# Charge to the Panel:
# Peer Review of the 2024 Draft Risk Evaluation for DIDP & Draft Hazard Assessment for DINP

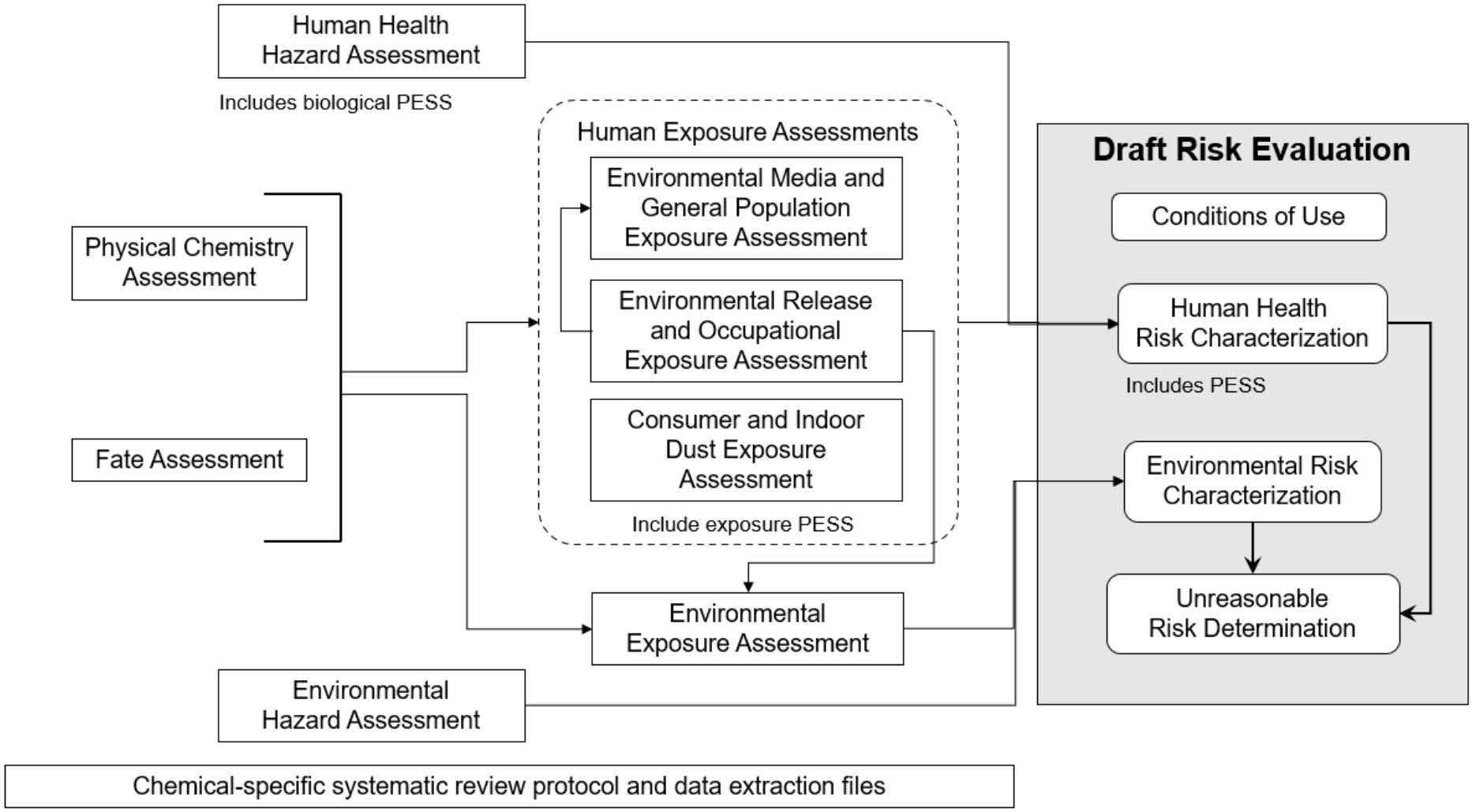
OFFICE OF POLLUTION PREVENTION AND TOXICS (OPPT)
U.S. ENVIRONMENTAL PROTECTION AGENCY (U.S. EPA)
JULY 23, 2024

EPA United States Environmental Protection Agency

# DIDP AND DINP MANUFACTURER-REQUESTED RISK EVALUATIONS

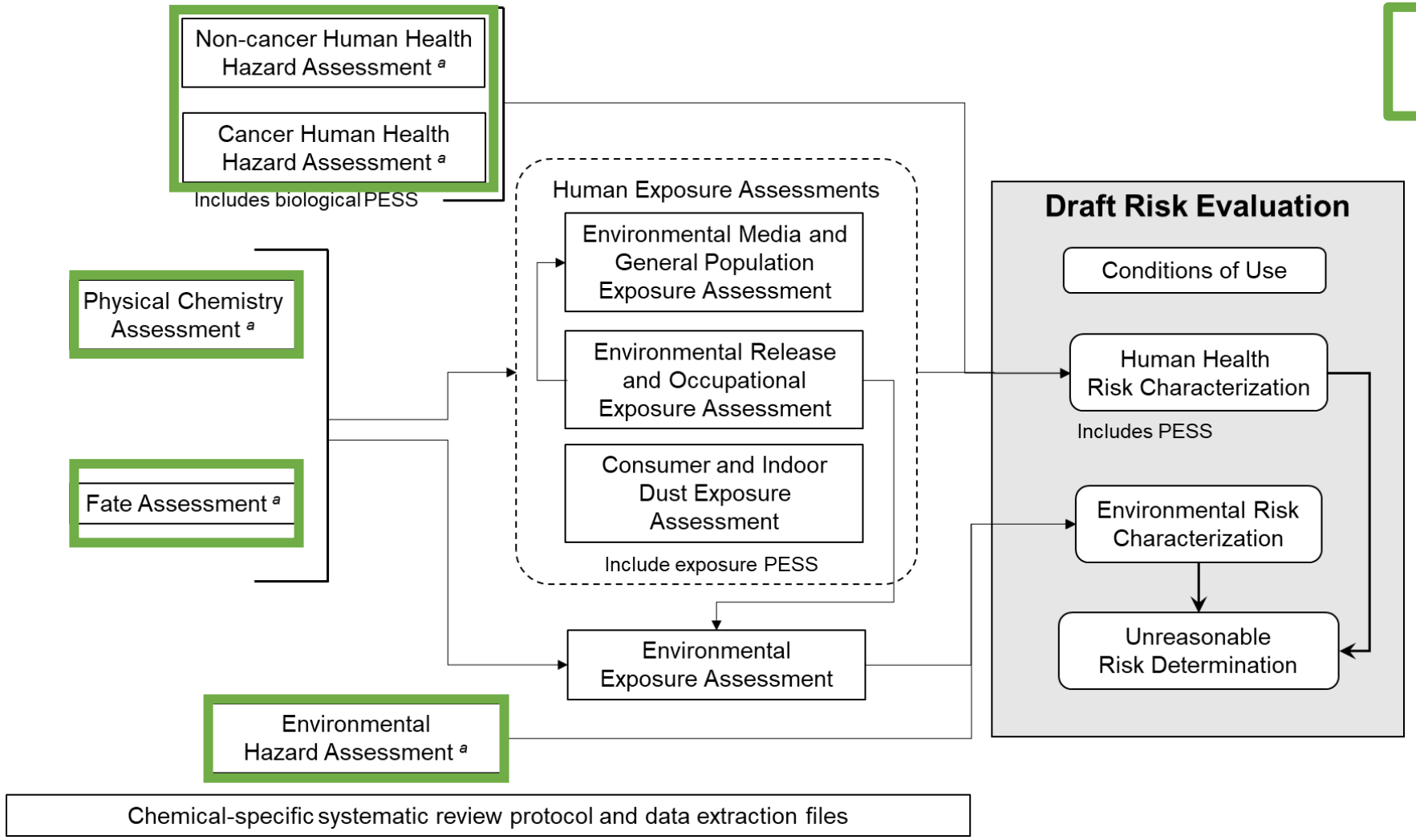
- TSCA allows a manufacturer of a chemical substance (or category of chemical substances) to request an EPA-conducted risk evaluation on the chemical substance (or category of chemical substances) for conditions of use of interest to the manufacturer.
- Requested by ExxonMobil Chemical Company, through the American Chemistry Council's High Phthalates Panel in May 2019
- Request approved by EPA in December 2019
- Draft and final scopes issued in 2020 and 2021, respectively

# DIDP DRAFT RISK EVALUATION: DOCUMENT SUMMARY MAP



# DINP DRAFT RISK EVALUATION: DOCUMENT SUMMARY MAP

Part of Current Peer-review



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# Charge Questions on the Draft DIDP Risk Evaluation

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# Exposure Analysis: Charge Question 1a

- EPA relied on data from several sources to derive consumer exposure estimates that include products representative of the conditions of use, as described in Sections 1, 2, and 3 of the "Draft Consumer and Indoor Dust Exposure Assessment" for DIDP.
  - i. Please comment on the strengths and uncertainties of the selected data and methods used in consumer products and indoor air exposure analyses.
  - ii. Please include a consideration of the Consumer Exposure Model assumptions for analysis of suspended and surface dust through inhalation and ingestion routes of exposure.
  - iii. Please also comment on mouthing behavior input parameters related to estimating chemical migration to saliva for infants and toddlers.
  - iv. For the remaining phthalates, EPA anticipates potentially needing to refine the exposure assessment for consumer and indoor dust exposure. Please suggest exposure data sources, models, and related methods for estimating dermal, inhalation, and ingestion exposures to chemicals from consumer products that are reasonably available and can be conducted in a timely

# Exposure Analysis: Charge Question 1b

- As described in Section 2 of the Draft Environmental Media and General Population Exposure for DIDP, EPA used sentinel exposures to conduct a screening approach for the DIDP exposure assessment.
  - i. Please comment on the strengths and uncertainties of the selected data and methods employed in the use of sentinel exposures in the screening approach.
  - ii. Please include a consideration of the strengths and uncertainties associated with methods related to calculating surface water concentrations (Section 5) for DIDP.
  - iii. For the remaining phthalates, EPA anticipates potentially needing to refine the exposure assessment for the environment and general population. Please suggest exposure data sources, models, and related methods for estimating concentrations in environmental media paying special attention to those media most relevant to phthalates, e.g. water, sediment, and soil. In your consideration, please keep in mind that methods, data, and approaches should be reasonably available and can be conducted in a timely fashion that allows EPA to meet statutory timelines for TSCA risk evaluations.

# Exposure Analysis: Charge Question 1c

- As described in Section 5 of the Draft Environmental Exposure Assessment for DIDP, EPA conducted a screening trophic transfer analysis to estimate dietary exposure resulting from modeled surface water releases and air deposition to soil, including use of monitoring and biomonitoring data. The resulting dietary exposure estimates were compared to the hazard threshold for semi-aquatic and terrestrial mammals.
  - i. Please comment on the methods and data used for estimating dietary exposures for ecologically relevant species and comparison of the exposure estimates to the hazard threshold for terrestrial mammals.
  - ii. For the remaining phthalates, EPA anticipates potentially needing to refine the environmental exposure assessment. Please suggest exposure data sources, models, and related methods for estimating dietary exposures via environmental media paying special attention to those media most relevant to phthalates, e.g. water, sediment, and soil. In your consideration, please keep in mind that methods, data, and approaches should be reasonably available and can be conducted in a timely fashion that allows EPA to meet statutory timelines for TSCA risk evaluations.

# Exposure Analysis: Charge Question 1d

- As described in Section 3 of the Draft Environment Release and Occupational Exposure Assessment for DIDP, production volumes for Manufacturing and Import/Repackaging OES were determined using Chemical Data Repository (CDR) information. The production volumes for the other OES came from CDR and/or percent production volume (PV) (percentage of manufactured DIDP used for a particular OES) reported in the European Union (EU) Risk Assessment on DIDP since the use rate of DIDP is similar in USA and EU.
  - i. For environmental release assessments ~~occupational exposures~~, please comment on the strengths and uncertainties of using EU PV % to estimate production volumes for DIDP.
  - ii. For the remaining phthalates, EPA anticipates potentially needing to refine the environmental release assessments ~~occupational exposure assessment~~. Please suggest additional data sources, models, and related methods for determining production volumes that are reasonably available and can be conducted in a timely fashion that allows EPA to meet statutory timelines for TSCA risk evaluations.

# Ecological Hazard: Charge Question 2a

- As described in Section 4 of the Draft Environmental Hazard Assessment for DIDP, EPA had limited empirical toxicity data available for terrestrial mammals and therefore relied on data from controlled laboratory animal studies using human health animal models to derive a toxicity reference value (TRV) to evaluate risk from chronic dietary exposure to DIDP. Please comment on the strengths and uncertainties of the methodology and data used to derive a toxicity reference value (TRV) for DIDP.

# Ecological Hazard: Charge Question 2b

- Fate and transport modeling analyses indicate that when DIDP is released to the environment it is expected to partition primarily to soils and sediments, therefore, these media are of high priority for environmental exposure analyses. As described in Section 4 of the Draft Environmental Hazard Assessment for DIDP, no hazard data were identified for DIDP for soil invertebrates. DINP was selected as an analog for read across of soil invertebrate hazard data as described in Appendix A of the Draft Environmental Hazard Assessment for DIDP. Please comment on the appropriateness of the methods used to identify DINP as an analog for DIDP.

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# Human Health Hazard: Charge Question 3a

- As described in Section 6.1.4 of the Draft Human Health Hazard Assessment for DIDP, EPA has preliminarily concluded that the HED of 9.0 mg/kg (NOAEL of 38 mg/kg-day) from the two-generation study of reproduction of Sprague Dawley (SD) rats based on reduced F2 offspring survival on PND1 and PND4 is appropriate for calculation of non-cancer risk from acute, intermediate and chronic durations. Please comment on the strengths and uncertainties of EPA's preliminary conclusion.

# Human Health Hazard: Charge Question 3b

- As described in Section 5.3 of the Draft Human Health Hazard Assessment for DIDP, EPA has preliminarily concluded there is *Suggestive Evidence of Carcinogenic Potential* of DIDP in rodents. EPA's preliminary conclusion is based on evidence of mononuclear cell leukemia (MNCL) in male and female F344 rats and hepatocellular adenomas in male CB6F1-rasH2 transgenic mice. EPA has further preliminarily concluded that MNCL observed in F344 rats and hepatocellular adenomas observed only in male CB6F1-rasH2 transgenic mice are not appropriate for conducting dose-response assessment for human health risk assessment. Please comment on the strengths and uncertainties of EPA's preliminary cancer classification and rationale for not carrying forward rodent cancers into dose response assessment.

# Charge Questions on the Draft DINP Hazard Assessments

# Ecological Hazard: Charge Question 1a

- As described in Section 4 of the Draft Environmental Hazard Assessment for DINP, EPA had limited empirical toxicity data available for terrestrial mammals and therefore relied on data from controlled laboratory animal studies using human health animal models to derive a toxicity reference value (TRV) to evaluate risk from chronic dietary exposure to DINP. Please comment on the strengths and weaknesses of the methodology and data used to derive a toxicity reference value (TRV) for DINP.

# Human Health Hazard Charge Question 2a

- In Sections 4.1.1 and 4.1.2 of the Draft Non-Cancer Human Health Hazard Assessment for DINP, EPA has preliminarily selected the HED of 12 mg/kg-day (BMDL5 of 49 mg/kg-day) based on decreased fetal testicular testosterone production for assessing risks from acute and intermediate duration exposure to DINP. EPA is using benchmark dose (BMD) estimates calculated by the National Academies of Sciences, Engineering, and Medicine (NASEM, 2017). Please comment on the strengths and uncertainties in the selected acute/intermediate HED, including its appropriateness for these durations.

# Human Health Hazard Charge Question 2b

- In Section 4.1.3 of the and the Draft Non-Cancer Human Health Hazard Assessment for DINP, EPA has preliminarily selected the HED of 3.5 mg/kg-day (NOAEL of 15 mg/kg-day) based on a spectrum of liver effects, including incidence of spongiosis hepatis, increased liver weight, and serum chemistry for assessing risks from chronic duration exposure to DINP. This NOAEL has been selected by other regulatory agencies (*e.g.,* U.S. CPSC, Health Canada, EFSA, ECHA) to characterize non-cancer risks associated with exposure to DINP. Please comment on the strengths and uncertainties in the selected chronic HED, including its appropriateness for this duration.

# Human Health Hazard Charge Question 2c

- In the Draft Cancer Human Health Hazard Assessment for DINP, EPA considered MNCL (Section 3.2.1), kidney tumors (Section 3.2.2), and liver tumors (Section 4). EPA has preliminarily determined an alpha 2u-globulin (α2u-globulin) MOA for kidney tumors, and that there is too much scientific uncertainty associated with the incidences of MNCL observed in F344 rats to use quantitatively to estimate human risk from exposure to DINP. Therefore, EPA focused its MOA analysis and dose-response analysis on liver tumors. Please comment on the strengths and uncertainties of EPA's decision to focus its cancer assessment on liver tumors.

# Human Health Hazard Charge Question 2d

- In the Draft Cancer Human Health Hazard Assessment for DINP, EPA preliminarily concluded that the weight of scientific evidence supports a peroxisome proliferator activated receptor alph (PPARα) MOA for liver tumors in rats and mice (Section 4.1). Please comment on the strengths and uncertainties of EPA's preliminary conclusion. In your response, please include discussion of the strengths and uncertainties of available data supporting key events in the PPARα MOA and the scientific rationale for a threshold approach for cancer dose-response.

# Human Health Hazard Charge Question 2e

- As described in Section 4.8 of the Draft Cancer Human Health Hazard Assessment for DINP, EPA has preliminarily concluded that DINP is *Not Likely to be Carcinogenic to Humans* at doses below levels that do not result in PPARα activation and that the non-cancer chronic POD based on liver toxicity is appropriate. Please comment on the strengths and uncertainties of this preliminary conclusion.