Characterizing Determinants of Risk: Concentration, Duration and Timing of Exposure

What health effects are caused by peak concentration (high exposure, short duration) versus area-level exposures (e.g., in utero) at critical stages of development?

Exposures to chemical pollutants are often not at uniform concentrations for constant, continuous periods of time. Additionally, susceptibility of individuals can vary by life-stage or even time of day. A challenge for EPA is to determine the best approaches for considering risk from real-world exposures based on concentration, duration, and timing of exposure.

Concerns are linked to adverse health outcomes from:

- **Acute and episodic exposures**
  - Real world exposures are rarely at consistently low levels
  - Spikes in exposure levels may affect health more than averages
  - What health effects are caused by peak concentration (high exposure, short duration) versus area-under-the-curve?

- **Early-life exposures (e.g., in utero)**
  - Developmental and reproductive effects
  - Contributions to effects later in life (e.g., cancer)

- **Exposure concentration, duration, and timing influence response in different ways across different levels of biological complexity**
  - Links to biomarkers and AOPs provide opportunities for measurement and approaches to computational systems biology

**What strategy best protects public health for each exposure and effect?**

### Methods/Approach

The classical, two-dimensional dose-response curve has dose/concentration levels on the x-axis and response levels on the y-axis. Other factors can affect the relationship, including duration of exposure, intermittent or fluctuating exposures, consideration of adequate recovery time between exposures, etc. The dose-response relationship is also dependent on the MOA and choice of dose metric.

Accounting for these other factors leads to a multi-dimensional relationship. These multi-dimensional relationships are more appropriately rendered graphically as a three-dimensional surface (surface analysis).

- **Subtask: Case studies applying concentration-duration-response surface analysis**
- **Subtask: Evaluation of early life exposure for lifetime cancer and noncancer outcomes**
- **Subtask: Integration: Application of methods integrating concentration-duration responses within specific windows of vulnerability**

### Anticipated Products

**Short-term (FY16 – FY17)**
- Manuscript: Approaches to estimating health risks from less-than-lifetime and time-varying exposures

**Long-term (FY18 – FY19)**
- Categorical case studies for different endpoints and chemical classes to evaluate determinants of concentration-duration-response surface
- Characterize environmental exposure variability for chemical risk assessments

### Impact

**Short-term (FY16 – FY17)**
- Workshop report will advance approaches to address issues of duration and timing of exposure
- A better understanding of the impact of early life exposure to all outcomes
- Approaches to assess risks from acute, and episodic exposures (including those above a reference value)

**Long-term (FY18 – FY19)**
- Develop a more complete understanding of all aspects affecting adverse health outcomes
- Bridge to systems biology and integrate the nature of exposure patterns to observed health outcomes

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