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Short-Term Transcriptomic Points-of-Departure are Consistent with Chronic Points-of-Departure for Three Organophosphate Pesticides in Rodents

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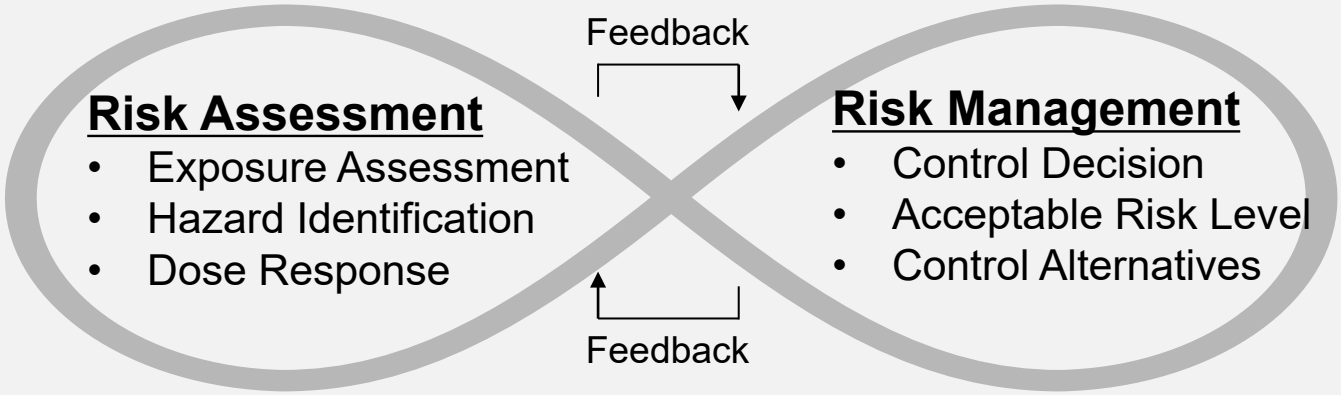
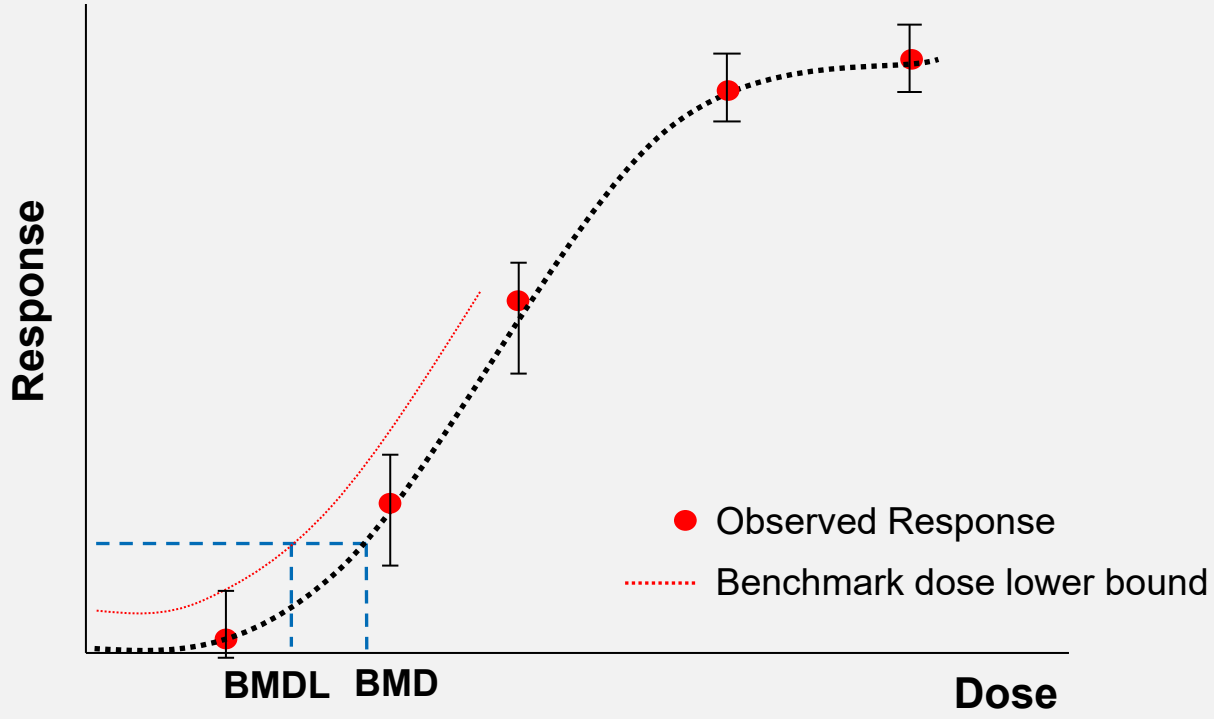
United States Environmental Protection Agency

Disclaimer

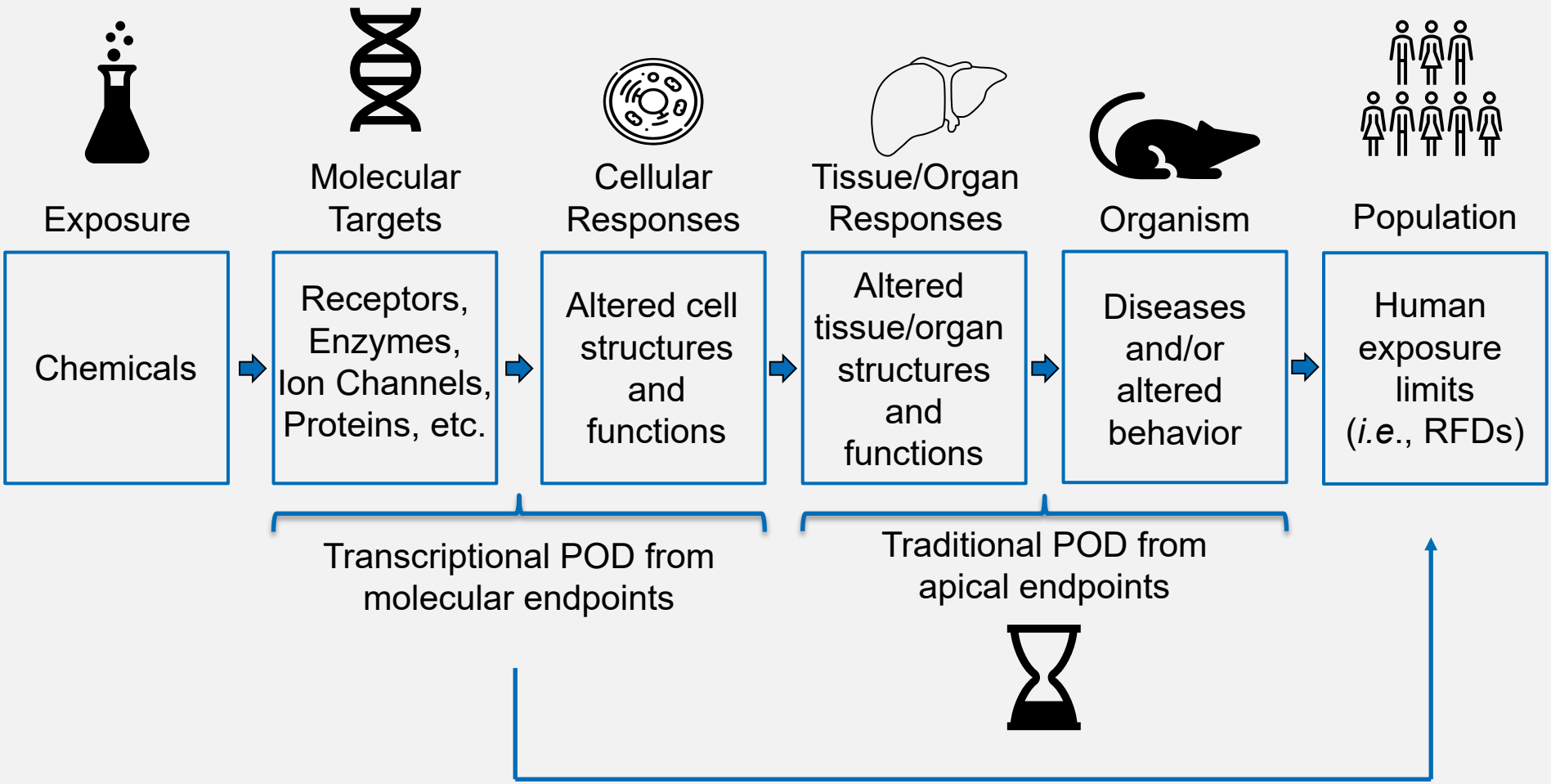
The views in this presentation do not necessarily represent those of the US EPA.

Benchmark dose-response modeling is superior to identifying a point of departure in risk assessment





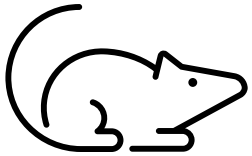
Molecular changes from short-term exposures can be modeled to estimate chronic exposure biological effects



Gene expression can provide a transcriptomic point of departure (TPOD)

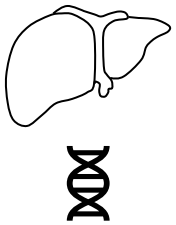
Liver transcriptome-based POD from short-term exposures can estimate apical PODs from long-term exposures

Organophosphate pesticides (OPPs)

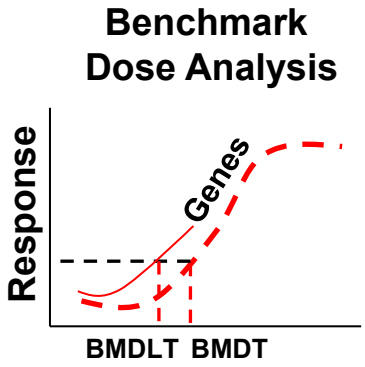


- Male mice
- 5 dose groups
- N=7/group

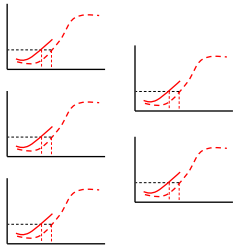
7-days



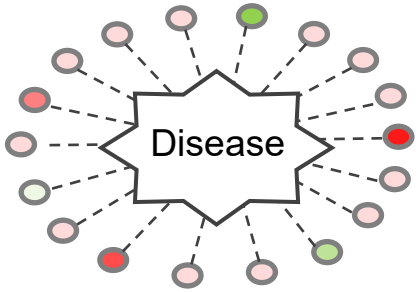
Liver Transcriptomics



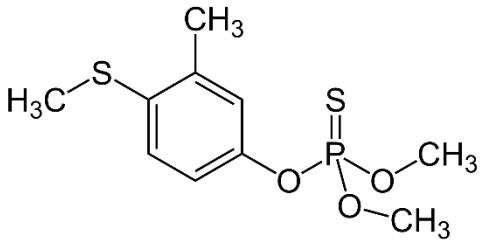
Gene Set
BMDLT = TPOD



Inform toxicity and risk

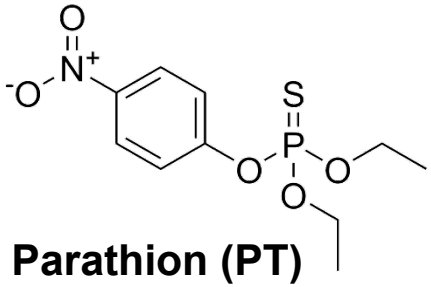


OPPs cause acetylcholinesterase inhibition, which was used to set the chronic apical POD (APOD) in rodents



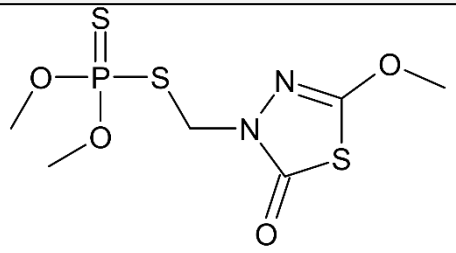
Fenthion (FT)

APOD: 0.03 mg/kg-day



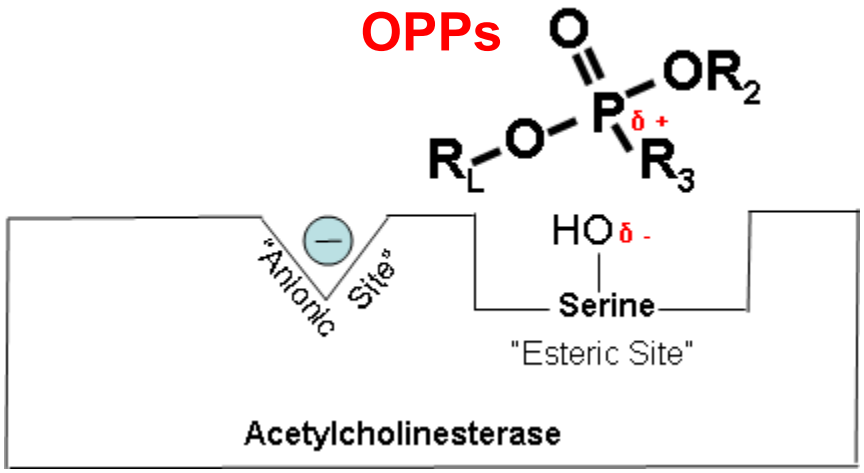
Parathion (PT)

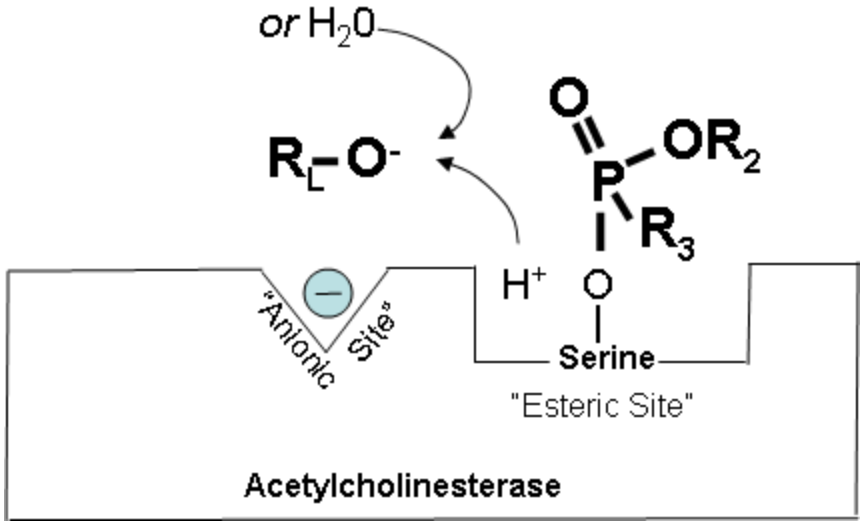
APOD: 0.10 mg/kg-day



Methidathion (MT)

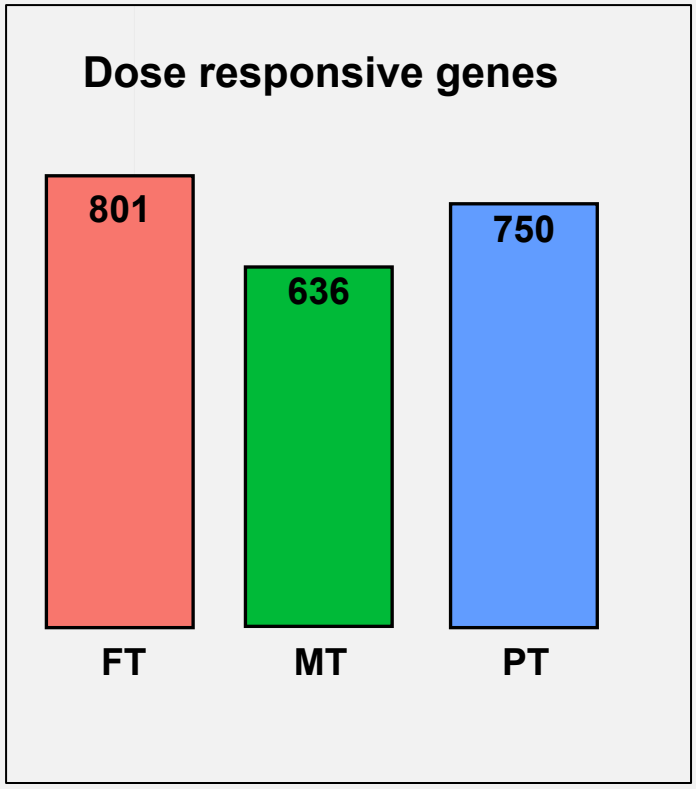
APOD: 1.60 mg/kg-day

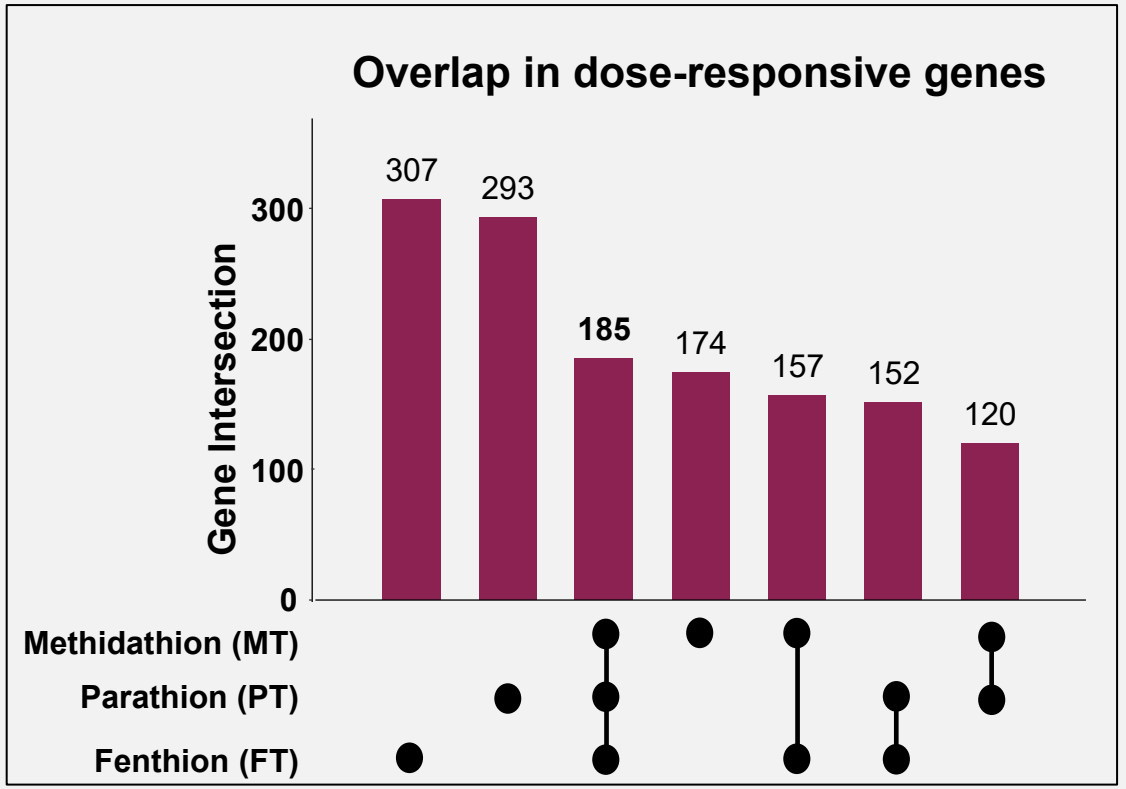




https://www.atsdr.cdc.gov/csem/cholinesterase-inhibitors/inhibitors.html

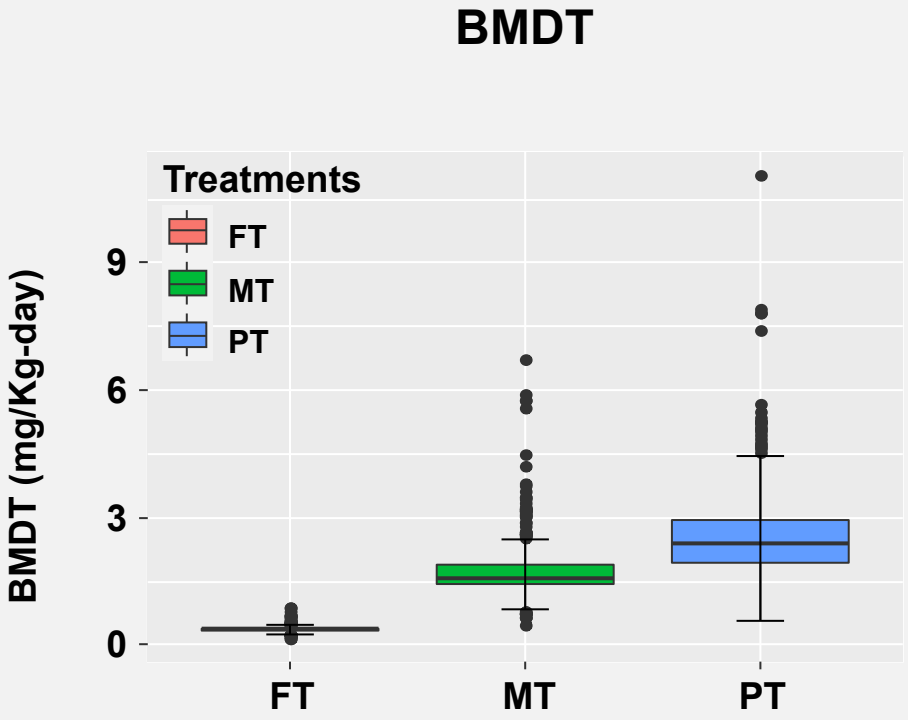
Several genes were considered to have a dose-responsive behavior at 7 days

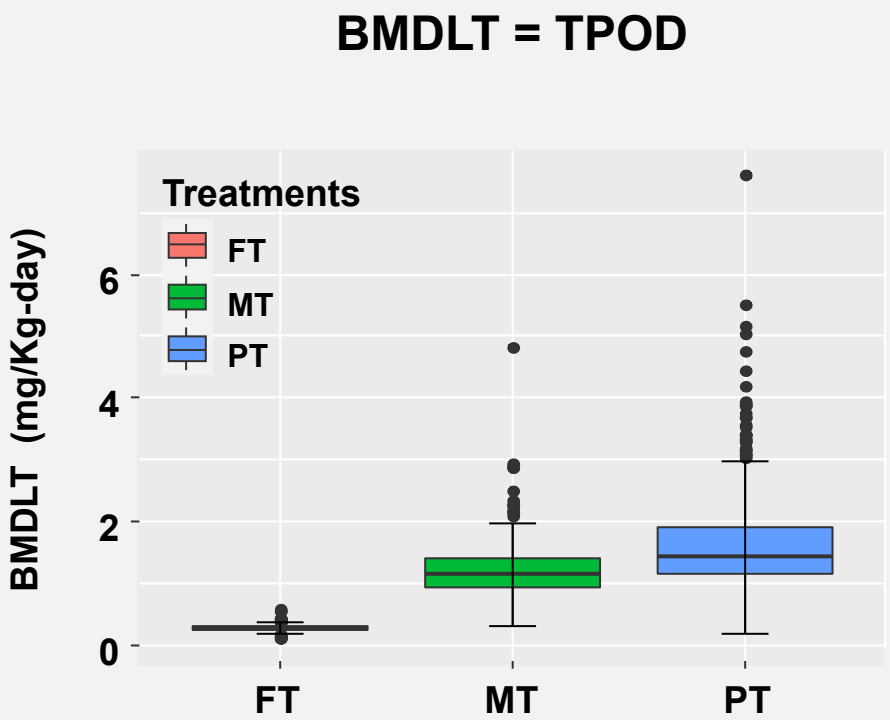




Diseases	P Value
Cancer	2.60E-05
Neurological diseases	1.40E-04
Immunological diseases	2.50E-04
Inflammatory Diseases	2.50E-04

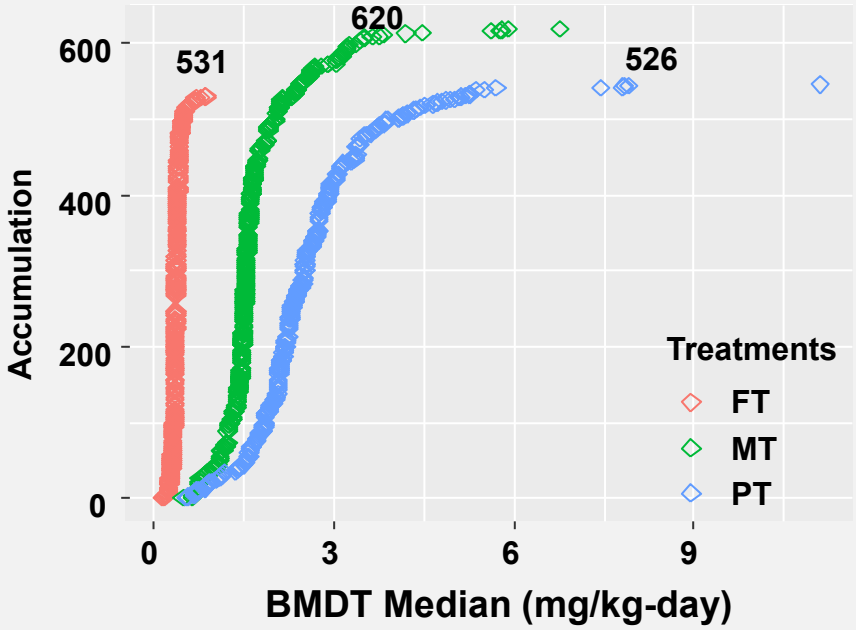
BMDT and BMDLT median levels and ranges suggest relative low variability in the modeled genes

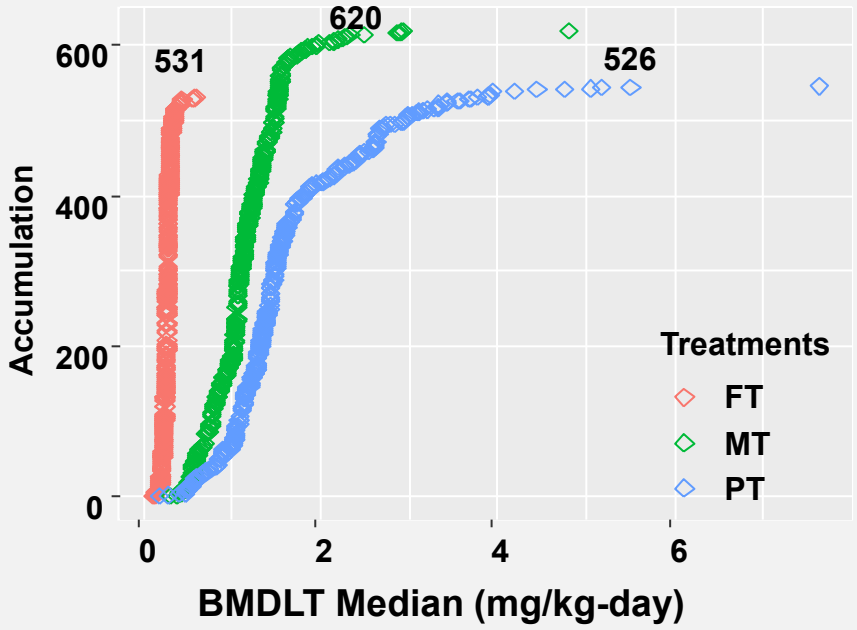




Dose-responsive genes were mapped to a wide range of GO biological processes (GO: BP)

Number of GO: BP categories for BMDT and BMDLT, respectively.





Transcriptomic BMDs for 7-day exposure lie within a factor of 10

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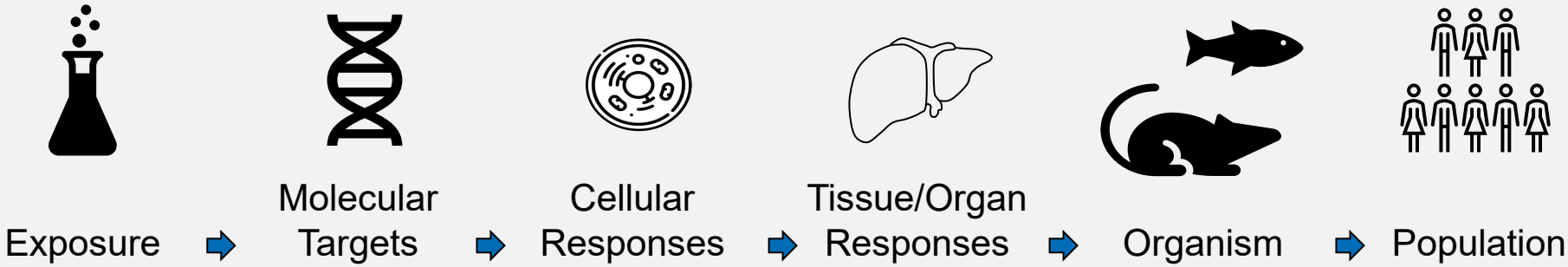
Comparison between transcriptomic PODs and apical PODs

Chemical	GO:BP	Gene Symbols	BMDT (mg/kg-d)	BMDLT or TPOD (mg/kg-d)	APOD (mg/kg-d)	Ratio APOD: TPOD
Fenthion	multicellular organismal water homeostasis	wfs1;scd1;plec;gba;cela2a	0.02	0.01	0.03	**3.4** ↓
Methidathion	G2/M transition of mitotic cell cycle	fbxl21;plk1;nes;ccna2;birc5	0.29	0.17	1.60	**9.4** ↓
Parathion	phosphatidylinositol phosphate biosynthetic process	socs2;fam126a;pik3r3;pik3c2g;socs3	1.54	0.19	0.10	**2.0** ↑

TPODs, derived from 7-day exposure, were generally more sensitive than APOD derived from acetylcholinesterase inhibition after chronic exposure.

Short-term, molecular-based assays help reduce reliance on chronic animal studies



- Molecular changes can be used to set PODs.
- Liver is a potentially useful surrogate for identifying TPODs.
- This approach is applicable to ecological studies.
- Short-term *in vivo* molecular changes can help translate *in vitro* transcriptomics data to chronic adverse effects.

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Acknowledgments

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Michael Devito, PhD

Previous ETTB members

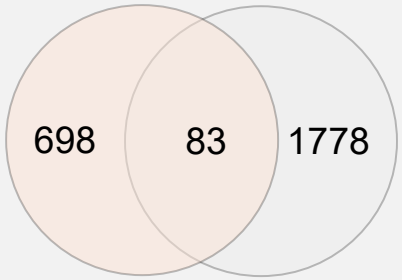
Nancy Urbano, PhD candidate
Sunita Chutkan, MSc

Reference

Rooney J. *et al. Tox 2021*
(doi: 10.1016/j.tox.2021.153046)

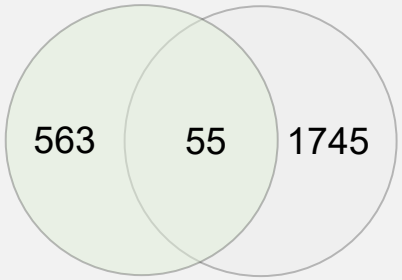
Questions

Several genes overlapped with known genes associated with organophosphate toxicity



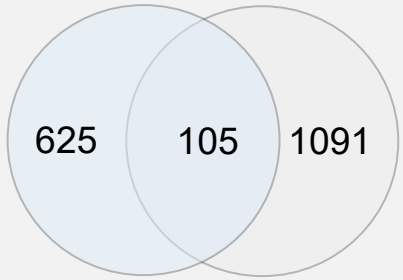
FT (my genes)

FT
(Comparative Toxicogenomic Database Oct 13th, 2022)



MT (my genes)

MT
(Comparative Toxicogenomic Database Oct 13th, 2022)



PT (my genes)

PT
(Comparative Toxicogenomic Database Oct 13th, 2022)

Ache was among the overlapped genes across all organophosphate treatments

Treatments	Genes	Best BMD	Best BMDL	P-Value	Max Fold Change
FT	*Ache*	0.26	0.20	4.09E-08	6.36
MT	*Ache*	1.54	1.17	1.09E-09	3.84
PT	*Ache*	0.70	0.19	4.87E-07	4.05