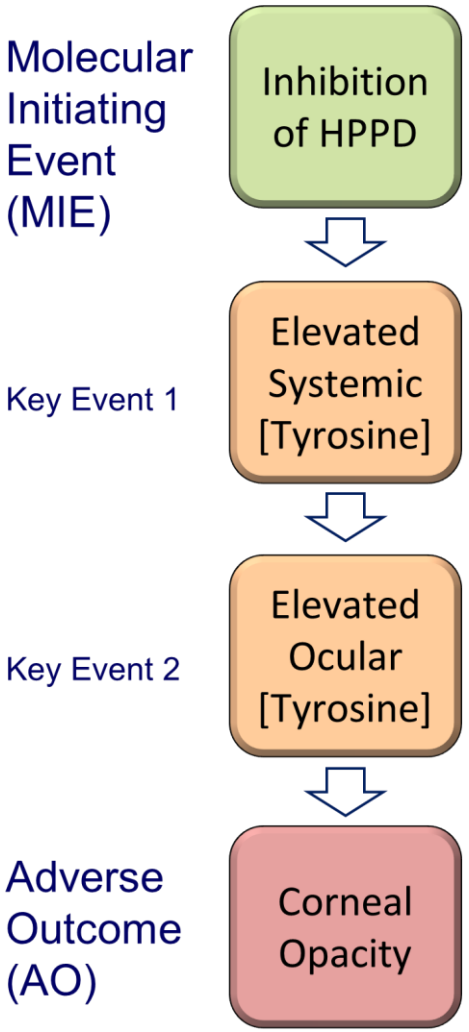
Prioritisation of Chemical Series Using a Risk 21 Framework

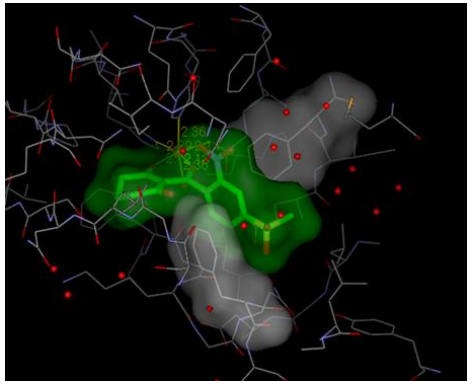
Problem Statement:

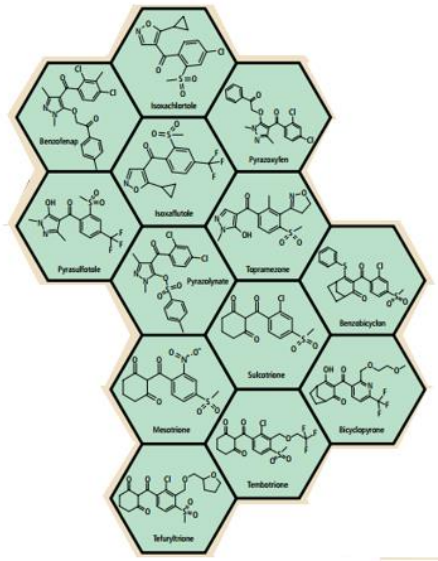
How do you differentiate chemical series and prioritise testing to assess consumer risk for a pre/e-post emergence soybean herbicide project?

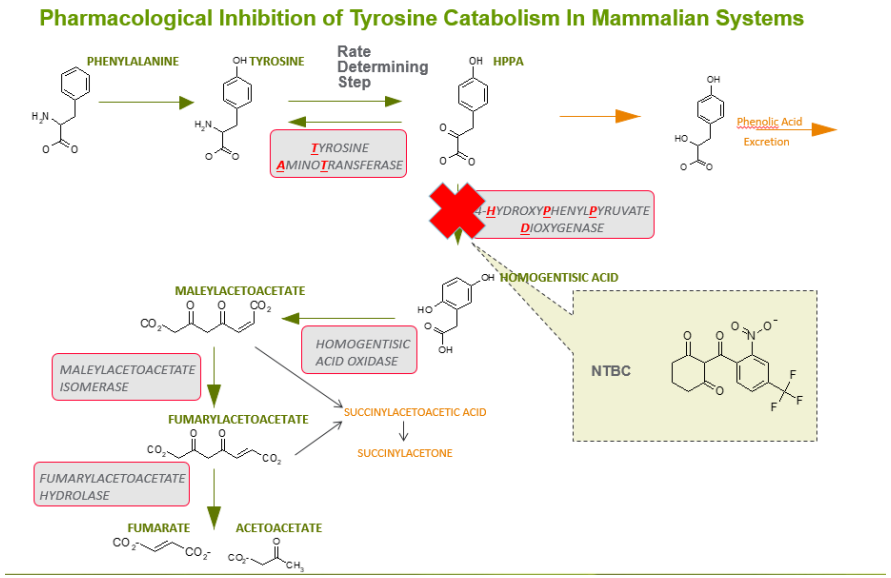
Scenario Knowledge:

- Known mode of action: 4-Hydroxyphenylpyruvate Dioxygenase Inhibition (HPPD)
- Extensive knowledge of MoA & use patterns
- No absolute chemical exposure data
- *Some* estimation of series specific toxicity

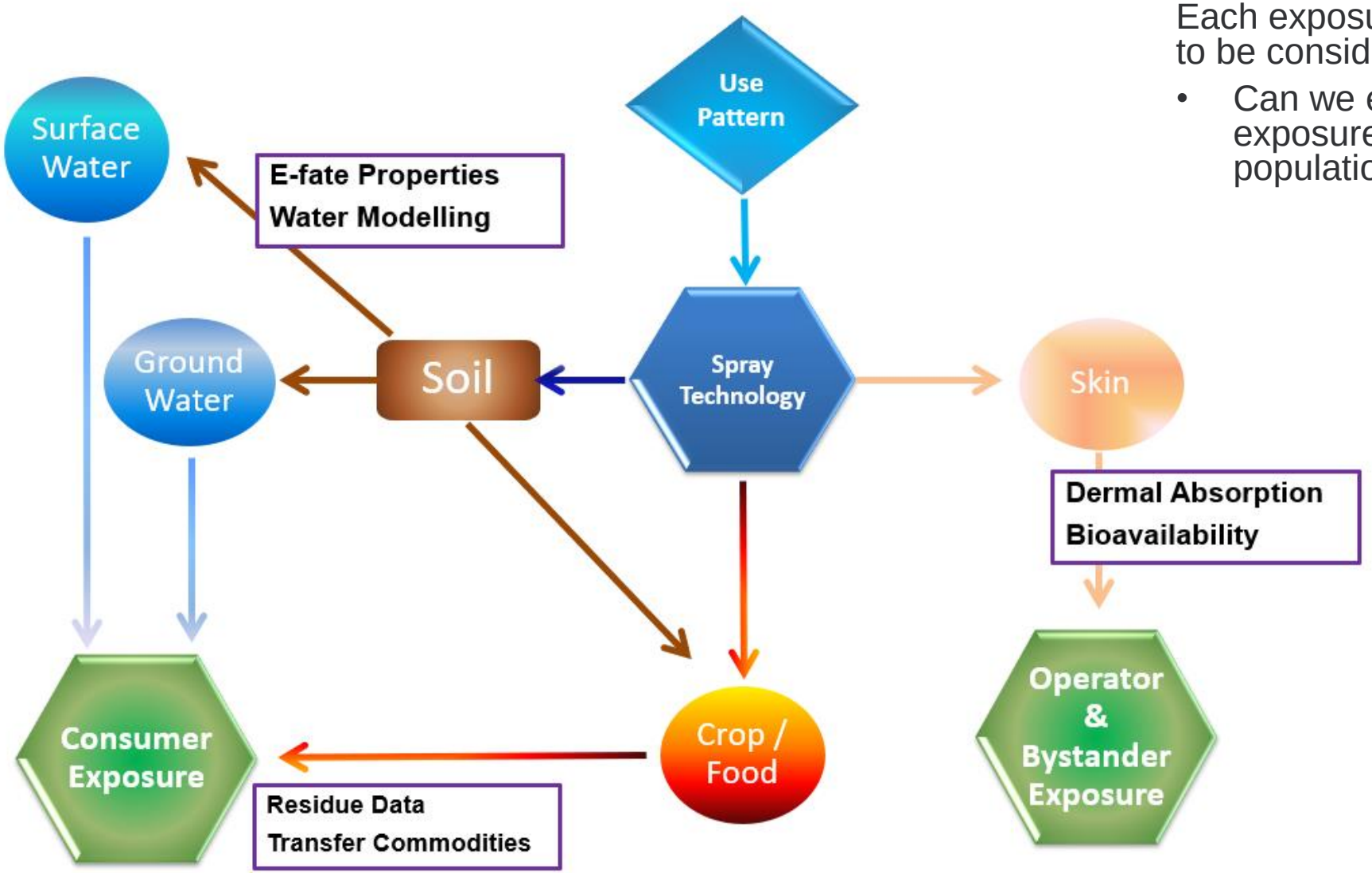








A Conceptual Model of Exposure Scenarios:



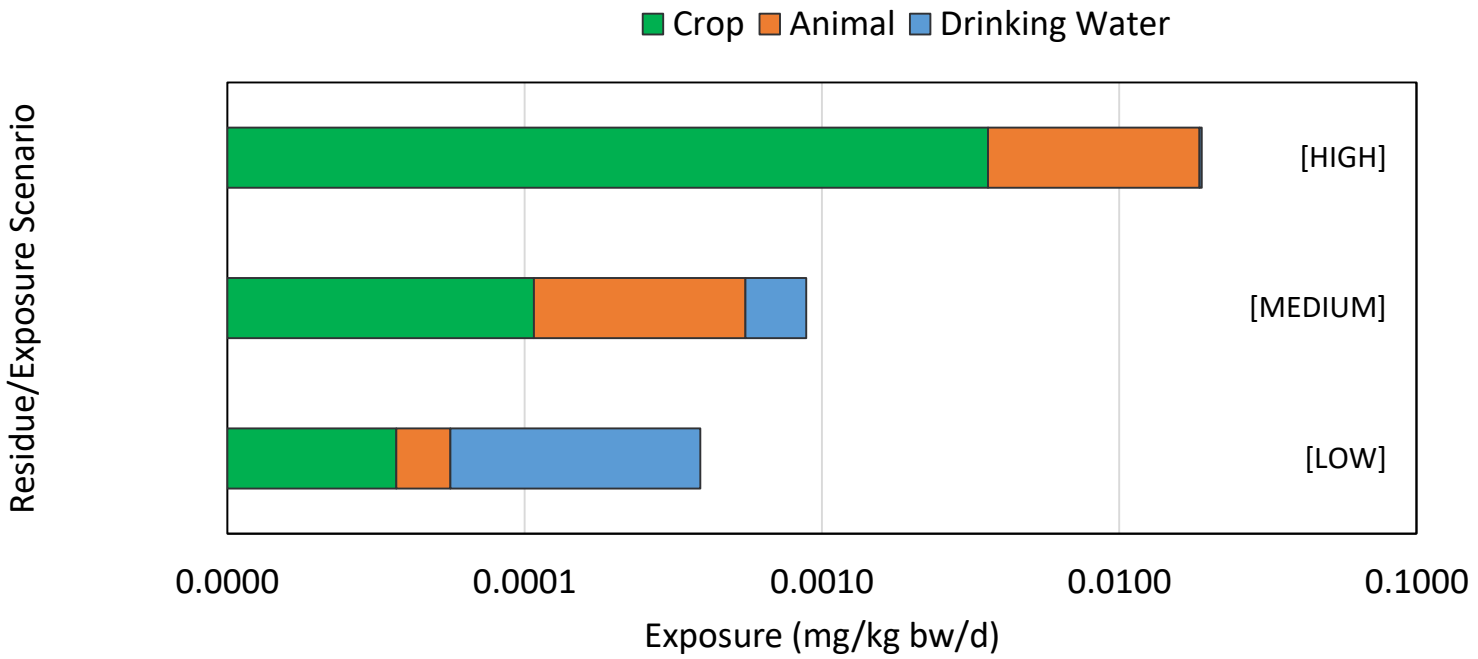
Each exposure scenario needs to be considered

- Can we estimate or refine the exposure for a given population?

Prioritisation of Chemical Series Using a Risk 21 Framework

Starting with Exposure:

- Surrogate residue data from a selection of pre-em / early post em soybean herbicides (n=9) used to estimate residues covering multiple exposure scenarios.
- Residues in animal commodities estimated using transfer factors aligned to physical chemistry.
- Residues in water (10 µg/L / conservative) have been modelled.



- **Use pattern consumer exposure prediction: <u>0.00039 – 0.018929 mg/kg/day</u>**
- **Crop residue appears to be major driver**

Utilise the huge amount of existing knowledge on HPPD Inhibitors:

- Discovered for herbicidal use in ~1980 (13 in class; 1 pharmaceutical).
- HPPD inhibitors are capable of binding & inhibiting HPPD in rat, mouse & human.
- Dose dependent increases in whole blood tyrosine concentrations are observed in rat, mouse & human.
- Tyrosine is the toxicophore.
- Clear, consistent spectrum of toxicities associated with elevated tyrosine.
- Species differences in the spectrum of tyrosine-related toxicological effects are understood.
- The species difference is attributable to differing capabilities to clear excess tyrosine via TAT.
- Species sensitivity to HPPD inhibitors is well understood.

Toxicity	Rat	Mouse	Man
% AA sequence sim to rat	(100)	96%	90%
Maximal tyrosine concentration (nmol/ml)	♂2500-3000 ♀1500-2000	♂♀ ~1000	Syndromes typically < 1250nmol/ml
Corneal opacity	+	-	+*
Thyroid proliferation	+	-	-
Sciatic demyelination	+	-	-
Glomerulonephropathy	+	-	-
Liver weight increase	+	-/+	**
Kidney weight increase	+	-/+	**
Body weight decrease	+	-/+	-
Reproductive effects (litter size, pup survival, hydronephrosis)	+	-	
Minor skeletal changes	+	-	

Evidence of toxicity endpoints in man based on Nitisinone experience

* Vision disorders observed due to tyrosine, all reversed upon adherence to restricted diet

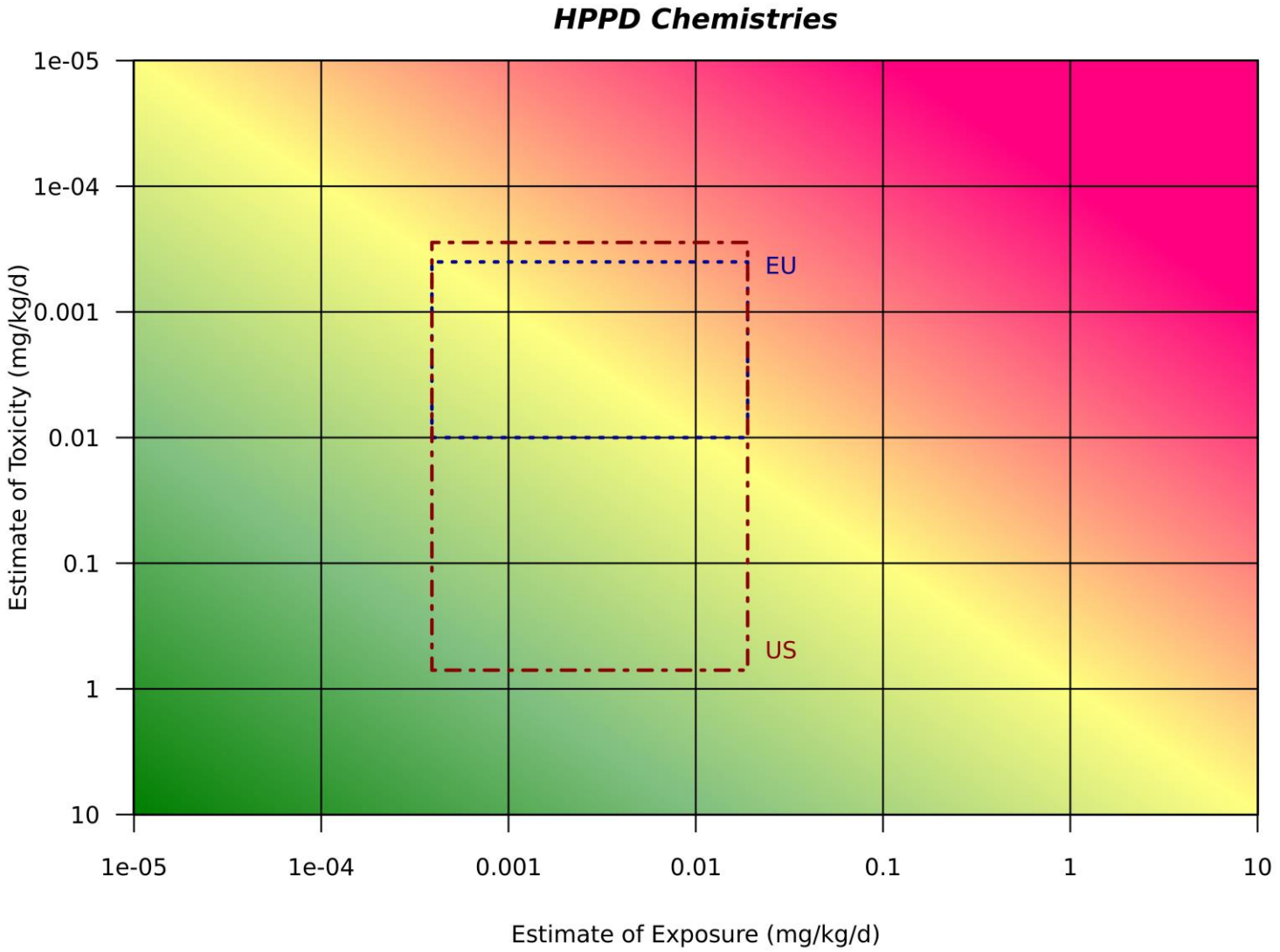
** No treatment related clinical chemistry effects

Utilise the huge amount of existing knowledge on HPPD Inhibitors:

- Discovered for herbicidal use in ~1980 (13 in class; 1 pharmaceutical).
- HPPD inhibitors are capable of binding & inhibiting HPPD in rat, mouse & human.
- Dose dependent increases in whole blood tyrosine concentrations are observed in rat, mouse & human.
- Tyrosine is the toxicophore.
- Clear, consistent spectrum of toxicities associated with elevated tyrosine.
- Species differences in the spectrum of tyrosine-related toxicological effects are understood.
- The species difference is attributable to differing capabilities to clear excess tyrosine via TAT.
- Species sensitivity to HPPD inhibitors is well understood.

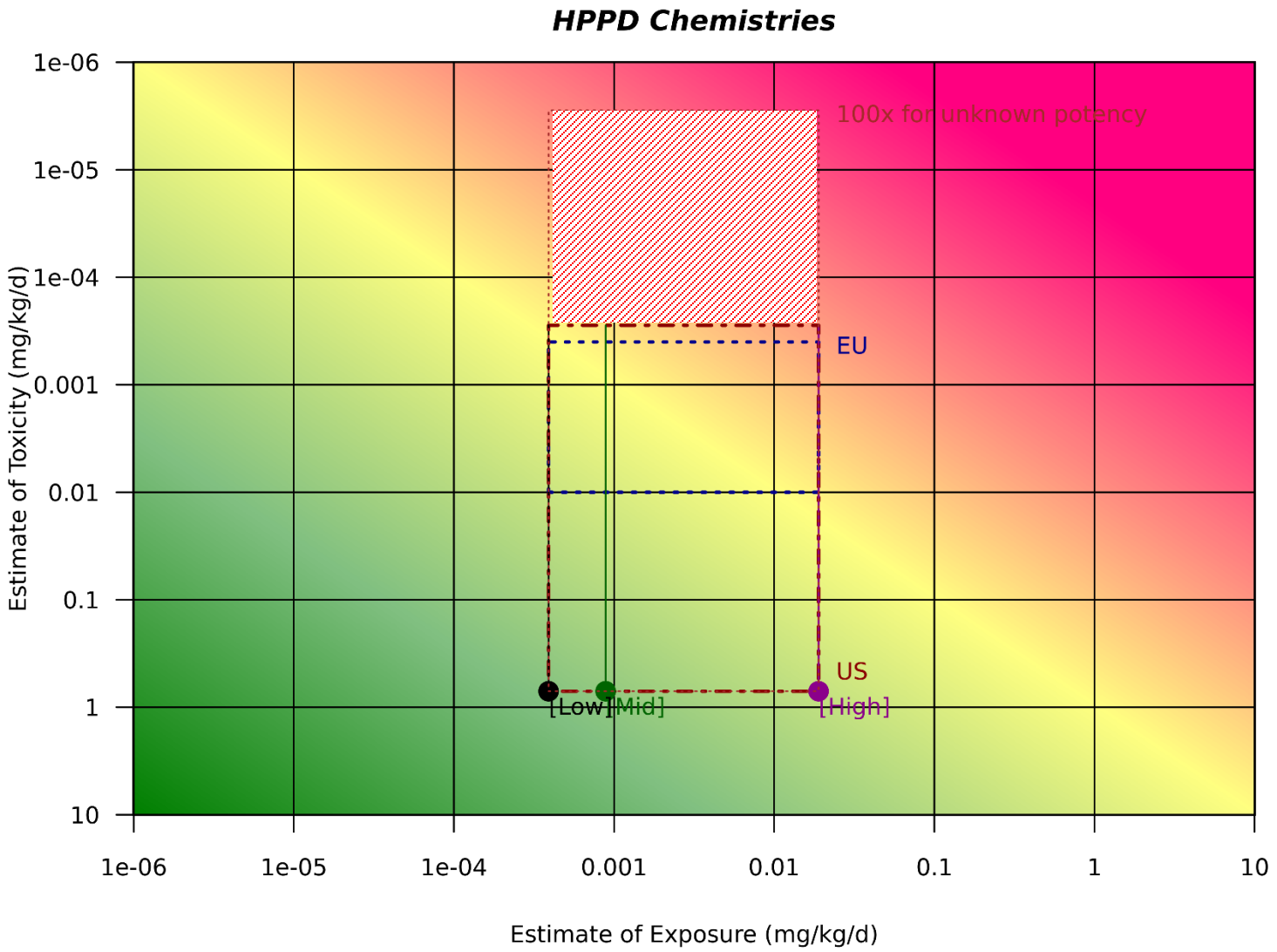
Chronic Reference Dose (ADI)	US	EU
HPPD 1	0.71mg/kg mouse multigen NOAEL 71 mg/kg SF 100	0.01mg/kg mouse multigen SF 200
HPPD 2	0.0004 mg/kg Ocular effects rat SF 1000	0.0004 mg/kg Chronic rat
HPPD 3		0.0004 mg/kg (SF100) Chronic rat LOAEL 0.04mg/kg
HPPD 4	0.00028 mg/kg LOAEL chronic rat - Ocular effects SF 1000	
HPPD 5	0.004mg/kg Ocular opacity rat chronic SF100	0.001mg/kg rabbit dev tox SF 500
HPPD 6	0.002mg/kg 2yr rat SF1000 Chronic rat NOAEL 2mg/kg Q* 1.14 $x10^{-2}$ mg/kg/day	0.02mg/kg 2yr rat SF100 Chronic rat NOAEL 2mg/kg

A HPPD chemistry risk 21 plot using existing information:



- Relatively simple way to understand the ADI versus exposure risk.
- 1:1 MoE.
- You can also separate out and show regional differences in interpretation of endpoint toxicity.

A HPPD Chemistry risk 21 plot using existing information:



- Relatively simple to understand the ADI versus exposure risk.
- 1:1 MoE.
- You can also separate out and show regional differences / challenges.

However..

- 100x adjustment factor used for unknown potency of new chemistry.
- A Tier 0 assessment for a novel HPPD inhibitor does not give assurance of safety.
  - High/Medium/Low exposure scenarios outlined.

Use of Knowledge of the HPPD MoA to Quantitate Chemical Potency:

Molecular Initiating Event (MIE)

Inhibition of HPPD

Key Event 1

Elevated Systemic [Tyrosine]

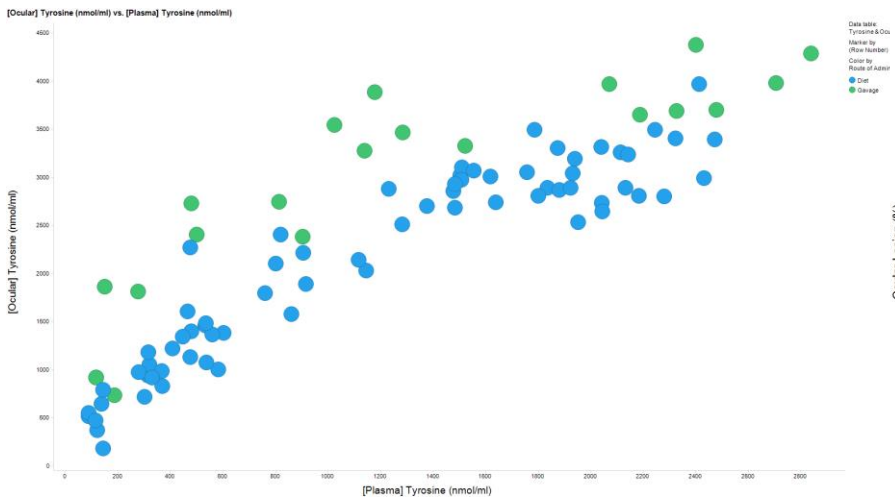
Key Event 2

Elevated Ocular [Tyrosine]

Adverse Outcome (AO)

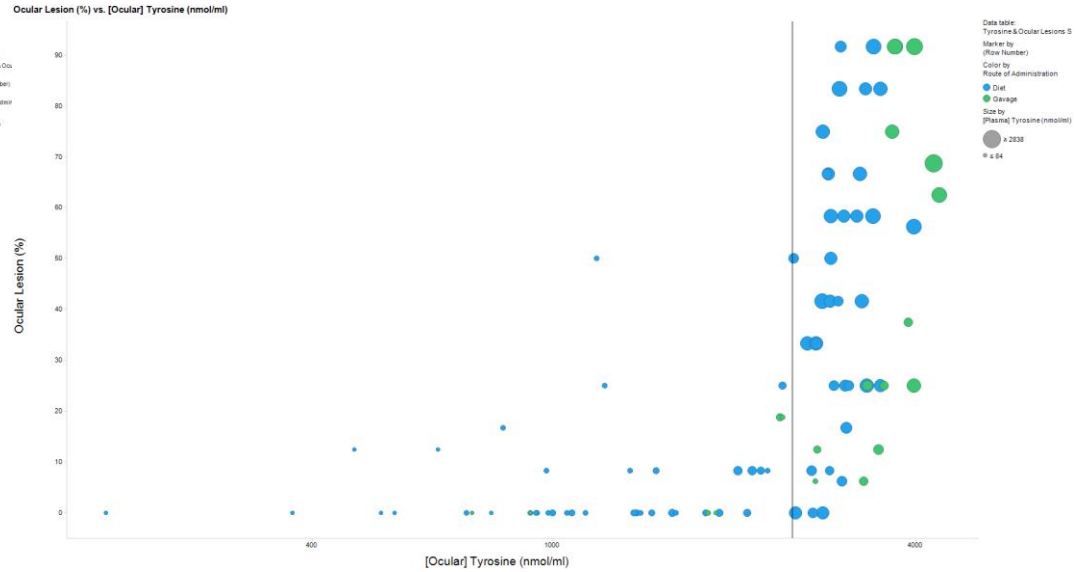
Corneal Opacity

KER1 : [Plasma Tyrosine] & [Ocular Tyrosine] Relationship



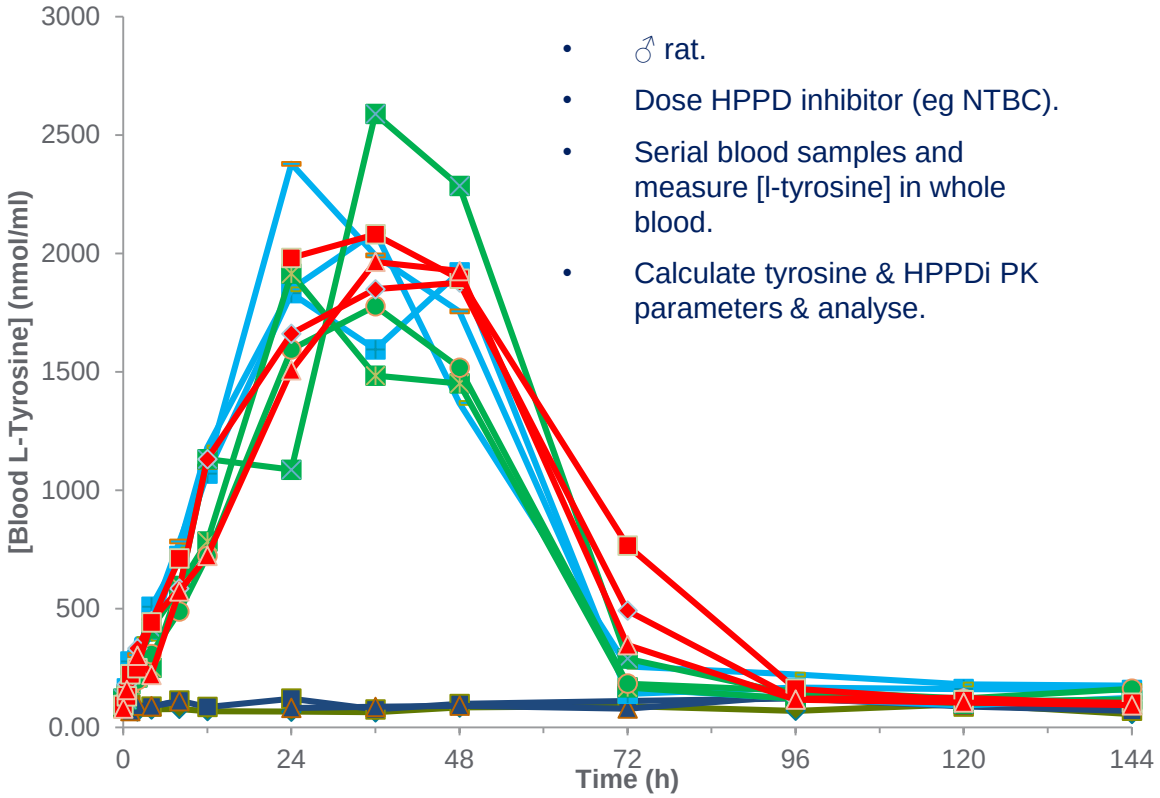
Linear Relationship ocular ~ 2-3x plasma [tyrosine]
Spearman's rank-order correlation R^2 = 0.78

KER2: [Ocular Tyrosine] & Ocular Opacity Relationship

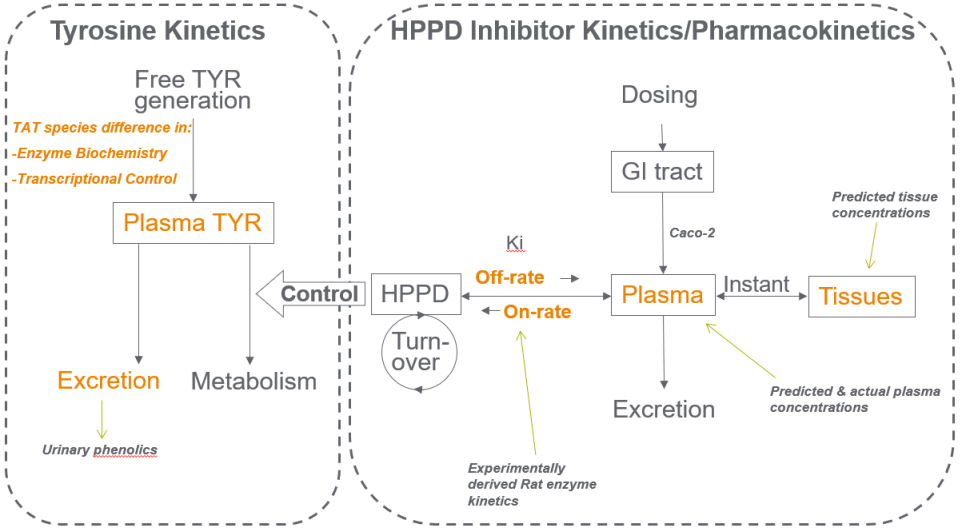


Threshold determined for ocular opacities:
~ 1000 nmol/ml in blood
~ 2500 nmol/ml in the ocular compartment

We can assess the potency of specific HPPD inhibitors:



- ♂ rat.
- Dose HPPD inhibitor (eg NTBC).
- Serial blood samples and measure [l-tyrosine] in whole blood.
- Calculate tyrosine & HPPDi PK parameters & analyse.



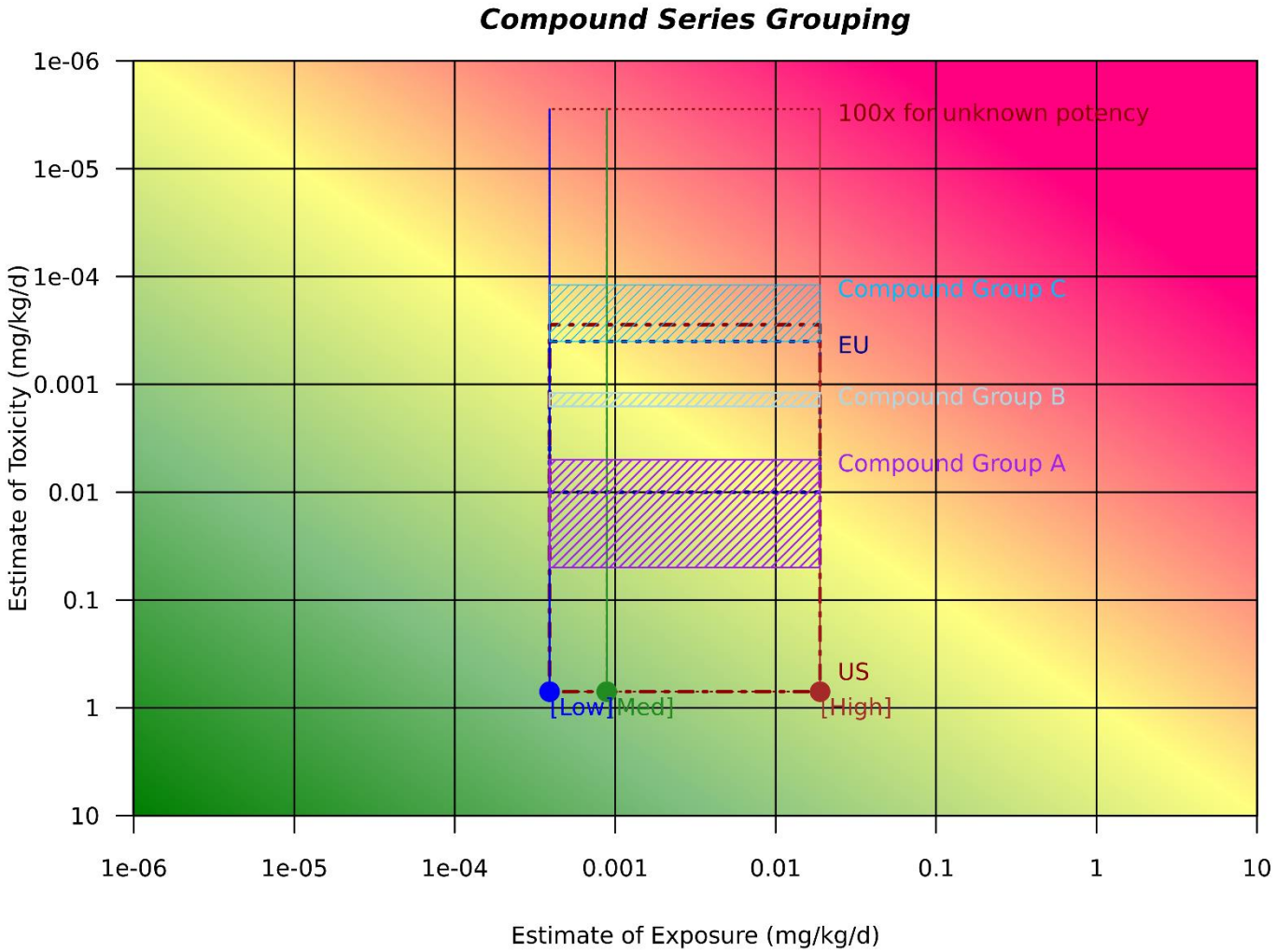
- Chemistry not amiable to predictive PBPK
- PBPK Modelling can be used to derive a systemic tyrosine AUC & Cmax from either PK data or single dose tyrosine data.
- *i.e you can identify a specific chemical risk factor*

Several HPPD chemistry series are available:

Group	Chemical Scope	Available data points	Endpoint range (mg/kg/day)		UF	Predicted ADI	
	Compounds	n	max	min	UF	max	min
Compound Group A	30	6	50	5	1000	0.05	0.005
Compound Group B	3	3	0.12	0.16	1000	0.00012	0.00016
Compound Group C	100	5	0.4	0.12	1000	0.0004	0.00012

- Chemistry teams have been busy…
- 3 different chemical chemotypes..
  - Structure
  - Physiochemical properties
- Some toxicology testing already conducted.
- Endpoints are derived from tyrosine PoD.
- A conservative 1000x uncertainty factor is used to extrapolate from single dose data to ADI.

Chemical series can be positioned versus business risk



- Using our knowledge of possible exposure scenarios and chemical grouping potency we can use this to assign relative risk to individual chemical groupings.

Compound Group A:

- Possibilities for both exposure and toxicity!

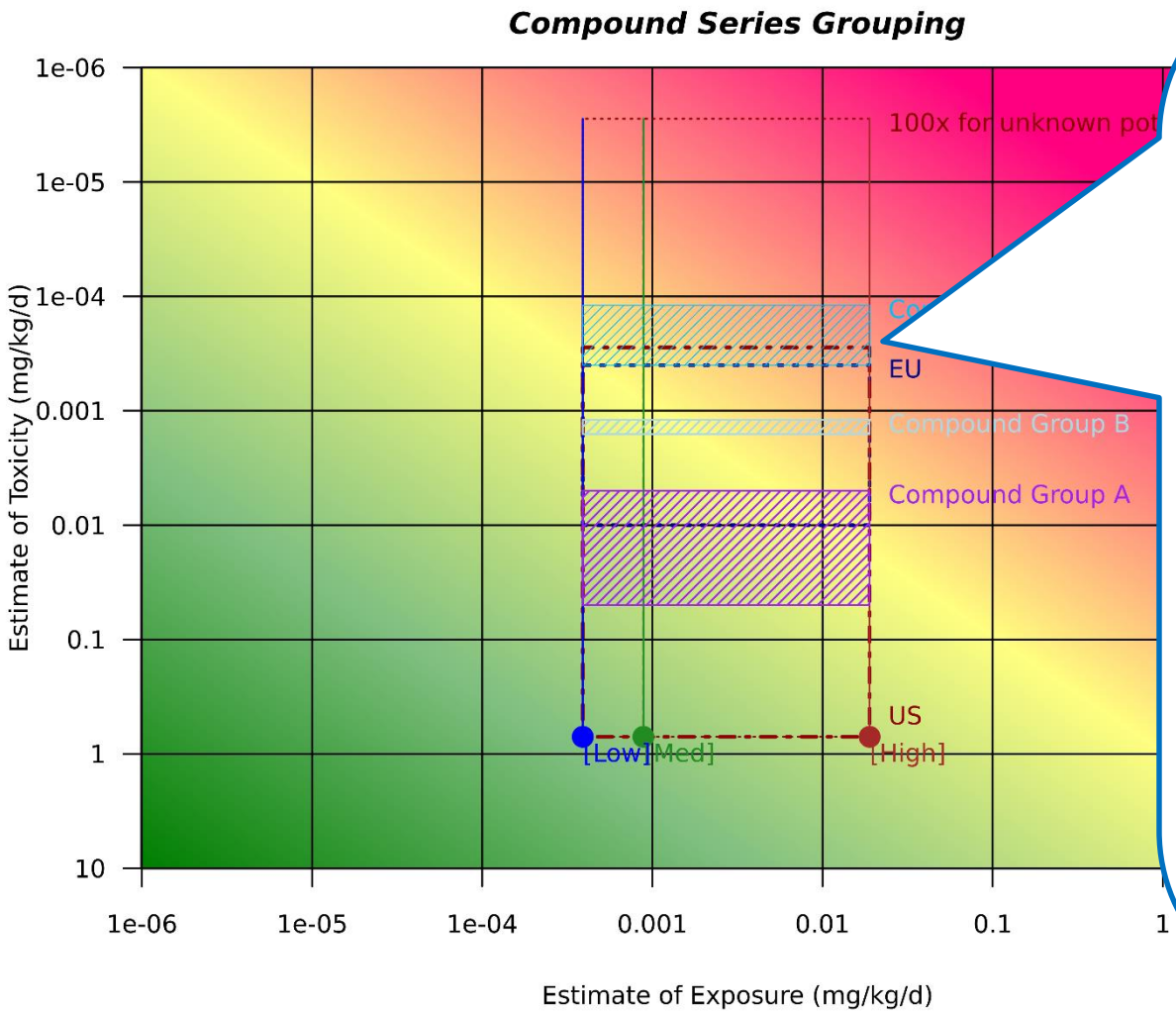
Compound Group B:

- Outcome highly dependent on exposure only

Compound group C:

- Outcome requires favourable exposure and toxicity endpoints

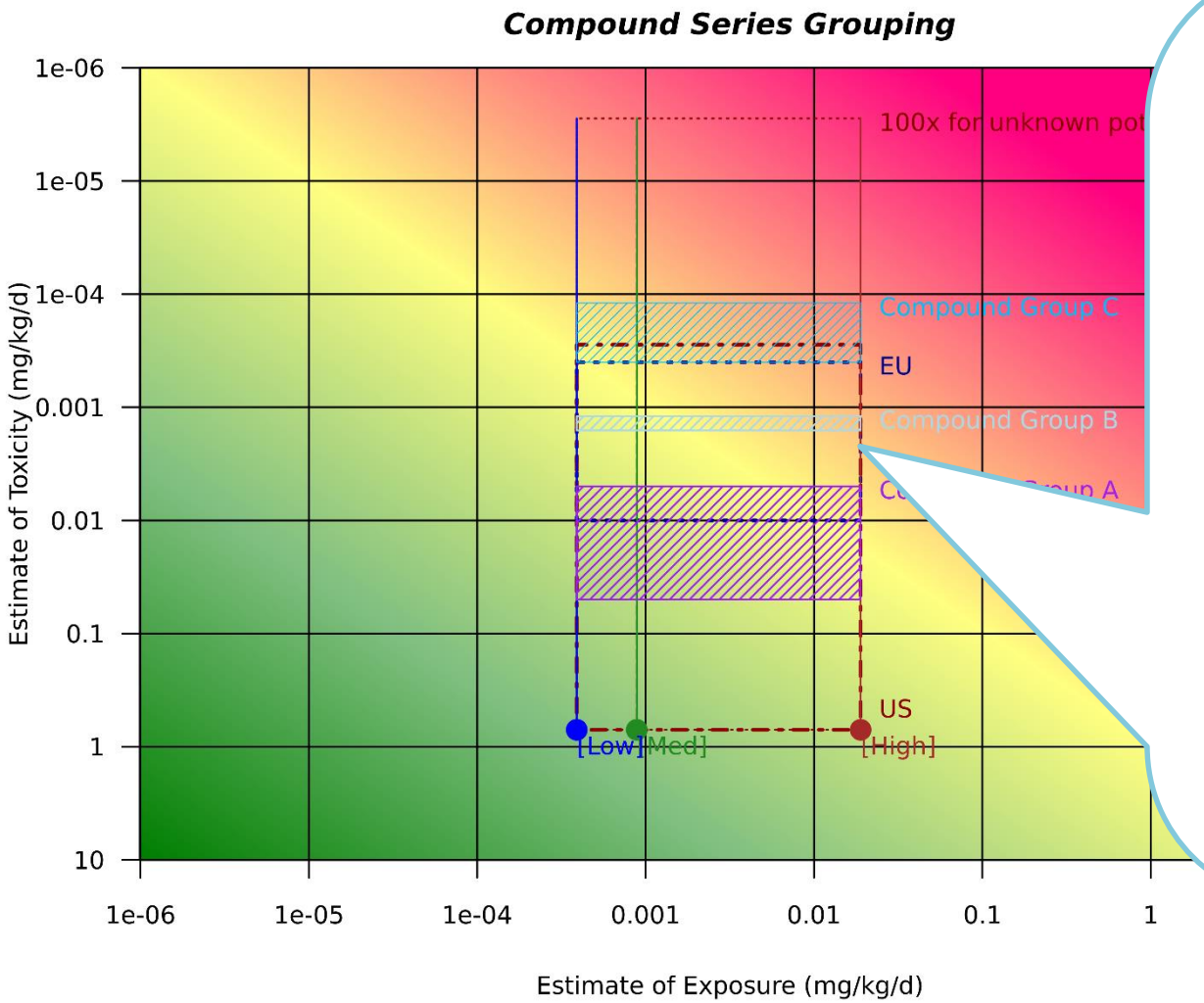
Chemical series can be positioned versus business risk



Compound Group C

- 'the most challenging scenario' / lowest chance of success
- A step wise approach
- Understanding residue data and commodities transfer has greatest value.
  - → is metabolism a detoxification process?
  - → what is in the residue?
- Ideally, conduct definitive crop metabolism & crop residue trials to establish the nature and magnitude of exposure.
  - → challenge in investment required per compound versus chemical scope and ability to make decisions
  - → what options are there for gaining preliminary information?
- Little value in clarifying endpoint at this stage.
  - → High confidence in both exposure and toxicity endpoint will be required to support a stop/go business decision.
  - → Low chance of success?

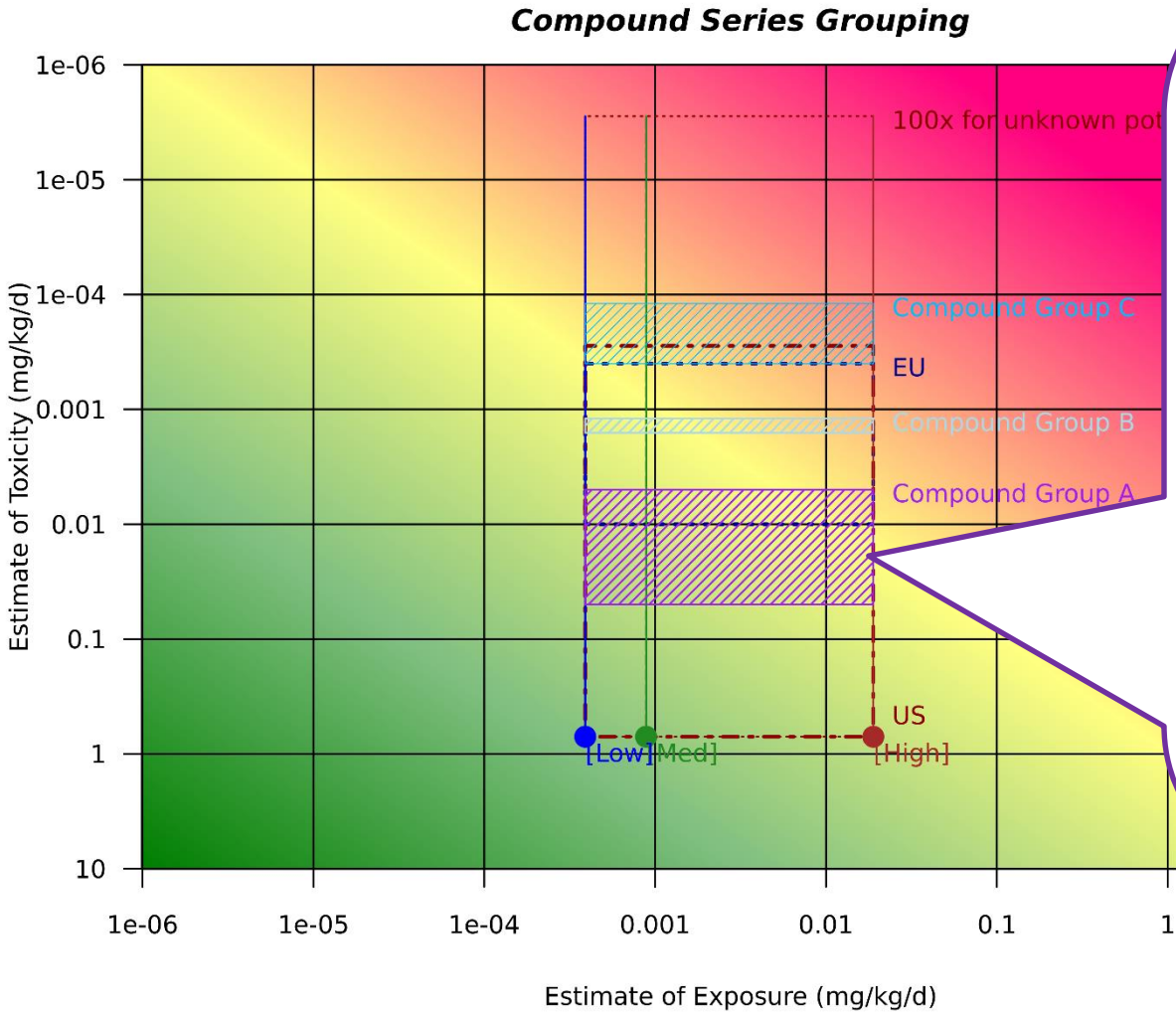
Chemical series can be positioned versus business risk



Compound Group B

- Understanding residue data and commodities transfer has greatest value.
  - → is metabolism a detoxification process?
  - → what is in the residue?
- Conduct definitive crop metabolism & crop residue trials to establish the nature and magnitude of exposure.
- Opportunity to use this strategy as limited chemical scope.
- Little value in clarifying endpoint at this stage
  - → exposure alone will give enough information for a stop/go business decision

Chemical series can be positioned versus business risk



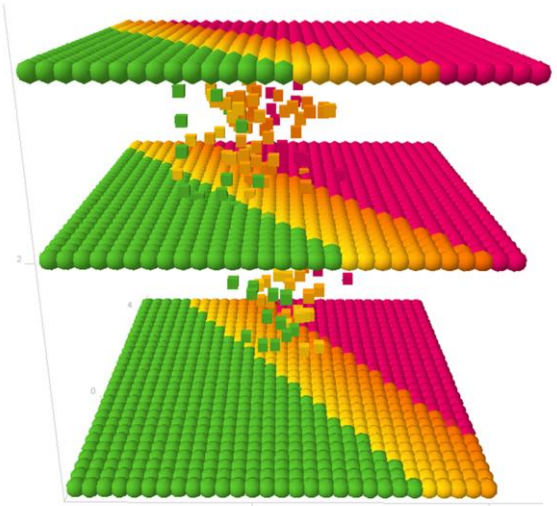
Compound Group A

- Opportunities to explore chemical space.

  The chemical scope is still relatively large

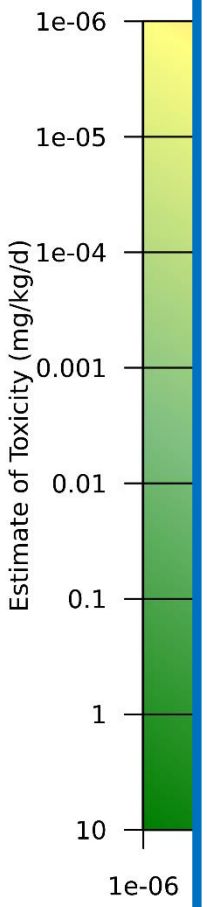
- Identify exemplar compounds based on physiochemical properties.

  → drives an iterative process of testing and refinement of toxicity and exposure.



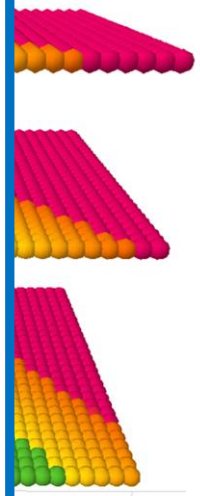
and toxicity endpoints

Chemical series can be positioned versus business risk



Summary

- Exposure / toxicity plots allow:
  - Easy identification of the parameter that gives the greatest impact on decision making.
  - Enables a tiered testing strategy focusing on mechanism of toxicity and exposure.
  - Optimises use of resources.
  - Allows a clear, visual, communication to stakeholders.



Thank You!