Task 7.4 - Characterizing Determinants of Risk: Concentration, Duration and Timing of Exposure

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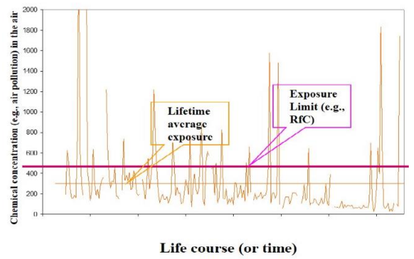
Relevancy to Risk Assessment and Project Goals

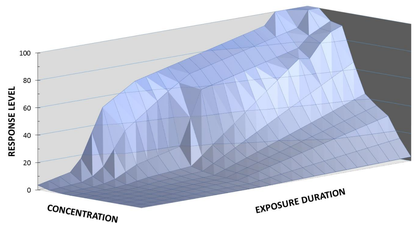
Exposures to chemical pollutants are often not at uniform concentrations for constant, continuous periods of time. Additionally, susceptibility of individuals can vary by life-stage or even time of day. A challenge for EPA is to determine the best approaches for considering risk from real-world exposures 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) at critical stages of development**
  - 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?



Stylized Concentration-Duration-Response Surface Chart



Methods/Approach

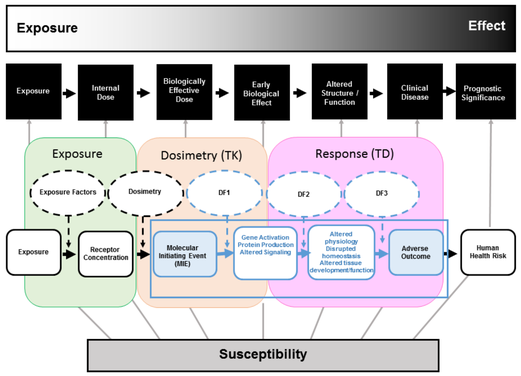
The classical, two-dimensional dose-response curve has dose/concentration levels on the x-axis and response levels on the y-axis. Other factors can affect the relationship, including duration of exposure, intermittent or fluctuating exposures, consideration of adequate recovery time between exposures, 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). The concept of a concentration-duration-response surface will be applied in this subtask to the analysis and interpretation of toxicological data. The approach will consist of two main subtasks and a third integration exercise:

- **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**

Background

This task builds upon several ongoing efforts within HHRA, other research programs (ACE and CSS) and Program Offices within EPA (OAQPS, OCHP, and OW), and leverages resources and expertise with key Federal partner agencies (FDA, NTP, and NIOSH). The work in this task will be informed by an upcoming workshop on temporal issues.



Conceptual construct developed for biomarkers, adverse outcome pathways (AOP, in blue) and mode of action (MOA) with components of exposure concentration, duration and response. DF = Determining factor

Anticipated Products

Short-term (FY16 – FY17)

- Report of the "Temporal Exposure Issues" Workshop (January 27-29, 2016) [http://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=307738]
- 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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