



New Approach Methods - Toxicokinetics

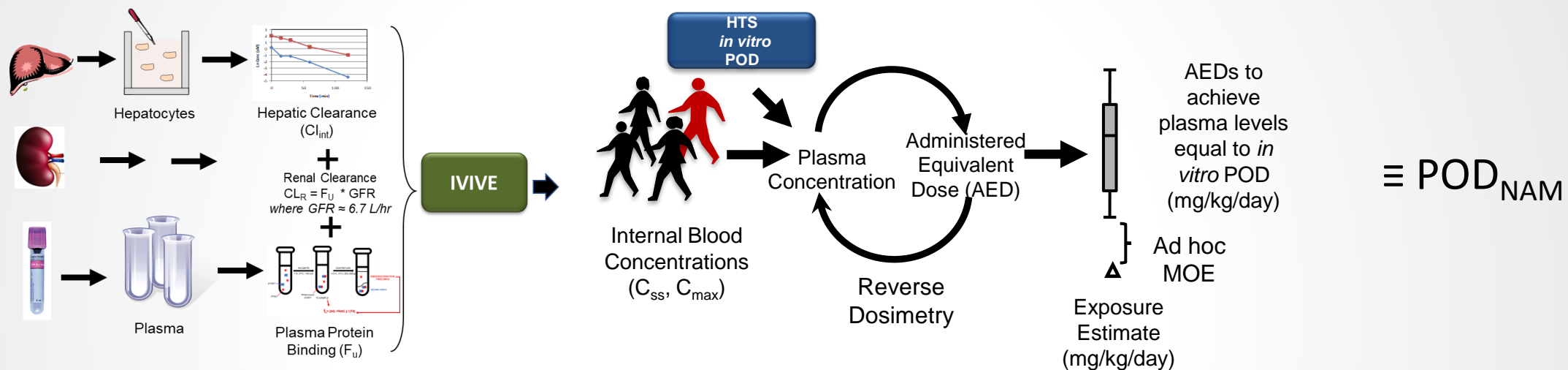
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1. Use new approach methods (NAMs) to characterize the toxicokinetic properties of a structurally diverse set of PFAS including:
 - Bioaccumulative potential
 - Half-life estimations
 - Biotransformation
 - Conversion of *in vitro* potencies to external administered doses
2. Refine structural categories based on toxicokinetic properties for grouping and read across
3. Develop targeted analytical chemistry methods that can be used to evaluate:
 - PFAS *in vitro* toxicokinetics, stability and disposition
 - Quality and stability of DMSO stocks



- 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 htk; 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
- Plasma protein binding data >95% complete
 - Methodologically challenging chemicals 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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