External Peer Review for a Report on Physiologically Based Pharmacokinetic (PBPK) Modeling for Chloroprene and a Supplemental Analysis of Parameter and Model Uncertainty: Introduction

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- **IRIS assessments contribute to decisions across EPA and other health agencies.**
- **Toxicity values**
  - Noncancer: Reference Doses (RfDs) and Reference Concentrations (RfCs).
  - Cancer: Oral Slope Factors (OSFs) and Inhalation Unit Risks (IURs).
- **IRIS assessments have no direct regulatory impact until they are combined with**
  - Extent of exposure to people, cost of cleanup, available technology, etc.
  - Regulatory options.
  - Both of these are the purview of EPA's program offices.

Chloroprene Background and Timeline

- **2010:** EPA finalizes the IRIS Toxicological Review of Chloroprene. EPA classifies chloroprene as a "Likely to be carcinogenic to humans" via the inhalation route of exposure.
  - Multiple tumor sites were identified in animals during EPA's evaluation of chloroprene.
- **2015:** EPA published the National Air Toxics Assessments (NATA). Updated assessment indicated high levels of chloroprene around the Denka Performance Elastomer LLC (DPE) plant in LaPlace, La.
- **2017:** EPA received a Request for Correction (RFC) provided on behalf of DPE under EPA's Information Quality Guidelines.
- **2018:** EPA denied DPE's Request for Correction. EPA concluded that the underlying information and conclusions presented in the IRIS Chloroprene assessment are consistent with the EPA's Information Quality Guidelines.
  - EPA conducted an evaluation of the literature published since the 2010 finalization of the IRIS Assessment of Chloroprene.
  - EPA did not identify evidence that would change its conclusions, including the availability of a physiologically based pharmacokinetic (PBPK) model published in 2012. EPA evaluated the suitability of the model for inclusion into the assessment, but uncertainties were identified that prevent its application to an IRIS assessment.

Chloroprene Background and Timeline (Cont'd)

- **2018:** DPE submitted a Request for Reconsideration of Denial of Request for Correction (RFR) with regard to EPA's decision. DPE entered discussions with EPA to address uncertainties identified by EPA regarding PBPK modeling for chloroprene.
- **2019:** DPE conducted additional laboratory studies and modeling work to address uncertainties identified by EPA.
- **2020:** EPA initiates an independent peer review on the documents, *Physiologically Based Pharmacokinetic (PBPK) Modeling for Chloroprene (Ramboll, 2020)* and *Supplement: Uncertainty Analysis of In Vitro Metabolic Parameters and of In Vivo Extrapolation (IVIVE) Used in a Physiologically Based Pharmacokinetic (PBPK) Model for Chloroprene (U.S. EPA, 2020)*.
- **2020:** Once the peer review report is finalized, EPA will evaluate the recommendations provided by the reviewers and respond to the DPE's Request for Reconsideration (RFR).
  - If the RFR is granted, EPA will evaluate the impact of the model on the conclusions presented in the finalized 2010 IRIS assessment of Chloroprene.