ECETOC Time4NGRA

TK and TD as a tools to support read across between chemicals and species

Energy lives here™

Aaron Redman, Daniela Holland
https://orcid.org/0000-0002-5933-7906

Outline

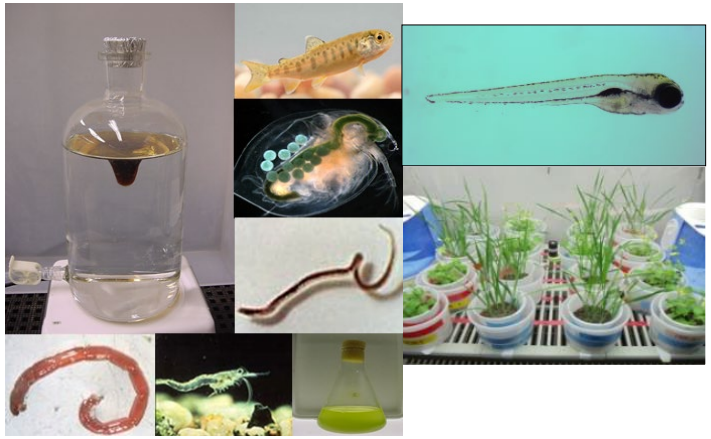
1) Need a common metric → **C_{free}** (e.g., the Fraction unbound)
2) Common **aquatic** bioassays and Exposure profiles

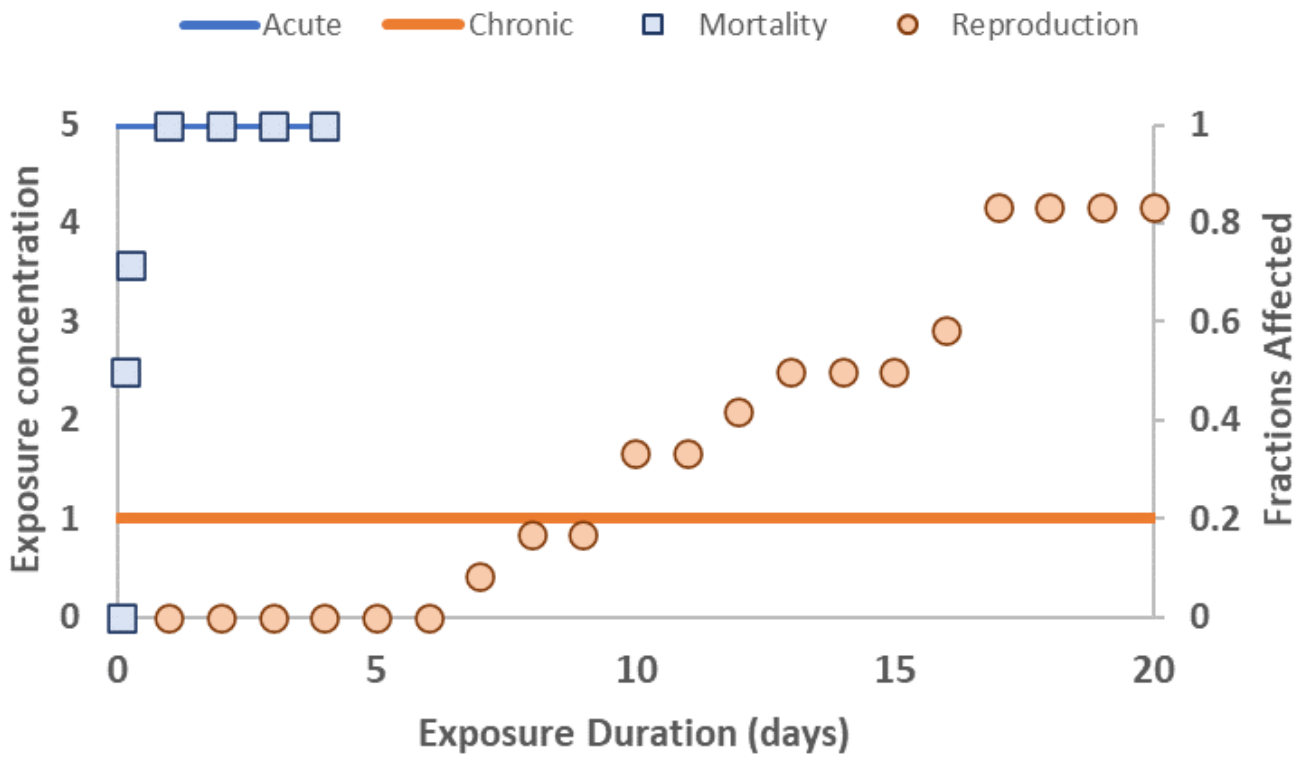
   A) Primer in Ecotoxicity assessments, and Acute to Chronic extrapolations
3) Common **rodent** bioassays and Exposure profiles
4) TKTD provide basis for read across using C_{free}
5) TD: Thresholds vs duration of exposure
6) Future work

Aquatic toxicity testing

- Acute:
  - 2 to 4d with constant exposure
  - Test organisms are small and at equilibrium
  - LC50, or EC50:
    - Mortality, growth, reproduction

- Chronic:
  - 6-21d with constant exposure
  - EC10, or NOEC
    - Mortality, growth, reproduction, biomarkers, behavioural, etc



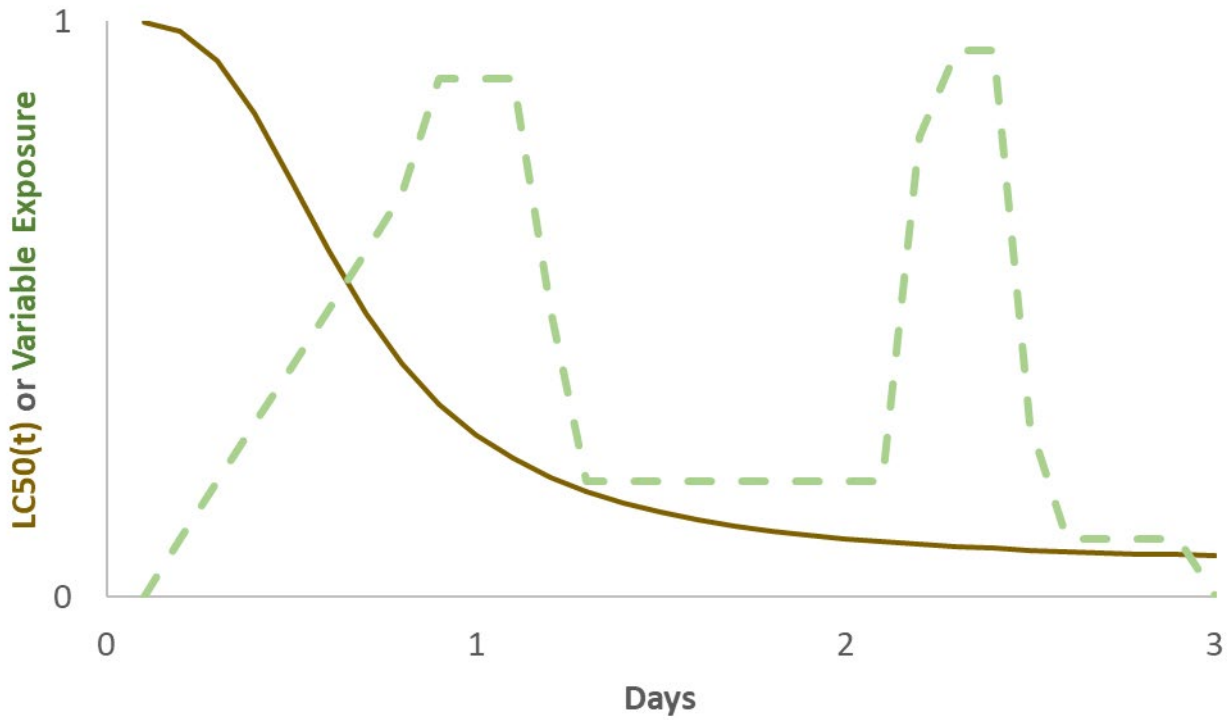


Aquatic toxicity evaluation for transient exposures

- Pulsed and transient exposures require TK-adjusted LC50s

$$\mathbf{Survival}(t) = \frac{1}{1+\left[\frac{C_L(0)\,(1-e^{-k_e t})}{LC50}\right]^{slope}}$$

Albert. (2016). http://dx.doi.org/10.1371%2Fjournal.pcbi.1004978
Ashauer (2016) http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4933929/
Jager. (2011). General unified threshold model of survival-a toxicokinetic-toxicodynamic framework for ecotoxicology. *Environmental science & technology, 45*(7), 2529-2540.
Redman et al 2023. https://setac.onlinelibrary.wiley.com/doi/abs/10.1002/etc.5476

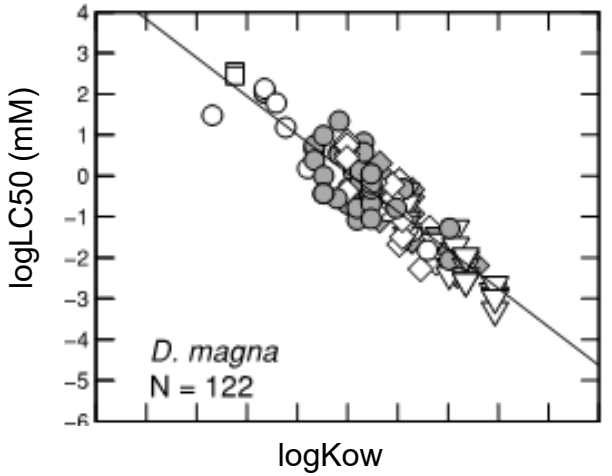


ExxonMobil

Ecotoxicity assessments → species sensitivity distributions

- QSAR
  - Data gap filling
  - Mixture Assessments
  - Converts aqueous exposures to internal exposure
    - **Critical Target Lipid Body Burdens (CTLBB, mmol/kg lipid)**
    - Within similar MoA

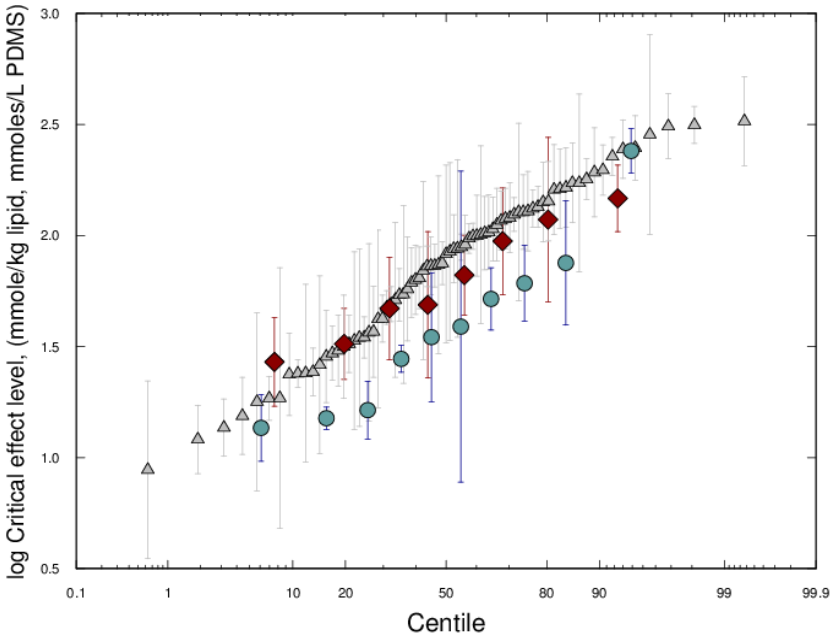
$$logLC50 = -0.94\ logKow + \log CTLBB$$



McGrath et al 2018
DOI: 10.1002/etc.4100

Redman et al 2018
https://pubs.acs.org/doi/abs/10.1021/acs.est.8b00614

- Species sensitivity distributions (SSD)
  - Ranked toxicity of all species
  - Variance and Uncertainty
  - Basis for predicted no effect concentrations (PNEC)



ExxonMobil

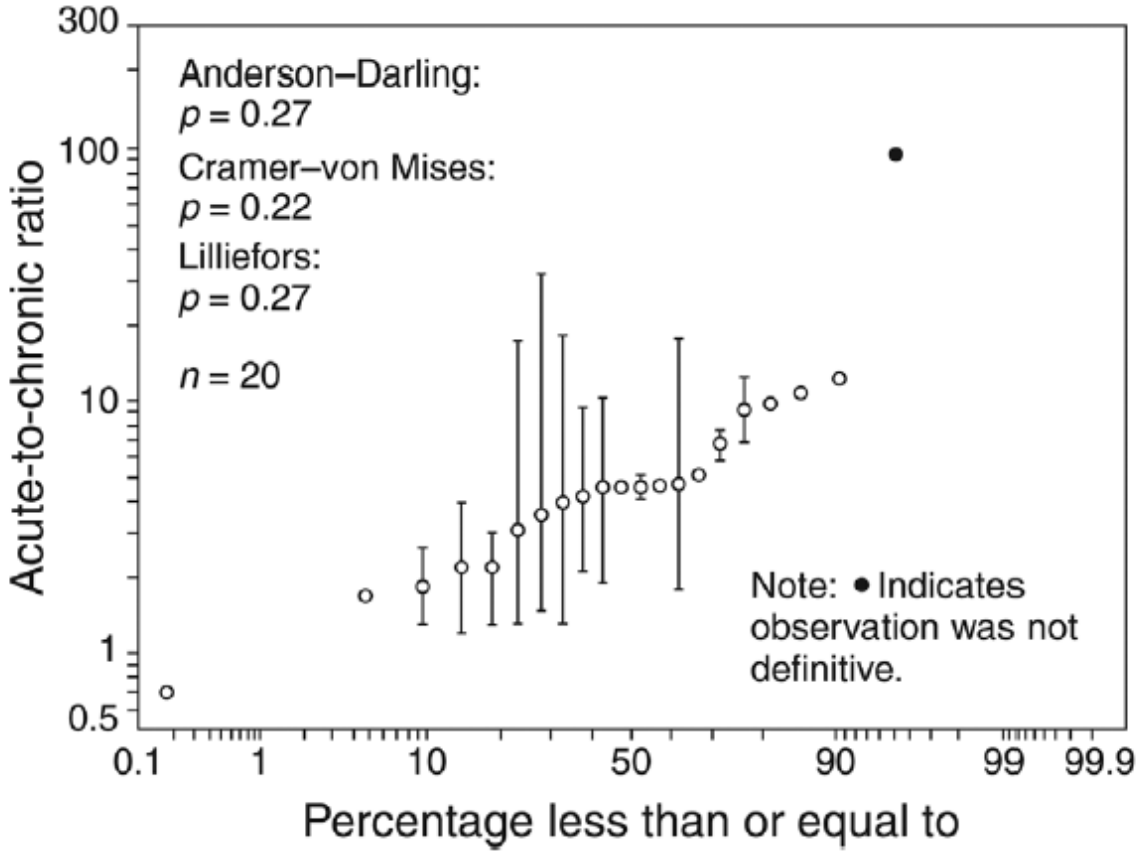
Ecotoxicity assessments: Acute to Chronic Ratios

- Acute to Chronic Ratios where chronic data are limited

  ACR = LC50 / NOEC

  median ACR = 5

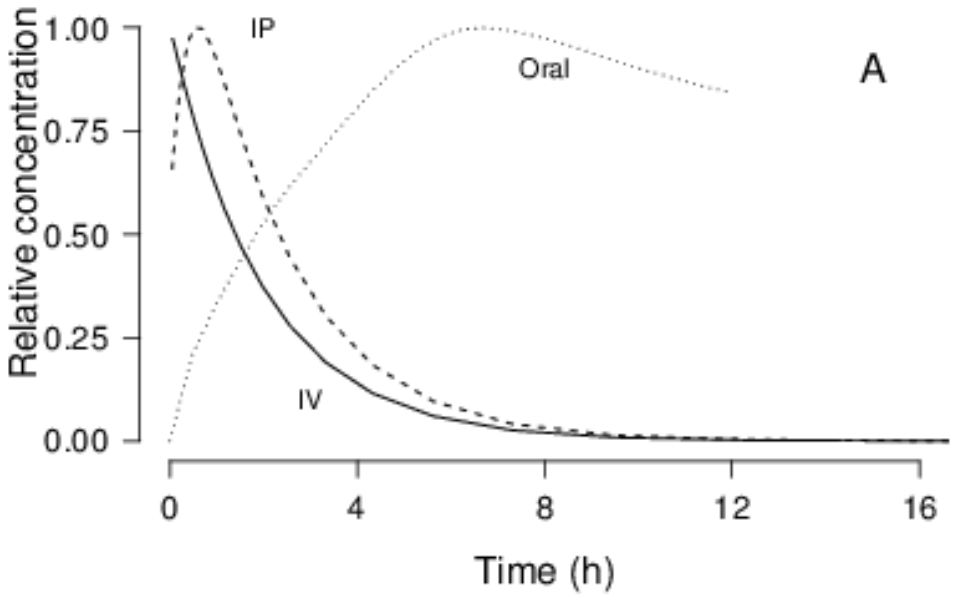
- PNEC based on Chronic effect data

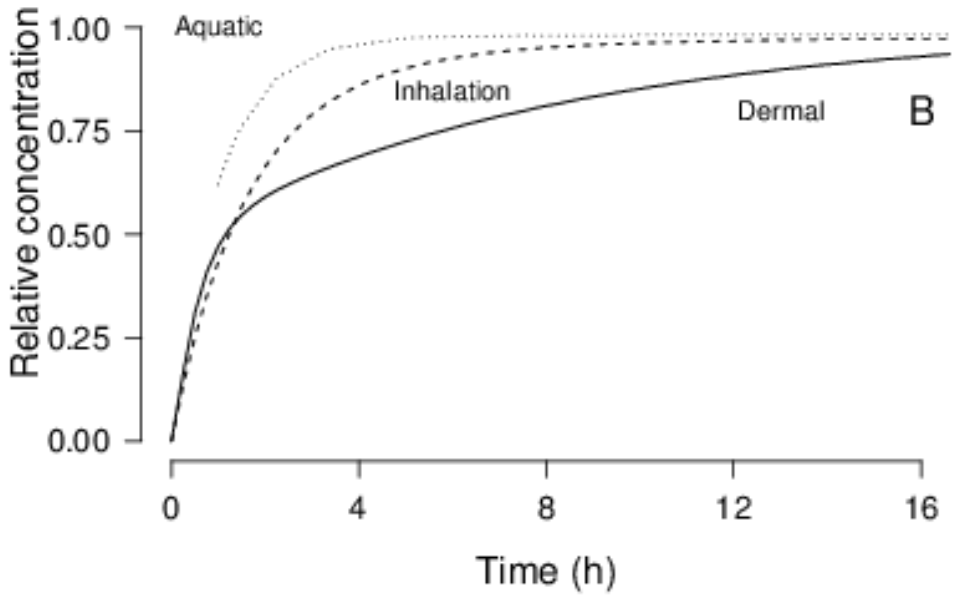


McGrath et al 2018
DOI: 10.1002/etc.4100

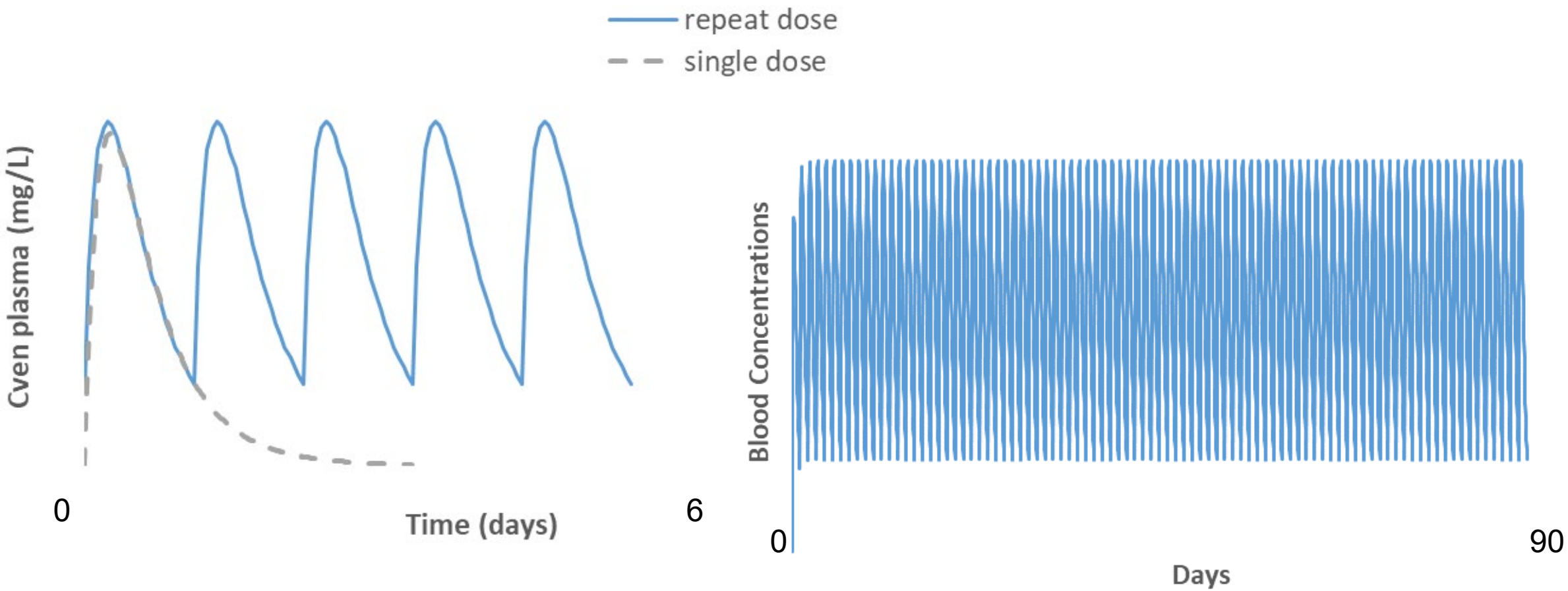
Rodent toxicity testing: single dose testing

- Different routes of administration result in very different internal exposure profiles





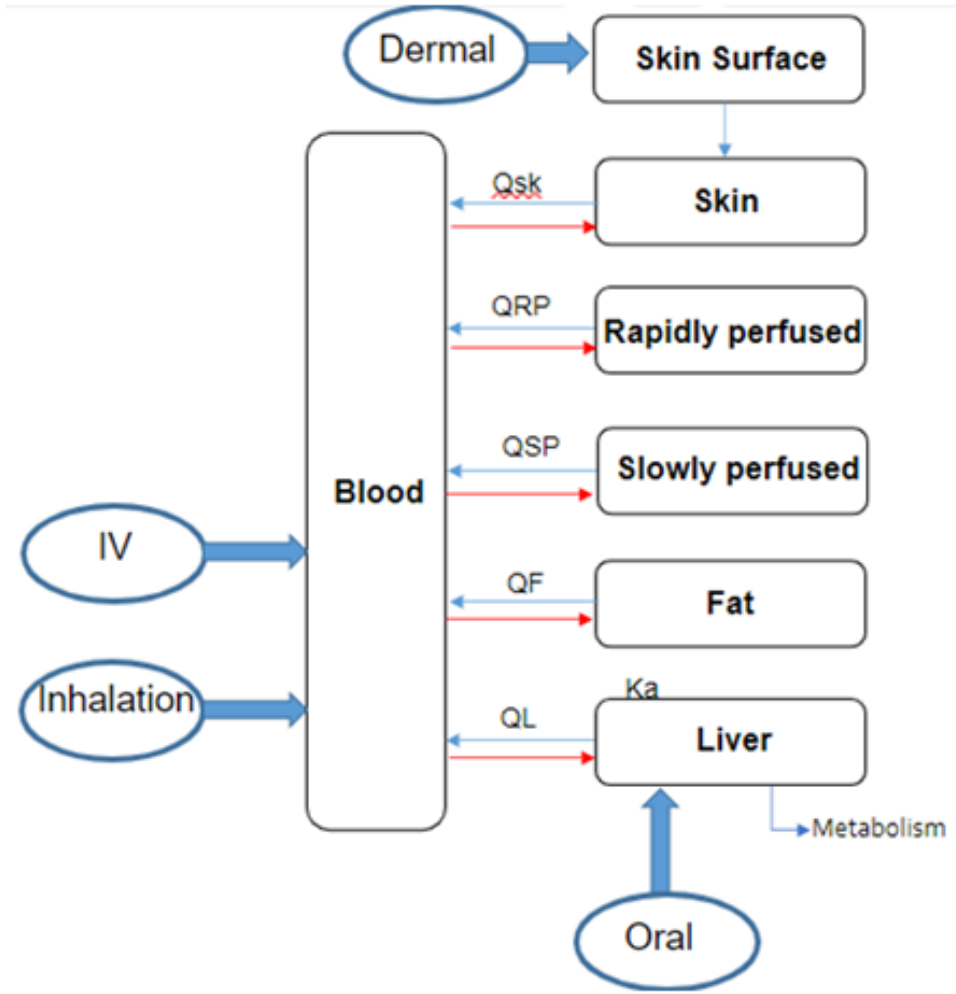
Rodent toxicity testing: repeat dose testing



Fraction unbound (or C_{free}) as a common exposure metric

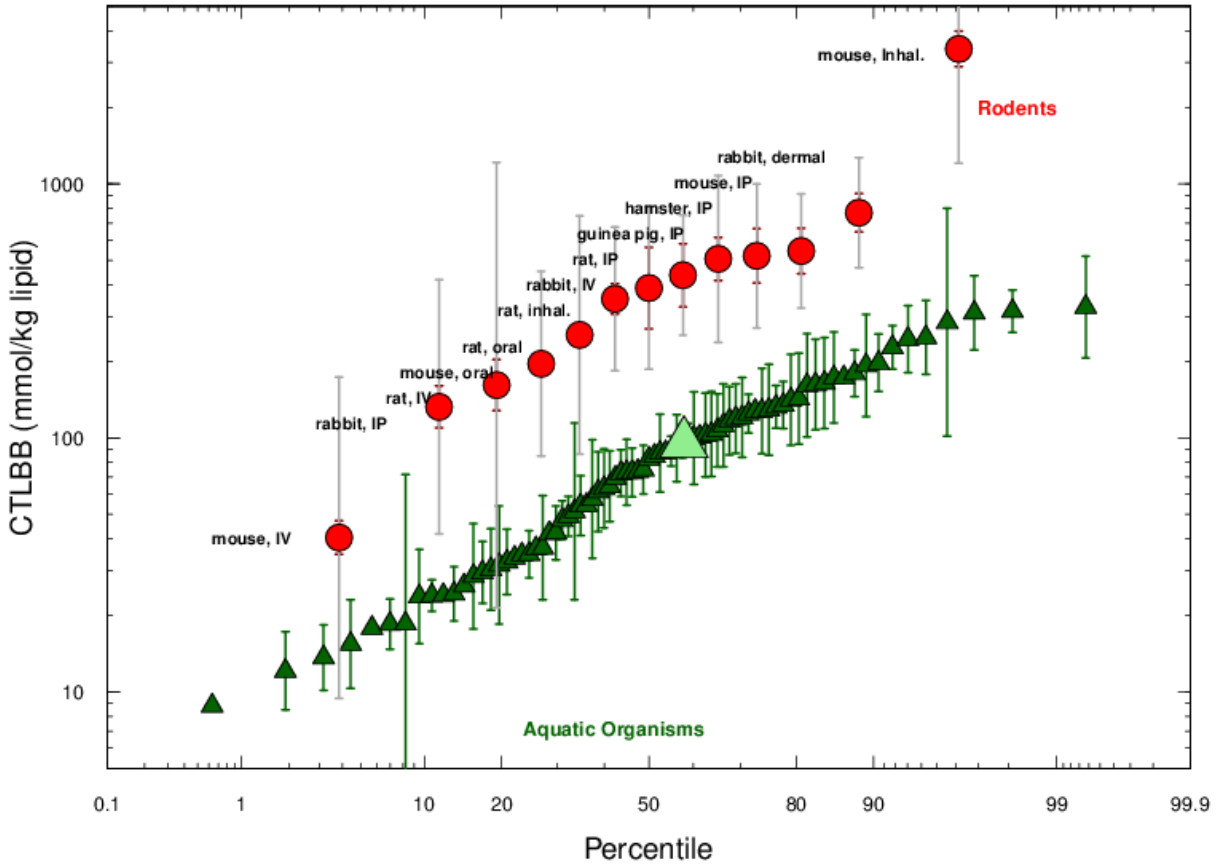
- C_{free} (fub) is the basis of many PBPK approaches
- C_{free} (fub) is often assumed to be the most bioavailable form

$$C_{tissue} = K_{tissue-water} C_{free}$$



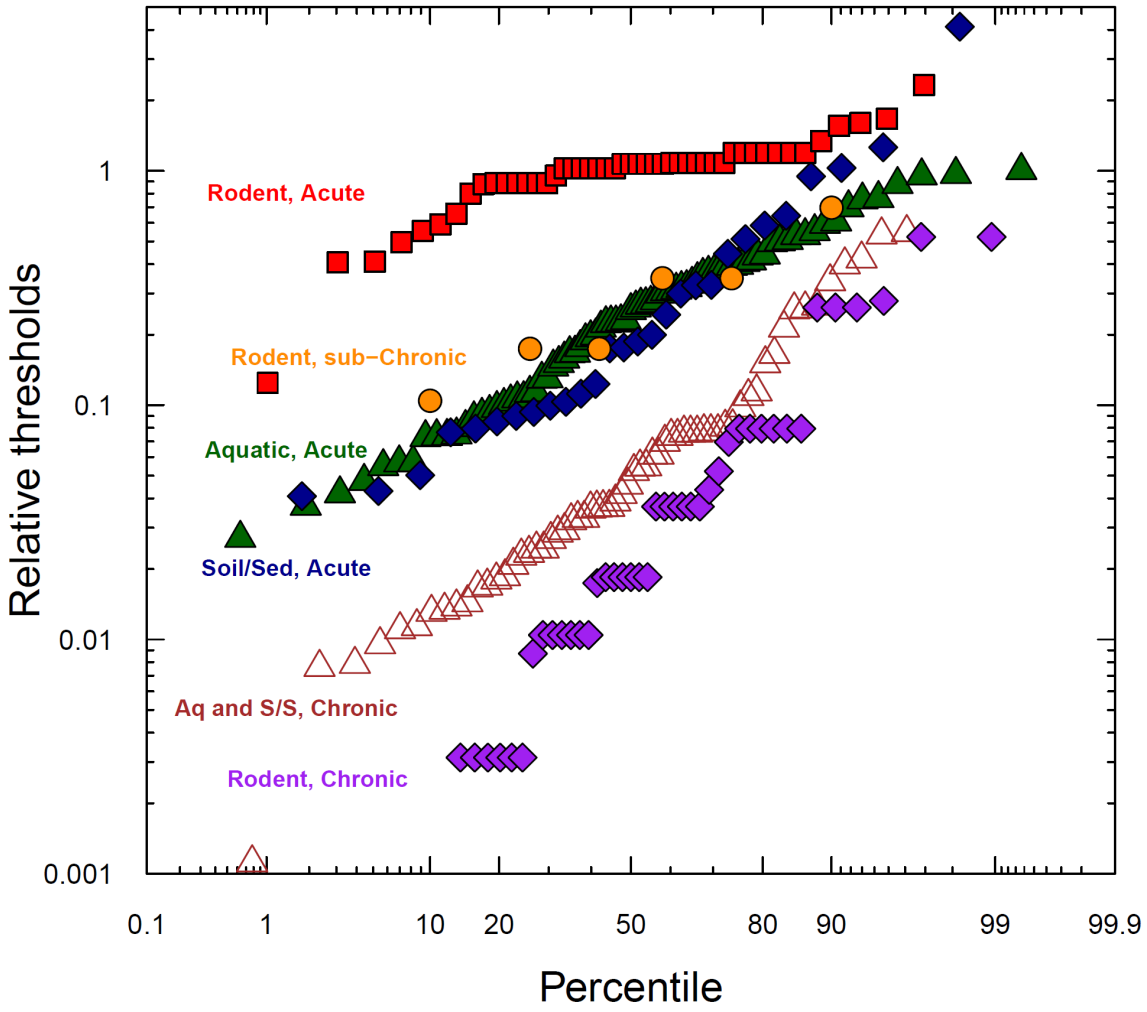
Comparison of Ecotox and Mamtox thresholds using C_{free}

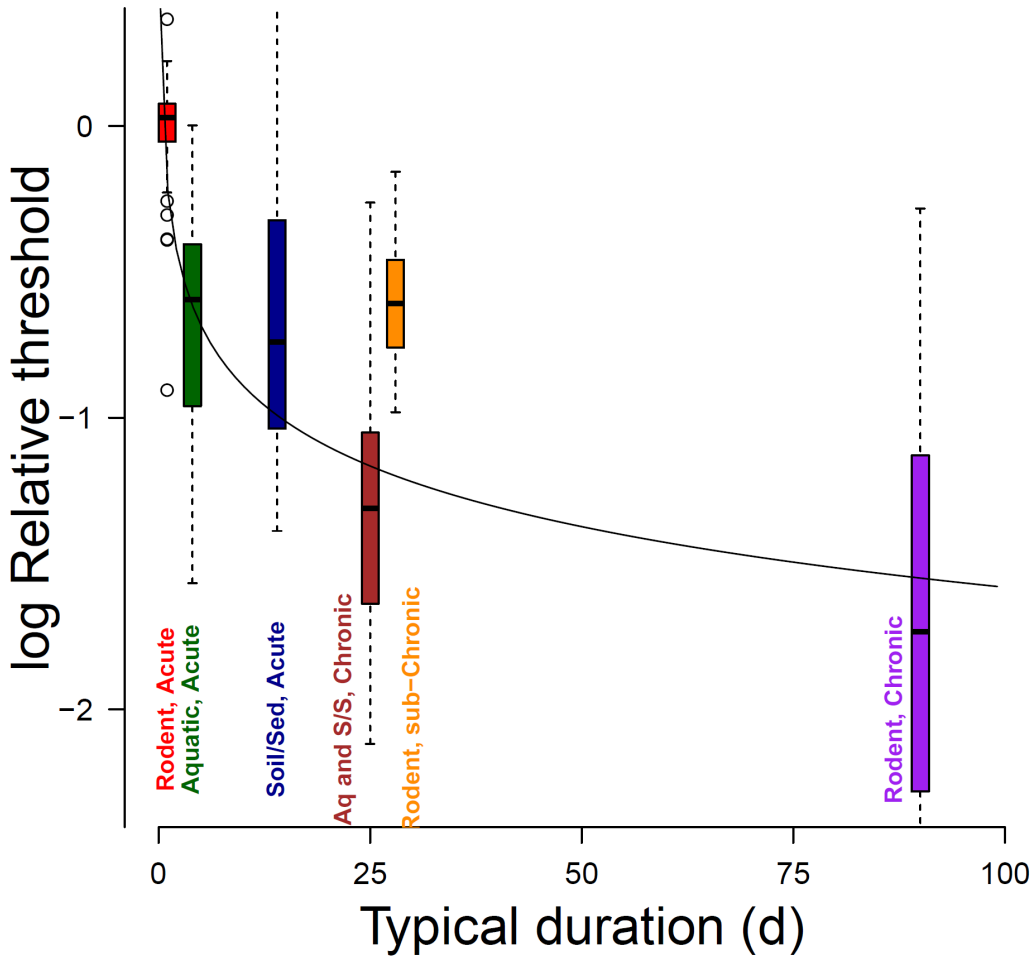
- LD50s converted to CTLBB using Cmax * fub and logKow
  - 6 routes of administration
  - 5 rodent species
- Common basis for comparison to aquatic CTLBBs
  - Rodent CTLBB are higher than Aquatic CTLBB due to duration of exposure



Redman et al unpublished

Change in Toxicity thresholds vs exposure duration



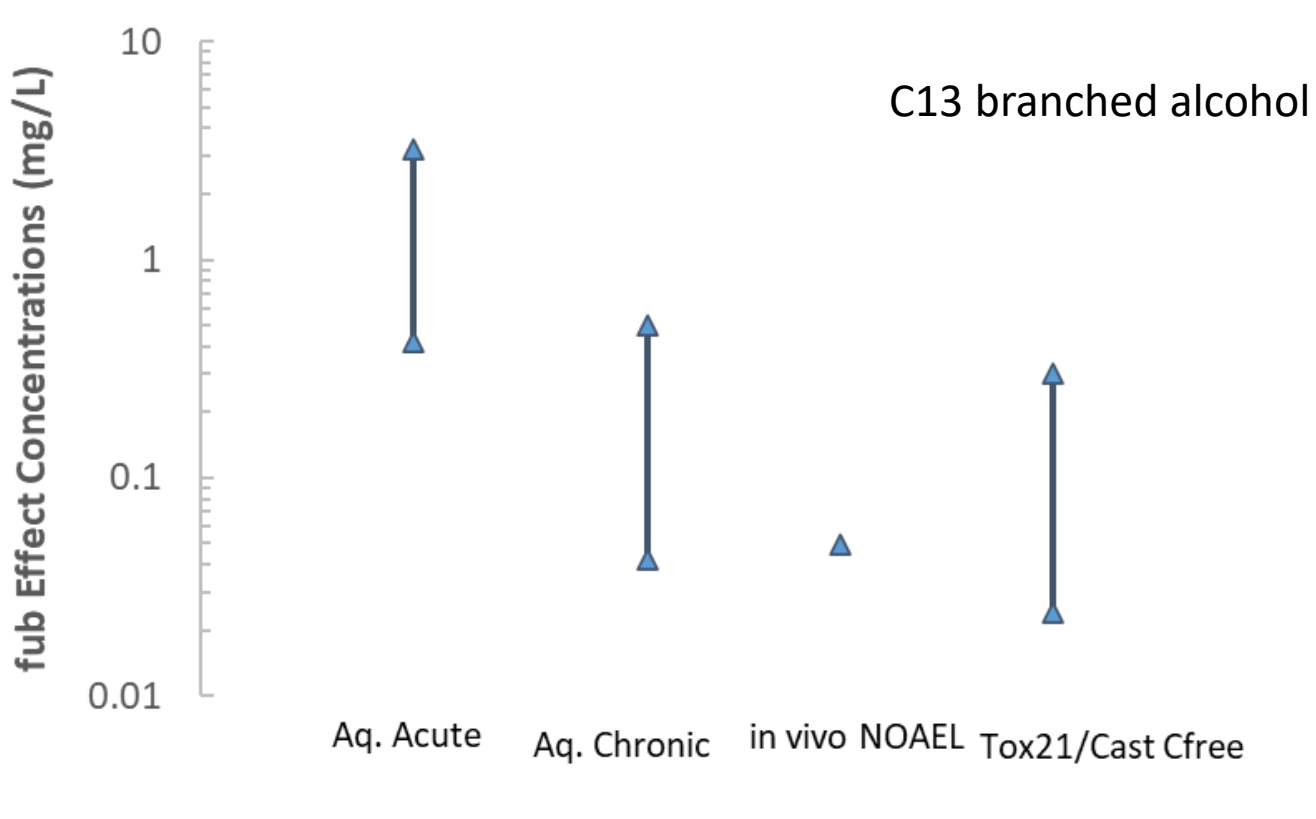


ExxonMobil

McGrath et al 2018; Redman et al 2014; ToxVal (PAH and Fuel oils); Redman unpublished (slide 10)
10.1002/etc.4100 ; 10.1002/etc.2737 ;

Considerations for *in vitro*

- General workflow (e.g., data from ToxDashboard)
  - Correct for fraction unbound
    - Serum-rich systems affect the chemical speciation
    - Exposures can be short (2-24h) so may need to adjust for kinetics
  - Evaluate the laboratory notes
    - because many of the chemicals volatilize out and result in no effects
  - Compare the C_{free} (AC50_free) to the other datasets.
  - Estimate CTLBB using modeling approaches
  - Compare the CTLBB to the SSD approach



Armitage et al 2014
https://pubs.acs.org/doi/abs/10.1021/es501955g
Fisher et al 2017
https://pubs.acs.org/doi/abs/10.1021/acs.chemrestox.7b00023

ExxonMobil

Future work

- Expand TKTD Rodent to Aquatic analysis to chronic endpoints
- Validate exposure metrics (Cmax * fub) as basis for read across between species and chemicals
- In vitro to in vivo extrapolation
  - Thresholds vs exposure time
  - Exposure methods
  - Applicability domain
- Apply to high through put safety assessments (e.g., EPA httk + exposure modeling)
- Extend to UVCBs and super hydrophobic substances

Backup