

Tox 21 Approaches for Reduced Animal Testing for Agrichemicals: Alternative Approaches to Identification of Points of Departure (PoDs) and Dietary Exposure for Fungicides

Freeman E¹, Parsons, P², Weidling, R¹, Barraj, L¹

¹ Exponent, Washington DC

² Exponent International, Harrogate, UK

Problem Formulation

For crop protection human health risk assessments, the problem formulation step is focused on the particular use(s) of the crop protection chemical, the exposure scenarios that arise from these uses, and the existing knowledge for the chemical active substance itself, other molecules in the same chemical class and molecules that have the same or similar pesticidal modes of action or human health modes of action.

Integrating the Exposure Estimation with Hazard Prediction

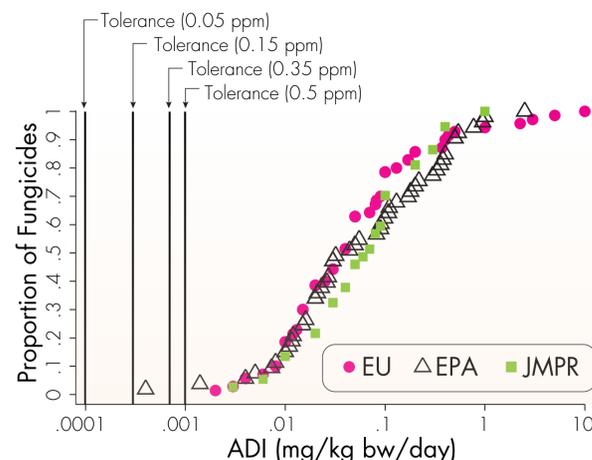
Exploring how to utilise existing data for reference doses established by regulatory agencies to provide a reliable risk determination in conjunction with the use-scenario based exposure predictions

Estimating the Point of Departure (POD)

Define ranges for existing reference doses:

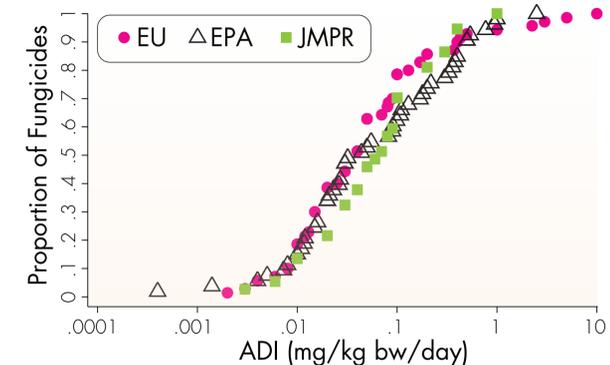
- All data sources
- Refine by Mode of action (MoA), chemistry, region
- NOELs/LOELs used to set reference doses (RfD) – accounting for uncertainty
- Identifying key studies from which RfDs were derived

Fungicide ADIs (or cPAD) Compared with Estimated Chronic Exposures from Soybeans Only at Various Soybean Tolerance Levels (Children 1–2 years)

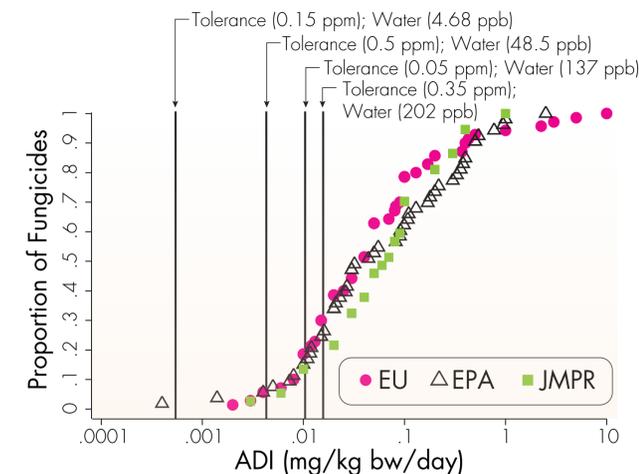


ADIs/cPAD Derived by EU and US EPA and JMPR (same compounds for each region) – Range of Values

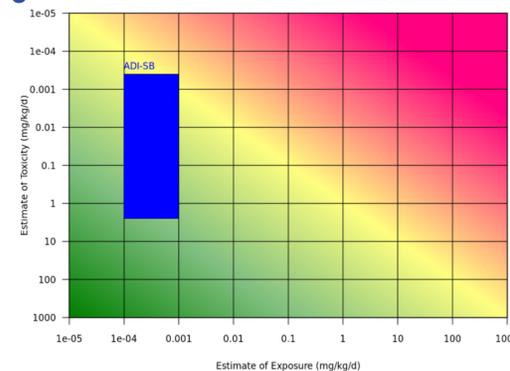
	EU ADI	EPA cPAD	JMPR ADI
Median	0.04	0.044	0.065
Minimum	0.002	0.0004	0.003
Maximum	10	2.5	1



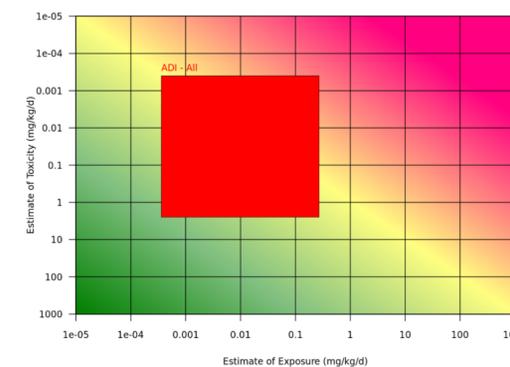
Fungicide ADIs (or cPAD) Compared with Estimated Chronic Exposures from Soybean Tolerance + Water for 4 Different Fungicide Labels (All infants)



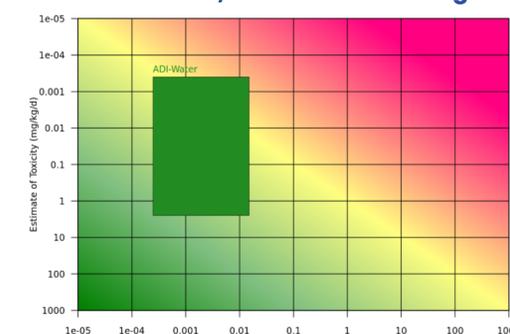
Risk 21 Fungicide US Chronic Dietary Exposure from soybean at tolerance only (DEEM) [mg/kg bw/day] and min/max cPADs all fungicides



Risk 21 Fungicide US Chronic Dietary Exposure Aggregate from soybean at tolerance only (DEEM) [mg/kg bw/day] and min/max cPADs all fungicides



Risk 21 Fungicide Chronic Dietary US Exposure from water and min/max cPADs all fungicides



Use-Specific Dietary Exposure Estimation Versus US EPA Assessment

Fungicide Example	Soybean Seed Tolerance (ppm)	Exposure from Soybean at Tolerance (mg/kg/day)	Exposure from Estimated Drinking Water Concentrations (EDWCs) (mg/kg/day)	Dietary Exposure from Soybean Tolerance + EDWCs (mg/kg/day)	Dietary Exposure (EPA Aggregate: All Food + EDWC) (mg/kg/day)
1	0.05	Chronic exposure US pop: 0.000027 All infants: 0.000064 Children 1–2: 0.000099	Chronic exposure US pop: 0.002768 All infants: 0.010340 (137 ppb for chronic. Driven by turf use.)	Chronic exposure US pop: 0.002795 All infants: 0.010403	Chronic exposure US pop: 0.004529 All infants: 0.009886
2	0.15	Chronic exposure US pop: 0.000082 All infants: 0.000191 Children 1–2: 0.000298	Chronic exposure US pop: 0.000095 All infants: 0.000353 (4.68 ppb for chronic. Driven by sugarbeets)	Chronic exposure US pop: 0.000176 All infants: 0.000544	Chronic exposure US pop: 0.000140 All infants: 0.000360 (refined analysis-average residues, PCT, etc.)
3	0.35	Chronic exposure US pop: 0.000191 All infants: 0.000446 Children 1–2: 0.000695	Chronic exposure US pop: 0.004081 All infants: 0.015245 (202 ppb for chronic. Driven by grape)	Chronic exposure US pop: 0.004272 All infants: 0.015691	Chronic exposure US pop: 0.008896 Child 1–2: 0.025382
4	0.5	Chronic exposure US pop: 0.000273 All infants: 0.000637 Children 1–2: 0.000993	Chronic exposure US pop: 0.000980 All infants: 0.003660 (48.5 ppb for chronic. Driven by turf use.)	Chronic exposure US pop: 0.001253 All Infants: 0.004297	Chronic exposure US pop: 0.010724 Child 1–2: 0.027728

Next Steps & Timelines

Point of Departure

- Evaluate further utility of POD spreadsheets for justification of study waivers – range of NOAELs/LOELs, key studies driving PODs
- Explore specific areas of chemistry (e.g. triazoles, pyrethroids, strobilurins)
- Develop decision tree for POD estimation, waiver justification and need for additional data generation

Exposure Prediction

- Evaluate herbicide and insecticide example use scenarios including water contribution
- Develop decision tree for POD exposure estimation and need for additional data generation
- Run POD comparisons with EU use-scenario exposure estimations

Integration for Risk Determination

- What tools need to be developed to facilitate the assessment and visualization
- Use of Risk 21 Web tool

Disclaimer:
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