

EPA Peer Consultation Workshop on Cumulative Risk Assessment of Phthalates: Potential Options and Methods for Evaluating the Cumulative Hazard Associated with Six Selected Phthalates

Background:

Phthalate esters are a group of chemicals used in the manufacture of polyvinyl plastics and other materials such as pharmaceuticals, detergents, toys, cosmetic and personal care products, medical devices and food packaging to increase flexibility and pliability. Humans are exposed to various phthalates in the environment through direct contact with these products resulting in phthalates or their metabolites being detected in human saliva, urine, amniotic fluid, and breast milk. Epidemiological studies have demonstrated a possible association between exposure to multiple phthalates and indicators of potential effects on the male reproductive system at exposure levels similar to background levels observed in the population.

Because humans are potentially exposed to multiple phthalates in the environment, EPA is evaluating the cumulative risk associated with these chemicals in an assessment of human health hazard of phthalates. Specifically, EPA asked external experts from the National Academies of Science (NAS) to evaluate the issues and approaches related to the cumulative hazard assessment of phthalates.

On December 18, 2008, the NAS released the report, "Phthalates and Cumulative Risk Assessment—The Tasks Ahead." The NAS recommended that EPA select phthalates for inclusion in a cumulative risk assessment based on common adverse outcomes rather than focusing exclusively on structural similarity or on similar mechanisms of action. The NAS concluded that a sole focus on phthalates which excluded other anti-androgens would be artificial and could seriously underestimate cumulative risk.

EPA is following the NAS' recommendation and is currently developing an Integrated Risk Information System (IRIS) human health assessment for six phthalates and a cumulative hazard assessment based on common adverse outcomes. The IRIS assessment includes the following phthalates: dibutyl phthalate (DBP), di(2-ethylhexyl)phthalate (DEHP), butyl benzyl phthalate (BBP), di-isobutyl phthalate (DIBP), di-isononyl phthalate (DINP), and dipentyl phthalate (DPP). The *IRIS Human Health Assessment for Selected Phthalates* will include qualitative and quantitative analyses of noncancer and cancer effects information. The *IRIS Human Health Assessment for Selected Phthalates* will result in a cumulative hazard assessment as well as separate IRIS summaries for each of the six phthalates. It is expected that this cumulative assessment will serve as a future framework for the evaluation of other compounds that cause similar adverse outcome(s). Agency review of the draft *IRIS Human Health Assessment for Selected Phthalates* is anticipated to occur in Spring 2011.

Overall Goals:

The primary goal of the workshop, scheduled for December 2010, is to discuss and evaluate the recommendations presented in the 2008 NAS report concerning methods for performing a cumulative hazard assessment for these phthalates. The purpose of the workshop is to discuss and evaluate strengths and weakness of various approaches for cumulative assessment. This conversation will apply to the existing phthalates data sets while also considering options for extension to other chemicals. This workshop is a significant step forward in the consideration of the risks of exposure to multiple environmental chemicals. The recommendations and comments

from this workshop will be taken into account as the *IRIS Human Health Assessment for Selected Phthalates* is developed and completed.

Specific Objectives:

- Identification of effect(s) to serve as the basis for hazard grouping(s) and determination of potential points of departure (POD) in a cumulative risk assessment method for the phthalates
 - Presentation of cumulative risk based on phthalate syndrome as a whole as the critical effect for determination of POD
 - Presentation of cumulative risk based on most sensitive outcome in phthalate syndrome ‘shared’ among individual phthalates as the critical effect for determination of POD
 - Other sensitive, noncancer endpoints? Alternative grouping parameters for non-cancer cumulative mixtures assessment?
 - Cancer endpoints: Which phthalates? What target organ(s)?
- Identification of data sets that should be used in the estimation of the cumulative risk associated with the phthalates
 - Presentation of cumulative risk based on mixtures data.
 - Human and/or animal data?
 - Presentation of cumulative risk based on individual phthalates data
 - Human and/or animal data?
 - Other?
- Identification of which method(s) should be used to accurately predict cumulative risk associated with the phthalates
 - NAS recommendations for aggregation of cumulative effects and animal to human extrapolation
 - Hazard Index
 - Point of Departure Index
 - Other methods?
- Discussion of assumptions and uncertainty associated with the proposed options for conducting a cumulative risk assessment for the selected phthalates
- Summarize and outline options and preferred methods for cumulative mixtures risk for the selected phthalates

Approach:

Conduct a workshop to explore the state of the science and discuss options for performing a cumulative risk assessment of six selected phthalates that elicit common adverse outcomes. Include scientists with expertise in phthalate exposure and toxicity, cumulative risk assessment, dosimetry, and reproductive and developmental toxicology. Outcomes from the workshop will facilitate subsequent deliberations by the EPA Phthalate Workgroup regarding options and preferred methods for development of the cumulative hazard assessment for the selected phthalates.

Expected Outputs of Workshop:

- Workshop report including summary of potential approaches that may be applied to cumulative hazard for phthalates
- Identification of any additional published studies that might be considered in cumulative assessment
- Identification of any ongoing studies that might potentially inform cumulative assessment.
- Identify any critical data gaps that may limit application of existing approaches for cumulative assessment.