



U.S. Environmental Protection Agency's IRIS Human Health Assessment of Selected Phthalates

Consumer Product Safety Commission

Second Meeting of the Chronic Hazard Advisory Panel on Phthalates

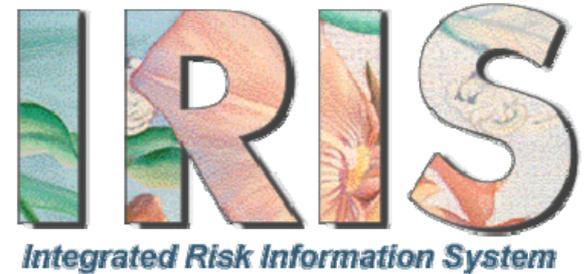
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EPA's Integrated Risk Information System

- IRIS provides qualitative and quantitative health effects information on over 540 substances.
- Addresses chronic exposures.
- Many high-profile, first applications of risk assessment guidelines and science policy.
- Noncancer and cancer hazard characterization.
- Mode of action analysis for noncancer and cancer effects.
- Derivation of reference doses and oral slope factors for effects from oral exposure and reference concentrations and inhalation unit risks for effects from inhalation exposure.
- Improvements in transparency, consistency, and public participation
- The new IRIS process was established on May 21, 2009



www.epa.gov/iris

Individual Phthalate Assessments (Noncancer) Currently on the IRIS Database

Phthalate	Principal Study and Critical Effect	RfD/RfC
Di-n-butyl Phthalate (DBP)	Increased mortality Subchronic to chronic oral study in rats (BioassaySmith, 1953)	1 x 10 ⁻¹ mg/kg/day
Di(2-ethylhexyl)phthalate (DEHP)	Increased relative liver weight Subchronic-to-Chronic oral bioassay in guinea pigs (Carpenter et al., 1953)	2 x 10 ⁻² mg/kg/day
Butyl Benzyl Phthalate (BBP)	Significantly increased liver-to-body weight and liver-to-brain weight ratios 6-month dietary study in rats (NTP, 1985)	2 x 10 ⁻¹ mg/kg-day
Diethyl Phthalate (DEP)	Decreased growth rate, food consumption and altered organ weights Subchronic oral feeding study in rats (Brown et al., 1978)	8 x 10 ⁻¹ mg/kg/day
Dimethyl Phthalate (DMP)	Not available.	Not available.

Individual Phthalate Assessments (Cancer) Currently on the IRIS Database

Phthalate	Weight-of-Evidence Characterization	Oral slope factor/inhalation unit risk
Di-n-butyl Phthalate (DBP)	D; not classifiable as a human carcinogen.	Not available.
Di(2-ethylhexyl)phthalate (DEHP)	B2; probable human carcinogen. Orally administered DEHP produced significant dose-related increases in liver tumor responses in rats and mice of both sexes.	Oral Slope Factor: 1.4×10^{-2} /mg/kg/day Drinking Water Unit Risk: 4.0×10^{-7} per (ug/L) hepatocellular carcinoma and adenoma in male B6C3F1 mice; 103 week dietary cancer bioassay (NTP, 1982) Extrapolation Method- Linearized multistage procedure, extra risk
Butyl Benzyl Phthalate (BBP)	C; possible human carcinogen. Based on statistically significant increase in mononuclear cell leukemia (MCL) in female rats; the response in male rats was inconclusive and there was no such response in mice.	Not available. The qualitative weaknesses of the MCL response does not provide a compelling basis to model the dose-response data.
Diethyl Phthalate (DEP)	D; not classifiable as a human carcinogen.	Not available.
Dimethyl Phthalate (DMP)	D; not classifiable as a human carcinogen.	Not available.

EPA's IRIS Program and Cumulative Risk Assessment

- The concept of cumulative assessment of hazard and dose-response represents a paradigm shift for the IRIS Program.
- Science of risk assessment is increasingly complex; more data are available that lead to questions on how to address issues of multiple exposures, multiple risks, multiple exposure routes, and susceptibility in populations.

Rationale for the Cumulative Risk Assessment of the Phthalates

- Phthalate esters are a group of chemicals used in the manufacturing of polyvinyl plastics and other materials, such as pharmaceuticals, detergents, toys, cosmetic and personal care products, medical tubing and intravenous bags, and plastic food packaging and wrap, to increase flexibility and pliability.
- Humans are exposed to various phthalates and their metabolites in the environment, including through direct contact with these products.
- Multiple phthalates have been detected in saliva, urine, amniotic fluid, and breast milk in humans.
- Human epidemiological studies have demonstrated a possible association between exposure to some phthalates and their metabolites and indicators of potential effects on the male reproductive system at exposure levels that are similar to background levels observed in the population.
- In 2008, EPA elicited external expert consultation from the National Academies of Science in the evaluation of issues and approaches related to cumulative hazard and dose-response assessment of phthalates.

EPA's Charge to the Committee

- Identification and prioritization of data gaps and research needs
- Identification of the issues (e.g., technical) related to cumulative hazard and dose-response assessment for the phthalates
- Recommendation of the relevant phthalates for consideration in a cumulative assessment for this chemical class
- Discussion of the data required to perform cumulative assessment of the phthalates

NAS Panel Recommendations

- On December 18, 2008, the National Academies of Science (NAS) released the report, “Phthalates and Cumulative Risk Assessment—The Tasks Ahead”.
 - Include phthalates and other chemicals (i.e., other agents that cause androgen insufficiency or block androgen-receptor signaling) in a cumulative risk assessment based on common adverse outcomes and not focus exclusively on structural similarity or on similar mechanisms of action.
 - Although a variety of mechanisms clearly are involved, dose addition proved adequately predictive when the committee evaluated the available data for phthalates and other anti-androgens.
 - A focus solely on phthalates to the exclusion of other anti-androgens would be artificial and could seriously underestimate cumulative risk.

NCEA's Next Steps

- The report's implications are far-reaching and potentially impact the entire Agency.

- NCEA's plan:
 - Evaluate the underlying science behind the recommendations and consider the implications for the IRIS phthalate assessment.

 - Evaluate the options for performing a cumulative risk assessment for the phthalates presented in the report.

 - EPA workshop on specific recommendations presented in the NAS report on methods for cumulative risk for phthalates planned for Fall 2010.

IRIS Human Health Assessment of Selected Phthalates

- EPA has initiated an *IRIS Human Health Assessment of Selected Phthalates* which includes the following six phthalates:

Di-n-butyl Phthalate (DBP)	Di(2-ethylhexyl)phthalate (DEHP)
Diisononyl Phthalate (DINP)	Dipentyl Phthalate (DPP)
Butyl Benzyl Phthalate (BBP)	Diisobutyl Phthalate (DIBP)

- The assessment will include noncancer and cancer qualitative and quantitative human health effects information where the data are available for each of the phthalates.
- The assessment will also include a cumulative hazard and dose-response assessment for these six phthalates.
- The cumulative assessment for the phthalates may serve as a framework for extension to other phthalates or compounds that affect similar adverse outcomes in the future
- External Peer review of the *IRIS Human Health Risk Assessment of Selected Phthalates* is anticipated to begin in 2011.

General Issues Related to the Cumulative Risk Assessment of Phthalates

- Toxicokinetic issues
- Exposure issues
- Identification and selection of data to serve as the basis for a cumulative risk assessment method for the phthalates
 - Recognize that induction of any of the phthalate syndrome effects is representative of disruption of androgen action.
 - Focus on the effects common to the chemicals and base cumulative risk assessment on the most sensitive outcome within the syndrome.
 - Other non-reproductive, noncancer endpoints?
 - Cancer endpoints?
- Method(s) for cumulative risk assessment
- Inclusion/exclusion of other anti-androgenic chemicals

NCEA Workshop on Potential Options and Methods for the Determination of the Cumulative Risk Associated with the Phthalates

- The primary goal of the workshop is to discuss and evaluate the recommendations presented in the 2008 NAS report related to methods for performing a cumulative assessment for these phthalates.
- The purpose of the workshop is to facilitate a discussion of which options for conducting a cumulative risk assessment for the phthalates should be included in the assessment and the strengths and limitations of these options.
- NCEA recognizes the importance of the NAS recommendations related to the inclusion of other anti-androgens, in addition to phthalates, and the possibility that exclusion could lead to an underestimation of risk.
 - The focus on phthalate esters may serve as a framework for extension to other compounds that affect effect similar adverse outcomes.

Potential Workshop Objectives

- Identification of which method(s) should be used to 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?

- Identification of data sets
 - 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 sensitive effect(s) to serve as the basis for determination of potential points of departure
 - Presentation of cumulative risk based on phthalate syndrome as a whole as the critical effect
 - Presentation of cumulative risk based on most sensitive outcome in phthalate syndrome shared among individual phthalates as the critical effect
 - Other sensitive, non-cancer endpoints?