Regulatory applicability: How do we prioritize our next activities?

- How do the workshop discussions feed into regulatory testing requirements?
  - Mixtures additivity:
    - Evaluation of additivity equation ongoing with EPA pilot project (next step is to share results with data submitter stakeholders)
    - determine domain of best predictions to achieve reduction in animal use in the short term
    - “not toxic/less toxic” domains
    - Or where AI appears to be dominant driver of toxicity
    - examine poorly predicted mixtures
    - There may be a need to consider evaluation of evidence that might suggest a potential interactions of concern
    - For non-pesticide mixtures (Consumer products, devices, etc) not always data on components but could run in vitro assays for e.g. polar extractions
  - Take a tiered approach to use tools now where they work well
  - Assess CATMOS predictions for specific regulatory domains, perhaps degradants as well
    - What regulatory domains would applying CATMOS give us potentially less confidence? Are there varying levels of confidence for different applications? How do you enhance the confidence with other lines of evidence?
    - Domain may be purpose for which its applied—more confidence needed for quantitative risk assessment
    - ICCVAM ATWG: nominated substances to assess particular chemicals of regulatory interest—evaluation ongoing
    - EPA also currently assessing CATMOS prediction to see if it change the env. risk assessment conclusions

- Agencies other than EPA?
  - Need to follow up on ATWG testing project
  - Need to unravel regulation needs to see if model meets those needs
- What are implementation steps (i.e., demonstrations, discussions)?
  - Transparency of modeling steps and outputs
  - TRAINING for tool and data users
  - Refining confidence intervals/variability analysis; reflect where metadata exists to demonstrate protocol fealty and determine if in vivo study variability remains the same
  - Issue: control of/public access to proprietary models
  - Evaluation process need to balance type I and type II errors
  - Public engagement all along—PPDC?
- What other classification strategies can we discuss to cover specific sets of chemicals? I.e. can we envision using existing tools to cover the most or least severe classes of acute toxicants?
  - Formulations: additivity for least toxic categories?
  - CATMOS to predict most toxic?
  - Case studies with specific examples can show how to predict different classes/mechanisms

- Can mechanistic information improve prediction of acute toxicity of mixtures?
  - Potentially; for more toxic mixtures, may be essential
  - Can play a supporting or prioritizing role
- Could we cover a large part of the chemical space with assays for key mechanistic domains? If so, which ones?
  - Dan: receptor binding
  - Mitochondrial tox
  - A/L interface models for reactives
  - Next steps: tables of mechanistic toxicity; match w/chemicals and enter into wiki

- What ~~data~~ sharing needs exist?
  - Formulation characteristics, components
  - Data sets to build ADME/PBPK models
  - Mechanistic models—where to host? How do they get updated as new data becomes available?
  - ADME/PBPK modeling solutions
- Other steps: ADME, toxicity testing in vitro?
  - Project to catalog metabolic processes and tests to identify metabolites; link to in vitro toxicity tests and where they don't account for metabolism
  - Understand other limitations of specific in vitro tests (this is typical when method are characterized)
  - Add known mechanisms to the AOP Wiki to get engagement
  - Proof of concept case studies
  - Other geographic areas/regulations/requirements—are they open to these models?