



United States
Environmental Protection
Agency

Examining the Utility of In Vitro Bioactivity as a Conservative Point of Departure: A Case Study

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in collaboration with partners from A*STAR, ECHA, EFSA, Health Canada, OECD-JRC, and other EPA offices

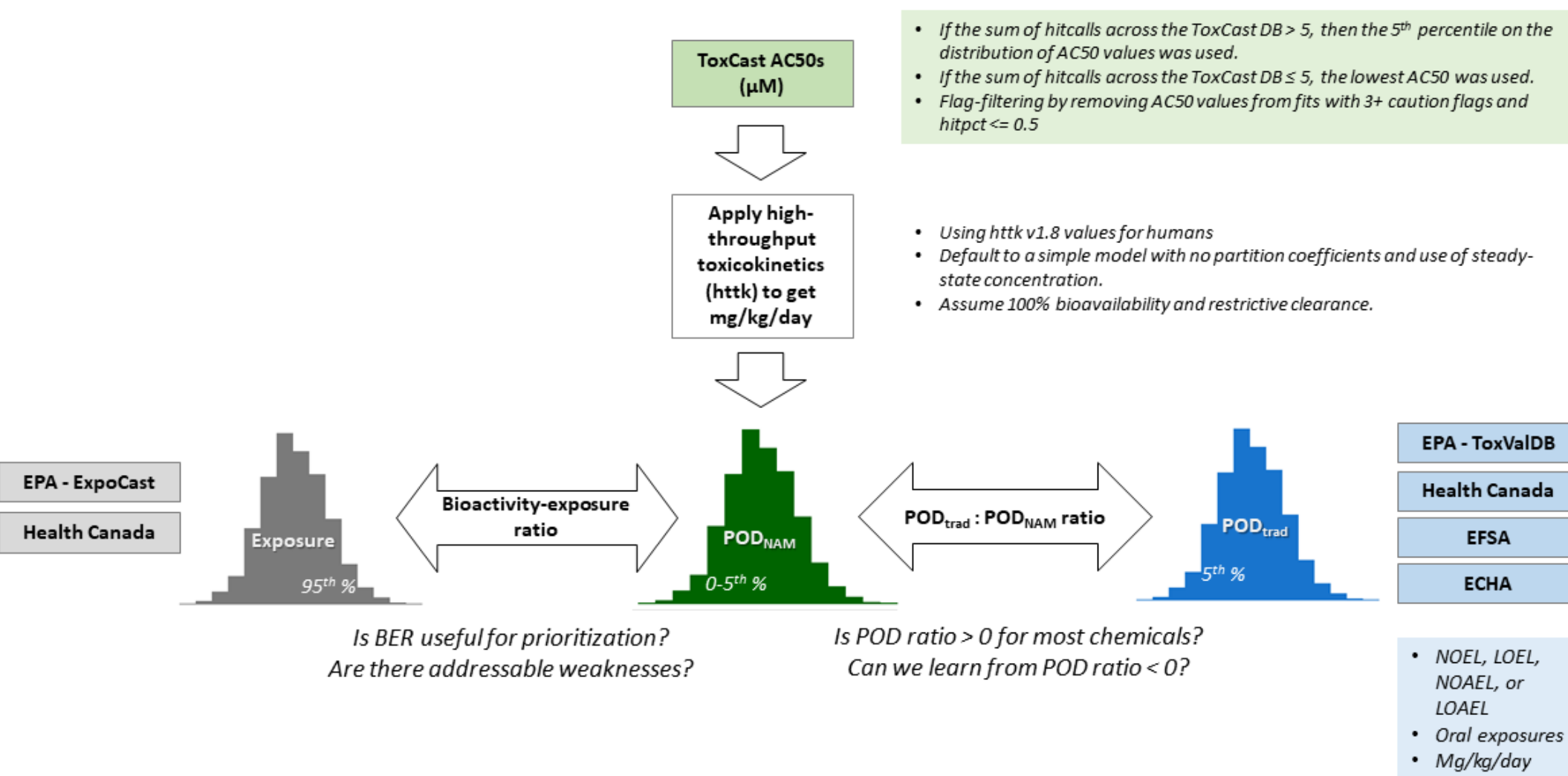
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Hypothesis: *in vitro* bioactivity can be used to derive a conservative point-of-departure (POD)

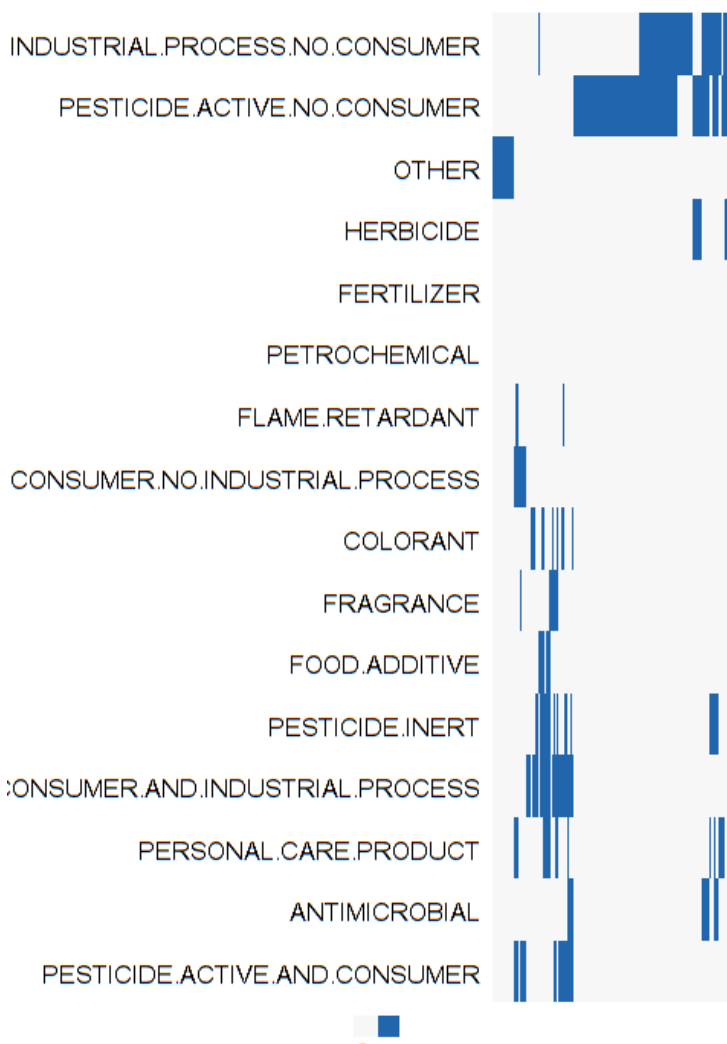
POD ratio: Do new approach methods (NAMs; *in vitro* bioactivity data) provide a conservative estimate of POD compared to traditional *in vivo* data?

Bioactivity-exposure ratio (BER): Useful for risk-based prioritization of chemicals for additional study and/or to serve as a low tier risk assessment approach?

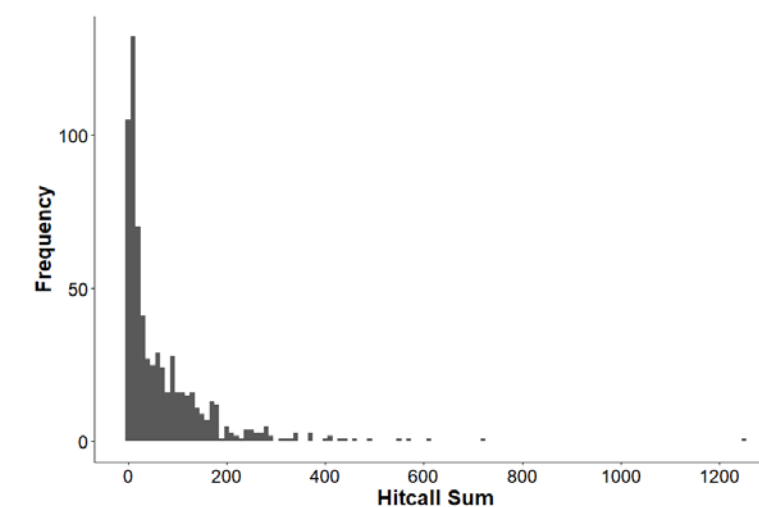


The chemical space available (448 chemicals)

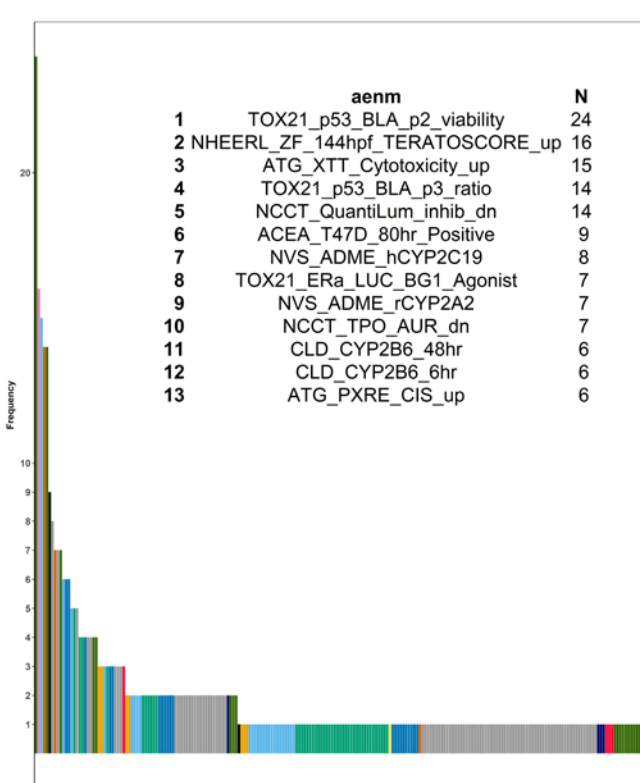
314/448 have functional use as pesticide actives (~70%).



The 448 chemicals demonstrate range of total positive hitcalls in ToxCast.

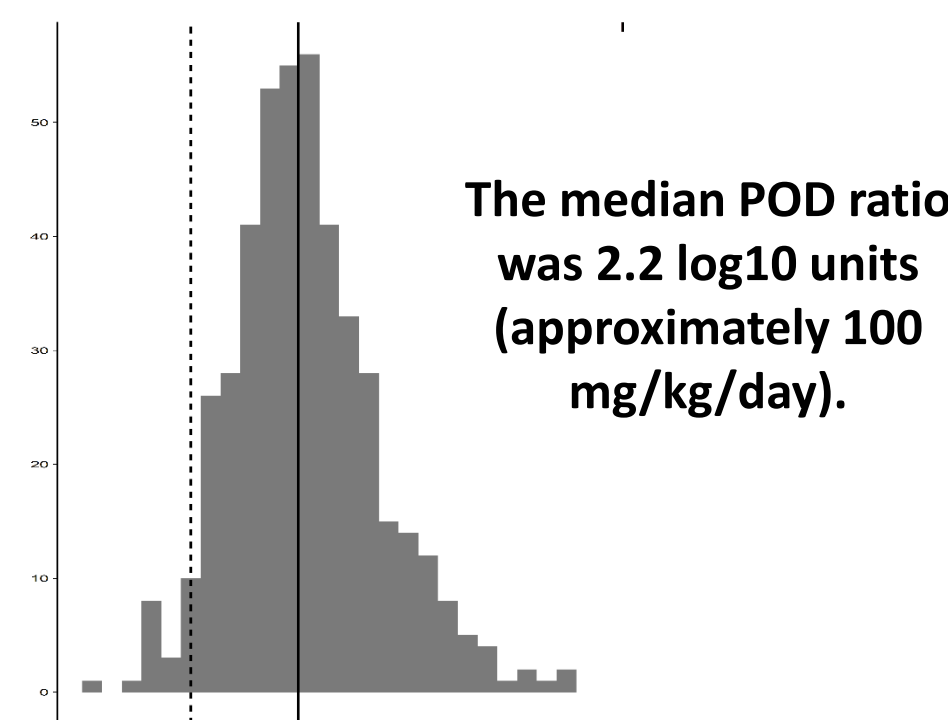
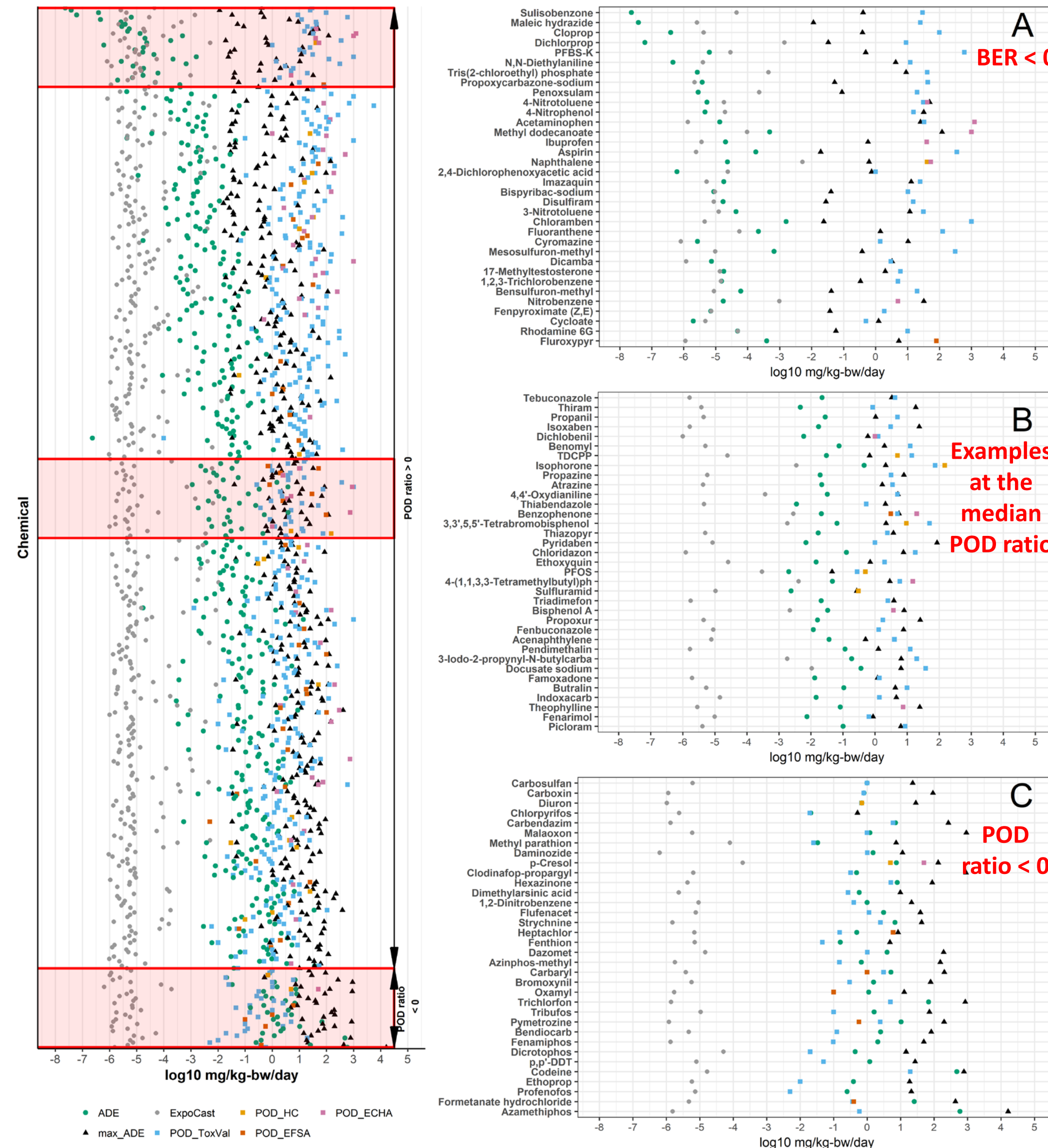


No single assay defined the minimums of the AC50 distributions.



92% of the time, POD-NAM < POD-traditional.

Chemicals are ordered by their POD-NAM:POD traditional, or POD ratio, largest to smallest.



The median POD ratio was 2.2 log10 units (approximately 100 mg/kg/day).

The maximum administered dose equivalent (ADE) possible based on 100 μM (top concentration in ToxCast) was less than the POD-traditional ~half the time.

Condition	MaxADE < minPOD	MaxADE > minPOD
POD ratio > 0	231	183
POD ratio < 0	0	34

Study types were not enriched for POD ratio < 0. But certain chemotypes were.

- 17 of 34 chemicals with POD ratio ≤ 0 are organophosphate pesticides.
- 20 of 34 chemicals corresponded to these chemotype enrichments.

Chemotype Information		Appearance of the ToxPrint			Metrics			Chemotype Information		Appearance of the ToxPrint			Metrics		
Label	ToxPrint	Total	POD ratio ≤ 0	POD ratio > 0	BA	OR	p-value	Label	ToxPrint	Total	POD ratio ≤ 0	POD ratio > 0	BA	OR	p-value
bondC_S_sulfide		53	11	42	0.57	4.2	0.000847	bondP=O_phosphorus_oxo		17	8	9	0.70	14	7.67E-06
bondC_X_halide_alkyl_C_nonoxo_1-3_1-1		4	2	2	0.71	13	0.031009	bondP=S_generic		27	9	18	0.64	7.8	5.48E-05
bondP=O_phosphate_thio		3	3	0	0.96	NA	0.000413	bondC=C(O)N_carbamate		20	6	14	0.62	6.1	0.002294
bondP=O_phosphate_thioate		9	3	6	0.63	6.5	0.025108								

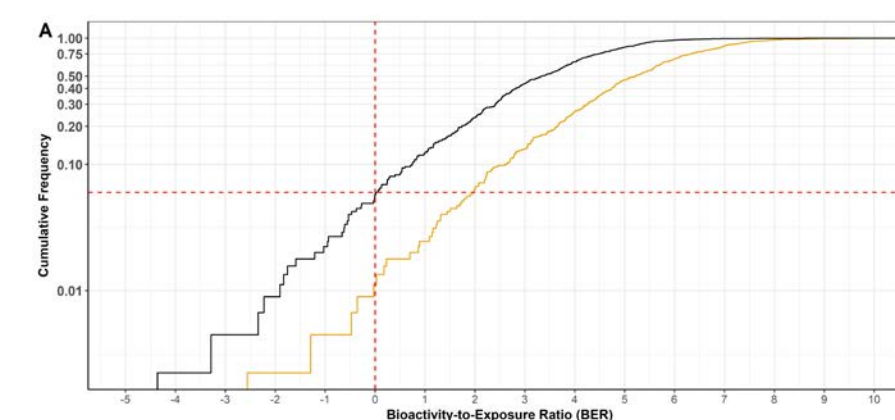
Condition	Dev/Repro is minPOD	Dev/Repro is not minPOD
POD ratio < 0	1	33
POD ratio > 0	44	370

Condition	Chronic is minPOD	Chronic is not minPOD
POD ratio < 0	23	11
POD ratio > 0	249	165

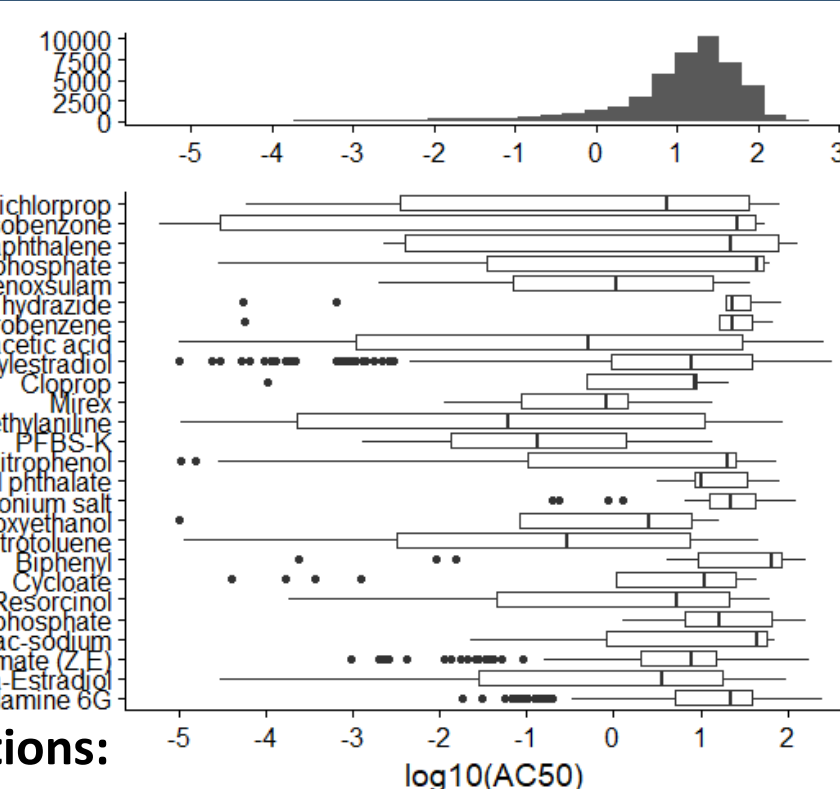
- Developmental/reproductive studies, did not define the POD-traditional more for chemicals with POD ratio < 0.
- Nor did chronic/carcinogenicity studies.

26 chemicals (6%) had BER < 0.

Using BER from more conservative ExpoCast value (95%-ile on the confidence interval for total US population exposure) results in a 2-log shift to the left for the BER ratio.



Top distribution: AC50s for all chemicals. Lower distributions: AC50s for the chemicals with BER < 0 not always lower.



TTC < POD-NAM 84% of the time.

The median TTC:POD-NAM ratio was 1.8 log10 units (~75 mg/kg/day), indicating that TTC tended to be more conservative than POD-NAM. POD-NAM may provide a complementary refinement to TTC.

