# Project 6: Cumulative Risk Assessment Methods and Applications
# Task 6.3. Applying Genetic and Epigenetic Data to Inform Susceptibility

Susan Y. Euling
National Center for Environmental Assessment
Office of Research and Development

HHRA
Human Health Risk Assessment

## Relevancy to Risk Assessment and Project Goals

By developing our understanding of how to utilize different types of susceptibility information for use in cumulative risk assessment, Task 6.3 is supporting HHRA's Project 6 as well as one of the EPA Administrator's themes, *Making a Visible Difference in Communities across the Country*. The products within Task 6.3 are designed to support risk assessors within (Regions and Programs) and outside of EPA.

The task is separated into subtasks that include a focus on utilizing two different types of molecular data, epigenetics and genetics, that can inform susceptibility or inter-individual response to chemical exposures, and use this information to improve community-based and cumulative risk assessment (CRA).

## Background

Susceptibility is defined by the NRC (2009) as the capacity to be affected. A person can be at greater or less risk relative to population median risk because of susceptibility factors such as life stage, sex, genetics, socioeconomic status, prior exposure to chemicals, and non-chemical stressors. Two important policy drivers requiring EPA to use susceptibility information in environmental chemical decision-making are:

- The Food Quality Protection Act (FQPA, 1996), mandated that EPA consider possible increased susceptibility of infants and children in the risk assessments of food use pesticides; and
- The Safe Drinking Water Act amendments (SDWA, 1996), required EPA to consider susceptible populations in risk assessments used in support of drinking water contaminant regulations.

In 2009, the National Research Council's *Science and Decisions: Advancing Risk Assessment* (NRC, 2009) report states that "*Variability in human susceptibility has not received sufficient or consistent attention in many EPA health risk assessments*," and charges the EPA to improve its understanding and incorporation of susceptibility in risk assessment. Approaches to incorporate new and emerging molecular data types to characterize susceptibility information in CRA are needed.

## Methods/Approach

**Epigenetics:** Twin studies have shown that expression of diseases is not concordant between monozygotic twins (Fig. 1) and thus, arise in part from differences in environmental factors. Data on epigenetics (heritable phenotypic traits due to chromatin changes without DNA sequence changes [Fig. 2]) have the potential to provide susceptibility information and are not routinely in risk assessment. Expert workshop findings, case studies, and literature reviews of epigenetic mechanisms and disease as well as current toxicity testing will be performed to develop knowledge and expertise in applying epigenetic susceptibility data to CRA.

Figure 1. Monozygotic twins later in life.

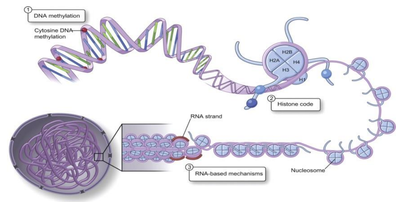
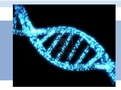



Figure 2. Epigenetic changes. 1) DNA methylation; 2) Histone coding; 3) RNA-based mechanisms.



**Genetic Susceptibility:** Defining genetic susceptibility, or inter-individual genetic variation, that impacts response to environmental chemical exposure across human populations can be useful in risk assessment. We will adapt the AOP framework (Ankley et al., 2010) to organize and integrate genetic susceptibility information (Mortensen and Euling, 2013; Fig. 3). This approach will be tested in a case study of a well-characterized AOP. Publicly available human genetic variation data sources (e.g., Tox21, NIEHS Environmental Genome Project) will be utilized to characterize genetic variation at loci associated with an adverse outcome.

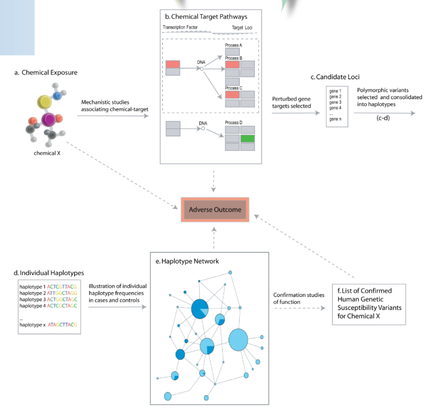



Fig. 3. Proposed process for the characterizing inter-individual genetic variation that influences the response to chemical exposure.

## Anticipated Products

### Short-term (FY16 – FY17)

- Report from the *Epigenetics and Cumulative Risk Assessment Workshop* held Sept. 2-3, 2015 and attended by epidemiologists, molecular biologists and toxicologists from academia, industry, and government
- Literature Review: Incorporating Transgenerational Testing and Epigenetic Mechanisms into Risk Assessment

### Long-term (FY18 – FY19)

- Human Epigenetic-Disease Case Study
- Case Study: Epigenetic Alterations - A Mechanism Through Which Nonchemical Stressors Increase Susceptibility to Chemical Stressors
- Case Study: Utilizing Genetic Susceptibility and Mechanism of Action Information to Inform Variability of Response in CRA
- Methods: Adapting the Adverse Outcome Pathway (AOP) Framework to Incorporate Intraspecies Genetic Susceptibility Information for CRA
- A Framework: Interpreting Epigenetic Data for Risk Assessment

## Impact

### Short-term (FY16 – FY17)

- ✓ Improved knowledge on use of epigenetic data for CRA
- ✓ Enhanced approaches to defining genetic variability that influence response to chemical exposures

### Long-term (FY18 – FY19)

- ✓ Establishment of EPA expertise in reviewing, evaluating and interpreting genetic and epigenetic data which will improve the characterization of susceptibility information in risk assessment.
- ✓ Enhanced CRA methods

*Disclaimer: The views expressed in this poster are those of the authors and do not necessarily represent the views or policies of the U.S. Environmental Protection Agency.*

Contact Susan Y. Euling I euling.susan@epa.gov I 703-347-8575