Moving Upstream: A Workshop on Evaluating Adverse Upstream Endpoints for Improved Decision Making and Risk Assessment
May 16 – 17, 2007
Doubletree Hotel, Berkeley, CA

May 16, 2007
8:00 AM  Registration
9:00 AM  Welcome and Words from Sponsors
  Joan Denton, Director, Cal/EPA OEHHA
  John Vandenbarg, Associate Director for Health, US EPA ORD NCEA
  Linda Giudice, Chair, UCSF Department of Obstetrics, Gynecology and Reproductive Sciences
  Martyn Smith, UC Berkeley Superfund Basic Research Program
9:20 AM  Meeting Process and Themes
  Tracey Woodruff, UCSF/US EPA NCEE & Lauren Zeise, Cal/EPA OEHHA
9:45 AM  Early Events as Predictors of Toxicity
  Linda Birnbaum, Director, Experimental Toxicology Division, US EPA ORD NHEERL
  Questions and Discussion
10:30 AM  Break
10:45 AM  Use in Risk Assessment of Tests Emerging from NTP’s Roadmap Initiative
  Chris Portier, Associate Director for Risk Assessment, NIEHS
  Questions and Discussion
11:30 AM  CASE STUDY: THYROID HORMONE RELATED TOXICITIES
  Moderator: Mark Miller, Cal/EPA OEHHA
  Our understanding of thyroid endocrinology is changing rapidly. New clinical and experimental research is providing insight into potential adverse effects of human exposure to endocrine disrupting chemicals. This new knowledge provides a context for interpreting toxicological studies of indicators of thyroid hormone toxicity. Here two examples are discussed: Perchlorate, a compound that blocks iodide uptake into the thyroid gland, and polychlorinated biphenyls, compounds that reduce serum thyroid hormone levels, but have complex actions on thyroid hormone signaling. Dose dependent interactions among chemicals acting via similar and different mechanisms will also be discussed.
  Introduction to the Thyroid Case Study
  Deborah Rice, Maine Environmental Toxicology Program
  Pathways for Toxicity from Thyroid Disruptions by Environmental Chemicals
  Tom Zoeller, University of Massachusetts Program in Molecular and Cellular Biology
12:00 PM  Lunch
1:00 PM  Mode-of-Action of Thyroid Hormones Disruption: Implications for Mixtures of Environmental Chemicals
  Kevin Crofton, US EPA ORD NHEERL
1:20 PM  Thyroid Hormone Related Toxicities in Risk Assessment
  Deborah Rice, Maine Environmental Toxicology Program
  Questions and Discussion
2:30 PM  Break
2:45 PM  CASE STUDY: ANTI-ANDROGEN MEDIATED MALE REPRODUCTIVE EFFECTS
  Moderator: Sue Euling, US EPA ORD NCEA
  Reproductive toxicology measures have included endpoints such as age at sexual maturation, semen parameters, fertility, number of live births, and age at reproductive senescence. However, emerging research includes an ever-broadening array of endpoints. Recent studies of anti-androgenic chemicals have focused on ano-genital distance, nipple retention in males, alterations in prostate size, changes in circulating levels of sex hormones (e.g. decreased testosterone) and alterations in gene expression in relevant tissues such as the testis. This case study will focus on a cluster of abnormalities characteristic of exposures to anti-androgens, and will examine the spectrum of.
mechanistic and endpoint-specific data to evaluate the utility and relevance of the new research to risk assessment. Exposures to mixtures of anti-androgenic chemicals will also be discussed.

**The Phthalate Syndrome of Effects on Male Reproductive Development**  
Paul Foster, Deputy Director, NIEHS NTP CERHR

**Diverse Mechanisms of Anti-androgen Action and Implications for Exposure to Mixtures**  
L. Earl Gray, US EPA ORD NHEERL

**Human Evidence of Anti-androgen Mediated Toxicity**  
Craig Steinmaus, Cal/EPA OEHHA

**Using Toxicogenomics Data in Risk Assessment for Anti-Androgens**  
Sue Euling, US EPA ORD NCEA

**Questions and Discussion**

4:45 PM **Wrap-Up and Adjourn**  
Tracey Woodruff, UCSF/US EPA NCEE & Lauren Zeise, Cal/EPA OEHHA

May 17, 2007

8:00 AM **Registration**

8:45 AM **CASE STUDY: UPSTREAM INDICATORS OF IMMUNOSUPPRESSION**  
*Moderator:* Greg Miller, US EPA NCEE  
Immunotoxicity is defined by a range of effects that disturb the normal function of the immune system. Hypersensitivity, autoimmunity, and immunosuppression are all considered immunotoxic effects, and may contribute to developmental toxicity during sensitive life stages. A number of environmental contaminants may interact with the immune system. This case study will focus in particular on immunosuppression, including sensitive life stages, and will describe immune assay results that are indicative of immunotoxicity as well as the implications of these findings overall for characterizing toxicity. Polychlorinated biphenyls and perfluorooctanoic acid will be used as examples.

**Immune Function, Immunotoxicity, and Resistance to Infection and Neoplasia**  
Robert Luebke, US EPA ORD NHEERL

**Evaluating Adverse Upstream Endpoints for Risk Assessment in Immunotoxicology: Are There Risk Assessment Models Available?**  
Michael Luster, Senior Advisor, NIOSH

**Evaluating Adverse Upstream Endpoints for Risk Assessment in Immunotoxicology: Case Study of Polychlorinated Biphenyls**  
Dori Germolec, NIEHS DIR

**Questions and Discussion**

10:45 AM **Break**

11:00 AM **Discussion: Scientific Considerations in Identifying Critical Effects**  
*Moderator:* Chris Portier, NIEHS  
*Discussants:* Linda Birnbaum, US EPA  
Frederic Bois, INERIS  
Jim Cogliano, IARC  
Elaine Faustman, University of Washington  
Dale Hattis, Clark University  
Tom Zoeller, University of Massachusetts

12:30 PM **Lunch**

1:45 PM **Discussion: Upstream Indicators in Regulatory Assessments: Using Results and Communicating Findings**  
*Moderator:* Amy Kyle, UC Berkeley  
*Discussants:* George Alexeiff, Cal/EPA OEHHA  
Henry Anderson, Wisconsin DPH  
Gary Ginsberg, Connecticut DPH  
John VandenBerg, US EPA ORD NCEA

3:00 PM **Wrap Up**  
Tracey Woodruff, UCSF/US EPA NCEE & Lauren Zeise, Cal/EPA OEHHA

3:30 PM **Adjourn**