# Application of Early Molecular Measurements to Develop Points of Departure for Risk Assessment

Society of Toxicology Workshop
Leah Wehmas, U.S. EPA, Chair
Connie Mitchell, HESI, Chair
March 13, 2024 (1:30 PM to 4:45 PM)

*This presentation does not represent U.S. EPA policy or endorsement and I have no conflicts to disclose.*

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Creating a Safer and Healthier World by Advancing the Science and Increasing the Impact of Toxicology

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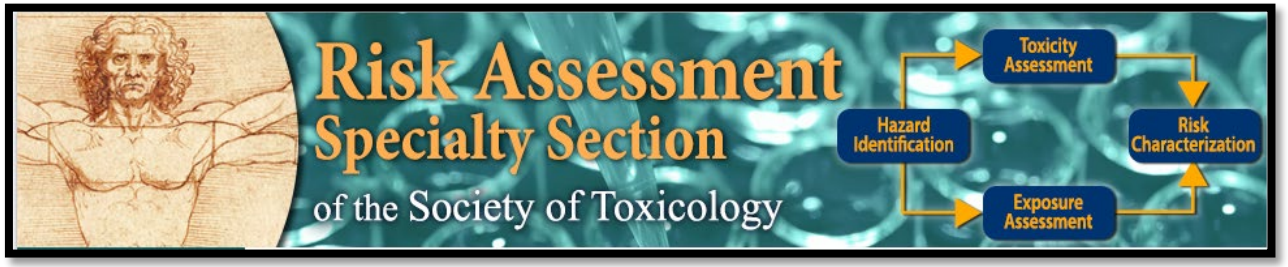
MSBSS

Molecular and Systems Biology Specialty Section




REGULATORY & SAFETY EVALUATION

Specialty Section

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# Application of Early Molecular Measurements to Develop Points of Departure for Risk Assessment

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|---|---|---|
| **Leah Wehmas (US EPA)** | *Introduction* | **1:30 PM to 1:35 PM** |
| **David Rouquie (Bayer)** | *Integration of NAMs and omics for determining points of departure* | **1:35 PM to 1:55 PM** |
| **Joshua Harrill (US EPA)** | *Evaluating the Impact of Cell Line Choice on Determination of Human Health Protective Molecular Points-of-Departure.* | **1:55 PM to 2:15 PM** |
| **Celeste Carberry (UNC)** | *Incorporating extracellular vesicle mediators of PFAS toxicity into NAMs-based points of department: a comparison against transcriptomic-based risk values* | **2:15 PM to 2:35 PM** |
| **Julia Malinowska (JCR-ISPRA)** | *Derivation of metabolic point of departure using high-throughput in vitro metabolomics: investigating the importance of sampling time points on benchmark concentration values in the HepaRG cell line* | **2:35 PM to 2:55 PM** |
| **Richard Currie (Syngenta)** | *Using omics for decision making and regulatory applications by Industry.* | **2:55 PM to 3:15 PM** |
| **Tara Barton-Maclaren (Health Canada)** | *Evaluating in vitro transcriptomics data for regulatory testing and assessment - Are we there yet?* | **3:15 PM to 3:35 PM** |
| **Panel Discussion** | *Q&A* | **3:35 PM to 4:15 PM** |

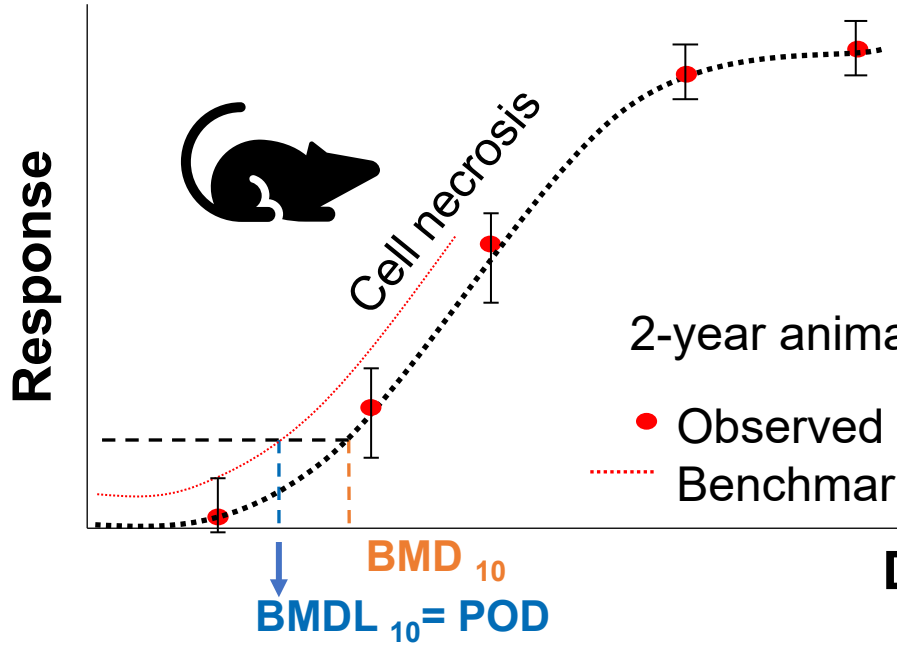
# Traditional chemical assessments rely on chronic animal studies

Feedback

**Risk Assessment**
- Exposure Assessment
- Hazard Identification
- Dose Response

**Risk Management**
- Control Decision
- Acceptable Risk Level
- Control Alternatives

Feedback




2-year animal study

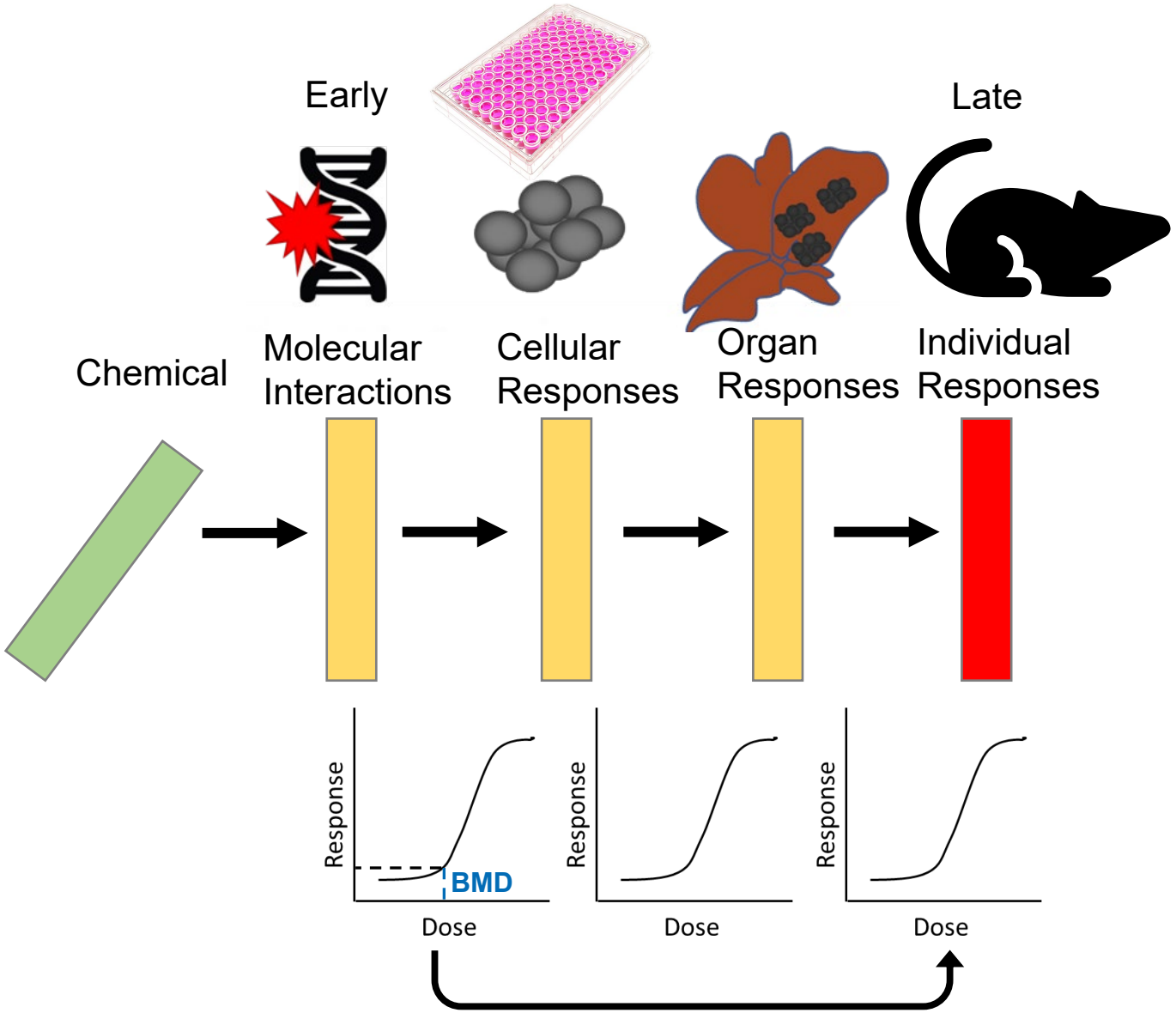
- Observed Response
- Benchmark dose lower bound

Reference value:

$$\text{POD} \rightarrow \frac{Human\ equivalent\ dose}{Uncertainty\ factor}$$

Benchmark dose (BMD) response modeling identifies point of departure (POD)

# Dose response assessment can be applied to molecular data




- Molecular changes occur with chemical exposure
- Changes often coincide or precede health effects
- Changes are measurable and dose dependent
- Coordinated changes across multiple genes, metabolites, miRNAs can identify a POD indicative of chronic toxicity

**EPA transcriptomic assessment product**