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

Discussion Questions

Case Studies

• What are the precursor effects or other early biological changes linked to the case study outcome?
• In the case study, is there sufficient evidence to associate the upstream events with the overt downstream effects?
• Can the association be quantified? With what degree of confidence (high/medium/low)?
• What information would or does enhance our understanding of the relationship between the upstream event and downstream effects? (e.g., knowledge from other chemicals, biology)
• Was a sequence of steps from the upstream event(s) to the overt downstream effect(s) identified? How does our understanding of this sequence inform the use of the upstream event as a basis for risk assessment, particularly in situations when we only have data on upstream events?
• Can the association between upstream events and downstream effects for chemicals considered in the case study be generalized to other chemicals that have the same upstream effects?
• How does an understanding of variability in background biological status (i.e. susceptibility, genetic or otherwise) affect our interpretation of the upstream event?
• What are the obstacles to the use of the upstream event in risk assessment (hazard identification; dose-response assessment)? How can they be overcome?

Scientific Considerations in Identifying Critical Effects Panel

• When is there sufficient scientific justification to assume that an early biological change will lead to overt downstream effects? What are the circumstances in which reversibility of an upstream measure does or does not indicate reversibility of downstream consequences? How can homeostatic reserve be taken into account in judging the potential for an upstream biological change to lead to an adverse health outcome?
• If we define as a susceptible group those with greater risk of harm than the average in a population of similarly exposed individuals, does the expanded information on upstream biological changes enable better identification of susceptible individuals and groups and characterization of their increased risk of harm? Are there specific approaches to consider in identifying and addressing susceptible life stages? What about groups of individuals with predispositions to disease?
• In considering an upstream biological endpoint that is measured as a continuous variable (e.g., thyroxine, thyroid stimulating hormone), what approach should be taken in deciding whether a certain degree of upstream change will lead to the overt downstream outcomes (e.g., neurodevelopment change)? In this context, how should changes in upstream indicators within “normal” ranges be considered in evaluating potential for overt downstream outcomes in susceptible individuals and populations?
• How might the emerging capacity to measure upstream effects and to biomonitor address the longstanding problem of taking into account other exogenous and endogenous exposures that also affect the same toxicological process?
• How can biomonitoring data further inform considerations about adversity?
• Can we generalize scientific information about the relationship between the upstream events and overt downstream outcomes for one chemical to other chemicals where we only have information on the upstream events?

Upstream Indicators in Regulatory Assessments: Using Results and Communicating Findings Panel

• Are there obstacles to using upstream events in risk assessment? If so what are they? What modifications to risk assessment practices would enhance the use of upstream events?

• How can we use information from a known sequence of events between precursor and downstream overt effects to inform risk assessment for chemicals about which we only have information and data on upstream events?

• How should uncertainty and variability be addressed in risk assessments based on data for precursors or early biological changes?

• For the upstream events discussed in the case studies: Is the association to overt downstream effects sufficient to support use of upstream events in risk assessment when chemical-specific information on downstream effects is unavailable? Please consider both hazard identification and dose-response assessment.

• How does human variability affect the development of risk assessments based on upstream events? Relevant aspects of human variability may include: variability in background exposures to other chemicals; inter-individual differences in pharmacokinetics (including those associated with genetic polymorphisms); and variability in background health/disease status or disease susceptibility.

• Can we draw more general conclusions about use of upstream data in risk assessment from the three case studies?

• Overall, what is your assessment of the value and applicability of looking at such upstream events?

• What are the next steps to appropriately further integrate such approaches into chemical assessment and environmental health policy?