

Charge to External Reviewers for the IRIS Toxicological Review for Di-n-Butyl Phthalate

The U.S. EPA is conducting a peer review of the scientific basis supporting the human health risk assessment of dibutyl phthalate that will appear on the Agency's online database, the Integrated Risk Information System (IRIS).

The draft documents for the external peer review contain a description of the oral reference dose, inhalation database, and a qualitative cancer assessment. Please provide detailed responses to the charge questions below.

General

Question 1 - Are there additional key published studies or publicly available scientific reports that are missing from the draft document that might be useful for the discussion of the hazards of dibutyl phthalate?

Question 2 - Does the hazard characterization discussion for dibutyl phthalate provide a scientifically-balanced, objective, and complete description that synthesizes the human and laboratory animal evidence for a human developmental hazard?

Consideration of Human Epidemiological Studies

Question 3 - Have the epidemiological data (Murature et al., 1987; Duty et al., 2003a, 2003b; Swan et al., 2005; Main et al., 2006) been objectively characterized and used transparently in the assessment?

Mode of Action for Effects on Male Reproductive Tract

Question 4 - Does the Toxicological Review provide sufficient information to support a conclusion that there is a relationship between lower testosterone levels in the fetal rat testis and structural anomalies and functional deficits in the male reproductive system? Do you agree that this mode of action is applicable regardless of the duration of exposure?

Question 5 - Has EPA provided a cogent and objective analysis of existing information to justify the conclusion that the mode of action based on the decrease in testosterone concentration in the fetal rat testis is relevant for humans? If not, what information should be added?

Oral Reference Dose (RfD) for Dibutyl phthalate

A. Selection of Principal Study and Endpoint

Question 6 - Has the most appropriate principal study, critical effect, and method of analysis been chosen? The issues to be considered include:

- Is it appropriate to consider the results from Lehmann et al. (2004) as the principal study for all durations of exposure (acute, short term, subchronic, and chronic)?
- Is the number of animals examined in the study sufficient to support the scientific conclusion that the decrease in testosterone concentration is the critical effect?

- Is the statistically significant decrease in testosterone concentration of 61% at 50 mg/kg-day, called a LOEL by Lehmann et al. (2004), an adverse effect and a LOAEL as described by EPA?
- Do the available data and discussion support the use of a biochemical change (decrease in concentration of testosterone in the fetus) as the point of departure of 30 mg/kg-day as a NOAEL for deriving the reference values for all durations of exposure? Do you agree that this biochemical change is a no observed adverse effect level?
- Is it appropriate to use the NOAEL/LOAEL approach rather the Benchmark Dose approach on the decrease in testosterone concentration (Lehmann et al., 2004) to derive the RfD?
- Is it scientifically appropriate to assume that preventing the decrease in testosterone concentration in the fetus will prevent all developmental effects and other effects in children and adults?
- Has the decision not to use the exposure-response results from Salazar et al. (2004) been sufficiently justified?
- Lee et al. (2004) reported several biological changes at an exposure below that which is associated with the decrease in fetal testosterone (Lehmann et al., 2004). These include the changes in relative pituitary weight in males at postnatal week 11 and in females at postnatal week 20; the decrease in percentage of FSH producing cells in the anterior pituitary in females at postnatal week 20; the changes in the mammary gland of females at postnatal day 21; and the changes in the mammary gland of males at postnatal week 11 and 20. Do the available data and discussion adequately support EPA's conclusion that these effects should not be used to derive the RfD?
- Is there sufficient information to support the conclusion that monobutyl phthalate is the toxic metabolite?

B. Application of Uncertainty Factors

Question 7 - Has the rationale for the selection of uncertainty factors been objectively and transparently described in the draft document? Does the science support the selection of uncertainty factors?

Question 8 - EPA concluded that there are insufficient data to support reducing the pharmacokinetic portion of the interspecies uncertainty factor. Are there additional data that could be used to justify changing the pharmacokinetic portion of the interspecies uncertainty factor?

Question 9 - EPA concluded that there are insufficient data to support reducing the pharmacodynamic portion of the interspecies uncertainty factor. Is the role of testosterone in the development of the male reproductive tract sufficiently understood in all species to justify reducing the pharmacodynamic portion of the interspecies uncertainty factor?

C. Alternative Derivation of the Acute RfD

Question 10 - An alternative to using Lehmann et al. (2004) with exposure on GDs 12 - 19 to 30 mg/kg-day to derive the acute RfD is to use Thompson et al. (2005, 2004) with a single exposure on GD 19 at 500 mg/kg-day. This approach would require a uncertainty

factor of 10 for LOAEL to NOAEL extrapolation as this was the only exposure tested in the study. Is this approach preferable to using Lehmann et al. to derive the acute RfD?

C. Alternative Derivation of the Chronic RfD

Question 10 - An alternative to using the development toxicity study of Lehmann et al. (2004) to derive the chronic RfD is to derive the chronic RfD from a subchronic study showing hepatic toxicity from perinatal, lactational, and adult exposure with a NOAEL of 138 mg/kg-day (NTP 1995). Would it be appropriate to use an additional uncertainty factor of 10 for extrapolation from subchronic to chronic exposure on the hepatic toxicity from this study?

Inhalation Reference Concentration (RfC) for Dibutyl phthalate

Question 11 - Has the rationale and justification for not deriving an RfC been transparently described? Is the rationale scientifically justified and appropriate?

Carcinogenicity of Dibutyl phthalate

Question 12 - Has the appropriate cancer descriptor been chosen? Has the rationale and justification for not deriving a quantitative cancer assessment been transparently described? Do you agree with EPA's rationale, justification and conclusion?