New Approach Methods in Human Health Risk Assessment

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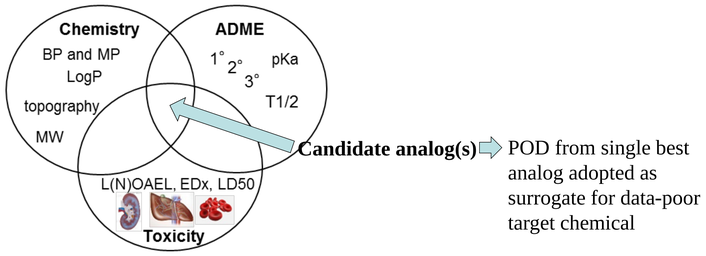
Integration of New Approach Methods-Theory

- Chemicals nominated for Human Health Risk Assessment (HHRA) have widely varying hazard and dose-response databases
- Integration of New Approach Methods (NAM) is therefore fit-for-purpose along a decision-based gradient:
  - Data-poor chemicals ⇨ NAM may be a driver
  - Data-rich chemicals ⇨ NAM fills data gaps
  - Same/similar assays, same/similar data can be used in different ways to answer specific questions
- NAMs currently being integrated or evaluated in EPA HHRA contexts include:
  - Read across (expert-driven; category-based)
  - Transcriptomics (*in vivo* short-term animal)
  - High-throughput bioactivity
- Although not NAM per se, transparency principles of systematic review and integration of toxicity pathway (e.g., AOP or MOA) information also paramount

Read-Across

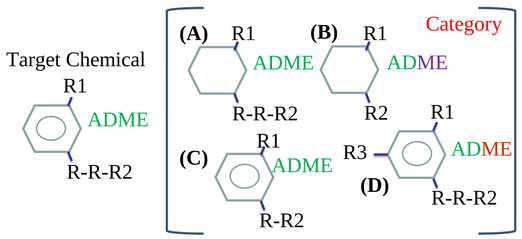
Expert-driven read-across

- 'Many-to-one approach'
- Approach is based on evidence across three information tiers (e.g., structural and physicochemical; toxicokinetic; and toxicity/bioactivity) to select analog(s)
- Hazard and dose-response information (e.g., point-of-departure [POD]) from single best analog used as surrogate for target chemical



Category based read-across

- 'One-to-many' approach
- Based primarily on structural and physicochemical properties
- Robustness of approach dependent on density of analogs populating a category
- Highly reliant on weight-of-evidence supporting toxicity endpoints across category
- Presumes common AOP or MOA across category members



Tox for category
(A)= liver
(B)= kidney, liver
(C)= liver
(D)= GI, liver, kidney

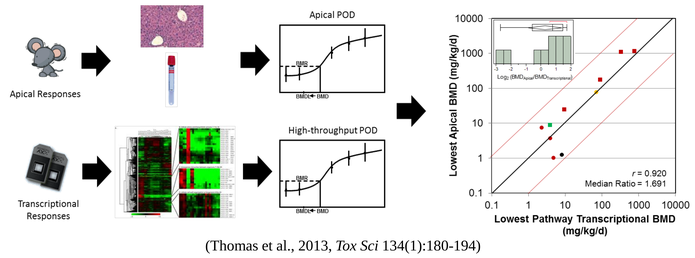
ADME = Absorption, Distribution, Metabolism, Elimination

HHRA application(s)

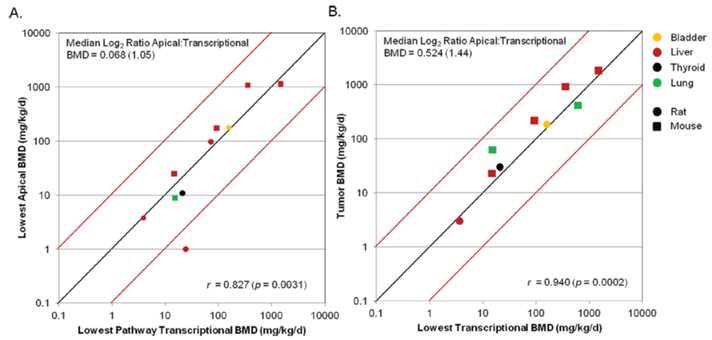
- Provisional Peer-Reviewed Toxicity Value (PPRTV) assessments; Superfund Technical Support memos to EPA Regions

Transcriptomics

Transcriptional perturbations and apical endpoints for both cancer and noncancer are evaluated in same organ tissues following short-term (e.g., 2-week) exposures

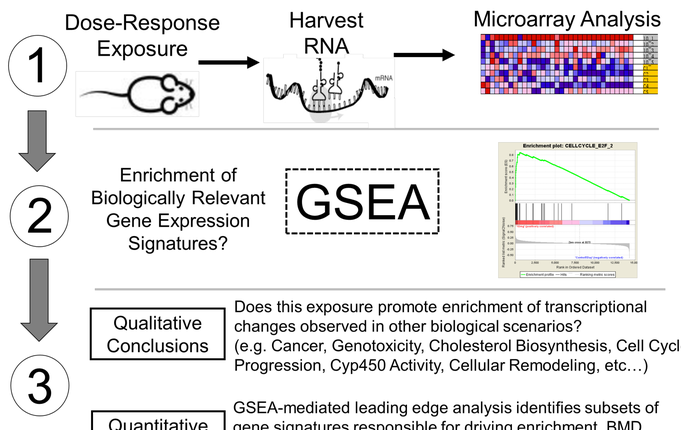


(Thomas et al., 2013, *Tox Sci* 134(1):180-194)



- Transcriptional pathway-based points-of-departure (PODs) from short-term *in vivo* assays were within 2-3 fold of both non-cancer (A) and cancer (B) apical PODs across different species, routes of exposure, durations of exposure, and target organ tissues
- Major challenge: relevance of transcriptional pathway perturbations to target organ toxicity?

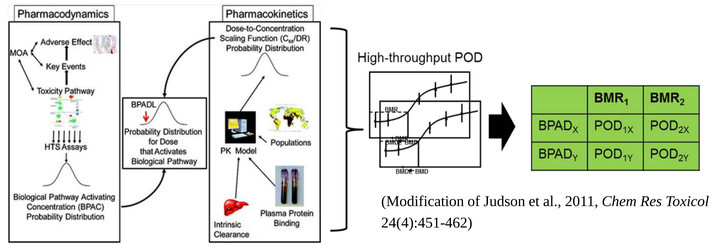
GSEA: Identifying Biologically-Relevant Transcriptional Alterations



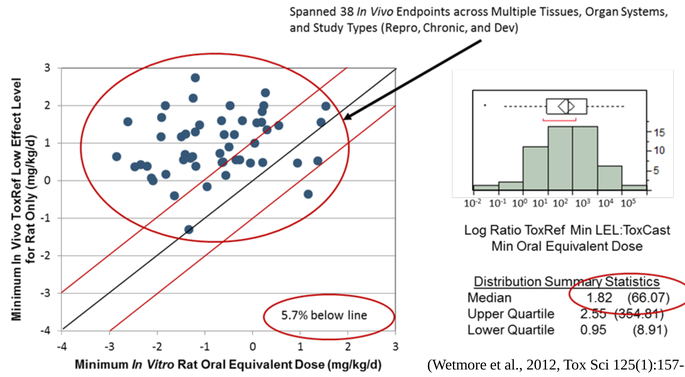
(Image courtesy of Dr. Jeffry Dean, EPA/ORD/NCEA-Cincinnati)

High-throughput Bioactivity

Integration of in vitro biological activity data (e.g., ToxCast/Tox21) and reverse toxicokinetic in vitro to in vivo extrapolation may facilitate identification of oral equivalent doses that can be benchmark dose modeled for identification of HTP-based PODs



(Modification of Judson et al., 2011, *Chem Res Toxicol* 24(4):451-462)



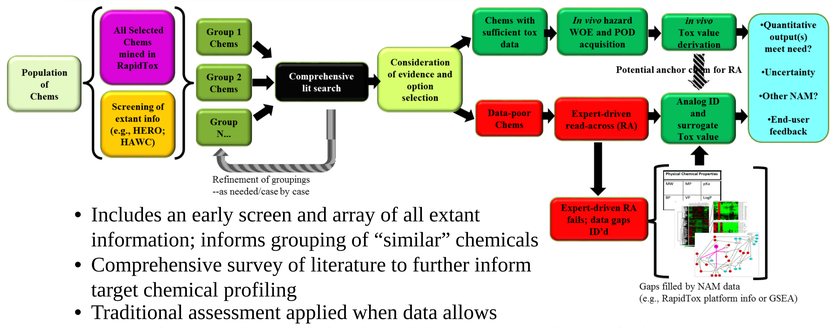
(Wetmore et al., 2012, Tox Sci 125(1):157-174)

HHRA application(s)

- Superfund Technical Support memos to EPA Regions; bioactivity information used as qualitative support for augmenting weight-of-evidence in analog(s) selection

Bringing it all together

Integrated Approach to Human Health Assessment



- Includes an early screen and array of all extant information; informs grouping of "similar" chemicals
- Comprehensive survey of literature to further inform target chemical profiling
- Traditional assessment applied when data allows
- Expert-driven read-across when hazard/dose-response data are lacking
- Integration of information from NAM data streams to fill gaps

**The collective Agency efforts presented here are in response to the NAS' suggestion to put research/processes in place to adapt to new and emerging methods

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