New approach methods - toxicokinetics

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Goals

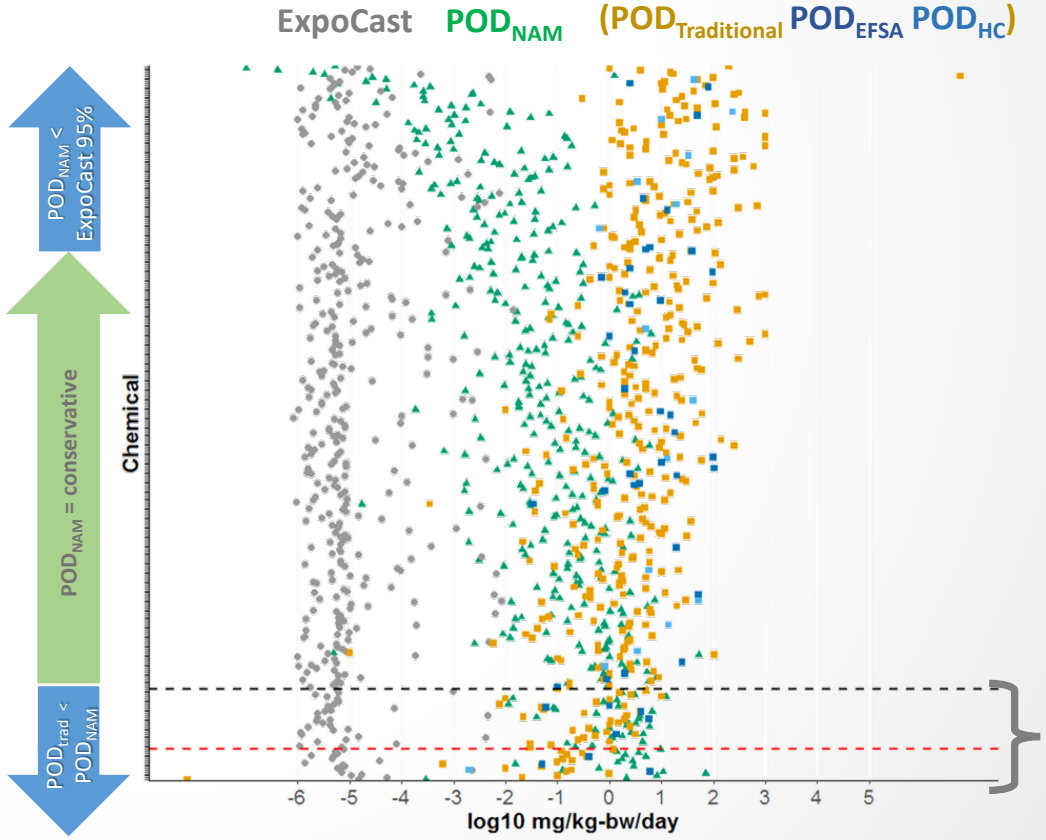
Toxicokinetics (TK) incorporates dosimetry with NAM bioactivity data to enable direct comparisons to anticipated external exposures – allowing risk evaluations.

TK evaluations also provide PFAS-specific information that can inform:

- Bioaccumulative potential
- Half-life estimations
- Read-across approaches
- Biotransformation

Targeted analytic methodologies are also being used to evaluate:

- PFAS *In vitro* stability and disposition
- Quality and stability of DMSO stocks



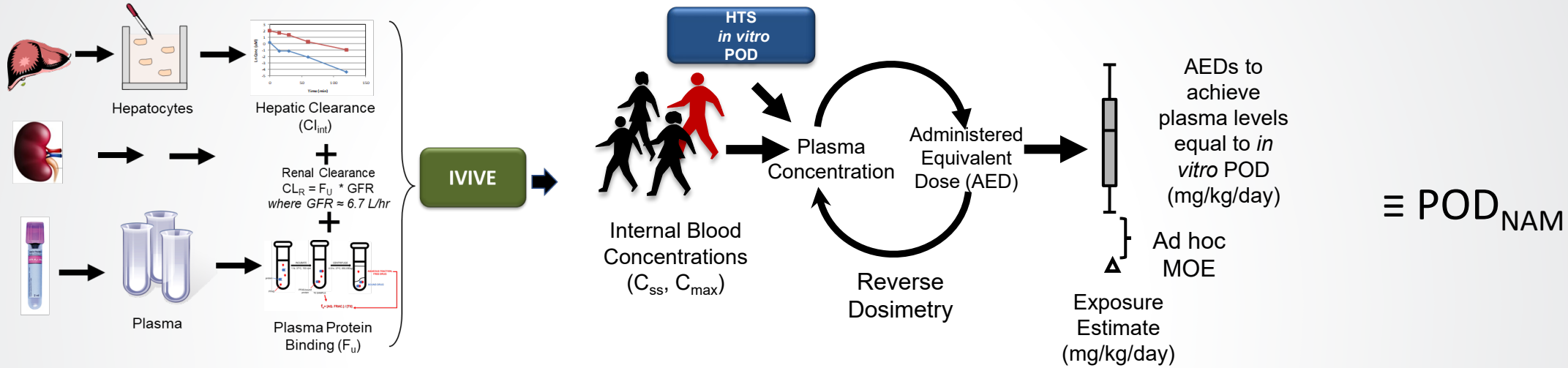
For ~89% of the chemicals, POD$_{NAM}$ was conservative.

(~100-fold on average), but less conservative than a TTC

Chemicals where POD$_{NAM}$ was not conservative enriched in OPs/carbamates

Paul-Friedman *et al.*, 2020 *Toxicol. Sci.*

Approach



- Experimental TK data generated across – ~130 PFAS
  - Plasma protein binding (Ultracentrifugation assay): F_u
  - Hepatocyte clearance (hepatocyte suspensions, loss of parent compound over time): Cl_{int}
  - Renal transport and clearance (MDCK-II model; transporters associated with PFAS uptake/efflux)
  - PFAS metabolite and biotransformation evaluations
  - Above work requires development of sensitive, targeted analytic methods for each PFAS
- Incorporate in vitro TK data in *in vitro-in vivo* extrapolation (IVIVE) approach to estimate steady state concentrations (C_{ss}); incorporation into httk; make available for QSAR development
- Evaluate PFAS *in vitro* disposition (distribution/binding to media, cells, plastics)
- Stock QC: Evaluate ORD PFAS stocks distributed to screening partners for quality and stability

Current Status

- QC of PFAS DMSO stocks complete
  - Over 470 unique stocks analyzed across multiple procurements; Pass/fail score; informational flags
- Plasma protein binding data >95% complete
  - Methodologically challenging PFAS still being attempted
- Hepatic clearance data (NTP and EPA collaboration)
  - 85% complete; to be completed by FY22 Q1
  - More methodologically challenging than plasma work
- Renal transporter data
  - Phase 1: assay work 80% complete
  - Phase 2: Targeted mass spectrometric analysis of samples underway
  - To be completed in FY22
- PFAS biotransformation
  - Chemical selection, study design underway, data generation in FY22
- PFAS *in vitro* disposition
  - Chemical selection, proof of concept design underway; data generation in FY22

Contributors

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