# Task 8.2: Characterization and Quantitative Application of High-throughput Screening (HTS) and Other Data-mining Derivations

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HHRA
Human Health Risk Assessment

## Relevancy to Risk Assessment and Project Goals

- Addresses need to develop approaches for interpreting and applying non-traditional, higher-throughput data to human health risk assessment and technical support efforts conducted within the HHRA program.
- This task is highly relevant and represents part of the collaborative integration of research efforts between scientists within the HHRA and CSS Programs on the incorporation of new technologies into chemical safety and risk assessment.
- This integration is designed to help facilitate the understanding and characterization of the utility of the application of higher-throughput data to various quantitative fit-for-purpose risk assessment and decision-maker needs within the Regions and Program Offices.
- The goals of this task are to perform methods development and proof-of-concept evaluations that inform how data from alternative platforms may ultimately result in the identification of quantitative screening estimates and other fit-for-purpose applications.

## Methods/Approach for Four Proposed Subtasks

**1) Methods development for estimating points-of-departure (PODs) from transcriptomic data.**

- This subtask is a proof-of-concept demonstration that aims to use tissue-specific gene signatures that represent critical signaling pathways from which to determine PODs based on differential transcriptomic changes.

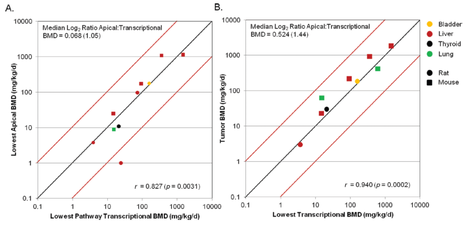


**Figure 1:** Scatter plots of the relationship between the BMD values for (A) cancer-related apical endpoints or (B) noncancer apical endpoints and transcriptional benchmark dose (BMD) values for the most sensitive signaling pathway following 13 weeks of exposure (figure from Thomas et al., 2013). Subtask 1 is unique in that in lieu of considering the most sensitive signaling pathway (where there is a high degree of correlation), it incorporates considerations of molecular mechanism and toxicological/pathological adversity into the analysis of transcriptomic data for HHRA application purposes.

**2) Characterization of data-derived extrapolation methods for derivation of alternative data-based screening risk estimates based on comparisons to traditional risk estimates.**

- This subtask will focus on the analysis of quantitative relationships between currently available high-throughput data and existing dose-response data associated with known peer-reviewed toxicity values.
- Approaches characterizing this quantitative relationship will be explored to further inform the potential use of high-throughput-based PODs in derivation of screening risk estimates.

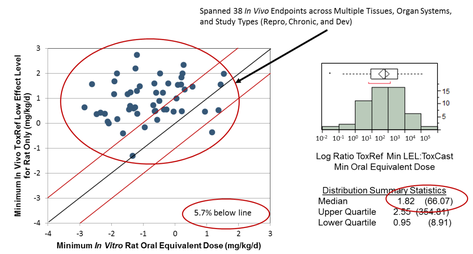


**Figure 2:** To illustrate an example approach (figure from Wetmore et al., 2012), a comparative evaluation of reference values based on in vivo data versus in vitro high-throughput data can be done in Subtask 2

**3) Adverse outcome pathway (AOP) footprinting: hazard grouping and quantitative analysis for assessment of mixtures of toxicologically uncharacterized stressors.**

- This subtask will focus on demonstrating how mechanistic information (e.g., AOPs) could be used to inform mixtures assessment applications such as hazard grouping and dose-response analysis for data-poor stressors.

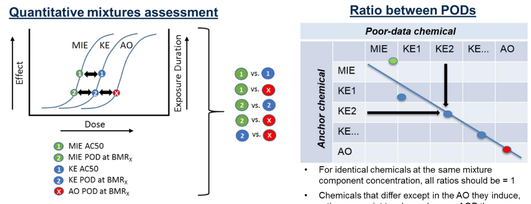


**Figure 3:** For hazard grouping, identification of causal node(s) within AOPs may provide a basis for common grouping of mixture chemicals based on pathway rather than chemical class (e.g., grouping at the key event [KE] or molecular initiating even [MIE] level). Quantitative relationships between PODs at each node level may facilitate identification of which AOP event(s) are most closely correlated to a health outcome of concern.

**4) Incorporation and application of high-throughput screening estimates into HHRA technical support products.**

- This subtask will integrate high-throughput PODs generated collaboratively with the CSS Demonstration and Evaluation (D&E) project (e.g., from read-across/SAR, QSAR, ToxCast, toxicogenomics data, other data repositories, etc.), as well as information gleaned from the other three subtasks within Task 8.2, to derive screening estimates for case study chemicals for which little-to-no data exist.
- Technical support products will provide gradations of information relevant to hazard identification and dose-response assessment, facilitating a broad range of assessment foci from basic hazard screening/prioritization to derivation of quantitative risk estimates.

## Background

- Several EPA Program and Regional Offices often require addressing the potential hazard(s) to human health and the environment of chemicals for which little to no data exist.
- This important need by the Program and Regional partners warrants basic identification of hazard and associated quantitative dose-response assessment for screening and prioritization purposes.
- This task will address an expanded universe of chemicals and endpoints (e.g., use of quantitative structure-activity relationship [QSAR] modeling to quantitatively predict developmental toxicity of halogenated compounds; see Craig et al., 2013), as well as evaluating alternative platforms or approaches such as structural read-across, in vitro biological activity assays (e.g., ToxCast), and toxicogenomics data. Additionally, this task can augment application of output data from the CSS Program.

## Anticipated Products

### Short-term (FY16 – FY17)

**1)** Scientific journal article; FY16 – Submitted to journal; FY17 – Published.

**2) and 3)** Scientific journal article; FY17 – Submitted to journal.

### Long-term (FY18 – FY19)

**2) and 3)** Scientific journal article; FY18: Published.

**4)** Scientific journal article on case studies; integrated hazard and quantitative technical support documents for fit-for-purpose applications. For journal article: FY19 – Submitted to journal; FY19 – Published; For HHRA products (i.e., technical support documents): FY19.

## Impact

### Short-term (FY16 – FY17)

**1)** The proof-of-concept demonstration within this subtask represents one of the necessary initial steps in understanding the potential utility of alternative data applied in quantitative HHRA assessment products.

**2)** The proof-of-concept demonstration and case studies generated from this subtask may significantly advance our understanding of the uncertainties associated with the quantitative relationship between high-throughput PODs and traditional in vivo PODs.

### Long-term (FY18 – FY19)

**3)** Proof-of-concept demonstration and application of AOP data in a mixtures context may significantly advance approaches in stressor (hazard) grouping and mixtures dose-response analyses using non-apical effect data/metrics.

**4)** Envisioned technical support products will significantly advance fit-for-purpose application of alternative data streams across multiple Program and Regional Offices.

*Disclaimer: The views expressed in this poster are those of the author and do not necessarily reflect the views and policies of the U.S. EPA.*

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