CHARGE to the TOXIC SUBSTANCES CONTROL ACT (TSCA) SCIENCE ADVISORY COMMITTEE ON CHEMICALS (SACC)

Peer Review of 2024 Draft Risk Evaluation for DIDP and Draft Hazard Assessment for DINP

BACKGROUND:

On May 24, 2019, EPA received requests to conduct risk evaluations for diisodecyl phthalate (DIDP) and diisononyl phthalate (DINP) under the Frank R. Lautenberg Chemical Safety for the 21st Century Act, the legislation that amended TSCA on June 22, 2016. In December 2019, EPA notified the requesters (ExxonMobil Chemical Company, Evonik Corporation, and Teknor Apex, through the ACC High Phthalates Panel) that the Agency had granted their requests.

DIDP is a common chemical name for the category of chemical substances that includes the following substances: 1,2-benzenedicarboxylic acid, 1,2-diisodecyl ester (CASRN 26761-40-0) and 1,2-benzenedicarboxylic acid, di-C9-11-branched alkyl esters, C10-rich (CASRN 68515-49-1). Both CASRNs contain mainly C10 dialkyl phthalate esters. DINP is a common chemical name for the category of chemical substances that includes the following substances: 1,2-benzenedicarboxylic acid, 1,2-isononyl ester (CASRN 28553-12-0) and 1,2-benzenedicarboxylic acid, di-C9-11-branched alkyl esters, C9-rich (CASRN 68515-48-0). Both CASRNs contain mainly C9 dialkyl phthalate esters. Both DIDP and DINP are high production volume chemical substances (100 million – 1 billion lbs reported to CDR in 2020) and are primarily used as plasticizers in polyvinyl chloride (PVC) and associated articles used in consumer, commercial, and industrial applications. In addition to evaluating DIDP and DINP, the Agency has initiated risk evaluations of five other phthalates (butyl benzyl phthalate (BBP), dibutyl phthalate (DBP), dicyclohexyl phthalate (DCHP), diethylhexyl phthalate (DEHP), diisobutyl phthalate (DIBP)). EPA expects the methods employed to determine exposure estimates will be similar among the individual phthalate assessments, but hazard values will vary resulting in different risk profiles for each. These 5 will be combined with the evaluation of DINP into a cumulative risk assessment. EPA anticipates SACC review of the remaining phthalates along with the cumulative assessment in early 2025.

The U.S. Environmental Protection Agency (EPA or the Agency) has evaluated risks posed by DIDP under the Toxic Substances Control Act (TSCA) to human health and environment, as presented in the Draft Risk Evaluation for DIDP. The Agency is requesting peer review by the TSCA Science Advisory Committee on Chemicals (SACC) of the Draft Risk Evaluation for DIDP. Additionally, EPA is requesting SACC peer review of draft human health and ecological hazard assessments for DINP. EPA is specifically seeking SACC review of its analyses and methodologies relevant to human health and ecological hazard values and exposure methodologies that have not been previously peer reviewed, which would be applicable to both DIDP and DINP.

The Agency employed sentinel exposure and screening approaches to estimate risk for consumers and the general population from exposures to DIDP via the conditions of use. These methods relied on determining risk for the highest anticipated exposures for a particular release scenario and pathway. Refinements and additional analyses were conducted only if risk values exceeded benchmark MOEs. EPA anticipates that the exposure methodologies demonstrated in the Draft Risk Evaluation for DIDP will be applicable to DINP exposure scenarios. The Agency is asking SACC to identify refinements that can possibly be made to exposure methodologies in upcoming assessments.

EPA identified ecological hazard endpoints for both DIDP and DINP. The Agency used data from laboratory animal studies models to derive a toxicity reference value (TRV) to evaluate risk from estimated dietary exposures resulting from surface water releases into water and sediment and air deposition to soil. The physical and chemical properties and environmental fate and transport analysis indicated that sediment and soils are primary media of importance for ecological exposures. Because no reasonably available information describing hazards from DIDP to soil invertebrates was identified, the Agency selected soil invertebrate hazard data from DINP to read-across to DIDP.

EPA identified human health hazard endpoints for both DIDP and DINP. Decreased F2 offspring survival in a 2-generation reproduction study in rats for acute, intermediate, and chronic exposure durations to DIDP, resulted in a point of departure (POD) based on the no observable adverse effect level (NOAEL) of 38 mg/kg-day (human equivalent dose (HED) 9 mg/kg-day). EPA concluded there is suggestive evidence of carcinogenic potential of DIDP in rodents, and consistent with the 2005 *Guidelines for Carcinogen Risk Assessment*, did not quantify cancer risk.

For DINP, EPA identified a POD for acute and intermediate duration exposures based on a benchmark dose limit ($BMDL_5$) of 49 mg/kg-day (HED 12 mg/kg-day) for decreased fetal testicular testosterone in rats during gestation. EPA identified cancer as a human health hazard from exposure to DINP and conducted a mode of action (MOA) analysis and drafted a weight of evidence narrative according to the framework outlined in the 2005 *Guidelines for Carcinogen Risk Assessment* and 2007 IPCS Framework. EPA considered the evidence presented in the MOA analysis to support a nonlinear approach to extrapolate to lower doses in its dose-response assessment. The non-cancer chronic POD (NOAEL of 15 mg/kg-day, HED 3.5 mg/kg-day) based on liver toxicity in a 2-year study in rats will adequately account for all chronic toxicity, including carcinogenicity. EPA is soliciting comments through peer review on the approaches used to characterize the cancer and non-cancer effects of DINP. Feedback from the SACC on the approach to cancer in the human health hazard assessment will inform the exposure and risk assessments for DINP.

EPA is releasing the draft risk evaluation and draft risk determination for DIDP and the draft hazard assessment for DINP as an interim step in the process for public comment and independent, expert peer review. EPA plans to issue the draft DINP risk evaluation later in 2024 for public comment. Once EPA receives comment and input from peer review and public comment, revisions will be made and the Agency will finalize its assessments and risk determination (*i.e.*, risk evaluation) for both DIDP and DINP. By taking the DIDP risk evaluation and DINP hazard assessments to peer review in this manner, EPA will obtain the necessary independent review and advice for the DINP risk evaluation.

CHARGE QUESTIONS:

DIDP Risk Evaluation

1. Exposure analyses:
    a. 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. EPA anticipates that the exposure methodologies demonstrated in the Draft Risk Evaluation for DIDP will be applicable to DINP exposure scenarios.
        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. In light of comments on charge questions 1.a.i through 1.a.iii, please comment on the weight of scientific evidence and its conclusions for the consumer and indoor dust assessment (Section 5 of Draft Consumer and Indoor Dust Exposure Assessment). Please include in these comments a discussion of the clarity and transparency of the data used, and EPA's interpretation of the exposure results.
v. For the remaining phthalates (*i.e.*, DEHP, DBP, DIBP, BBP, DCHP, DINP), 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 fashion that allows EPA to meet statutory timelines for TSCA risk evaluations.

b. 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. EPA anticipates that the exposure methodologies demonstrated in the Draft Risk Evaluation for DIDP will be applicable to DINP exposure scenarios.
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. In light of comments on charge questions 1.b.i and 1.b.ii, please comment on the weight of scientific evidence and its conclusions for the general population exposure assessment (Section 11.3 of Draft Environmental Media and General Population Exposure). Please include in these comments a discussion of the clarity and transparency of the data used, and EPA's interpretation of the exposure results.
iv. For the remaining phthalates (*i.e.*, DEHP, DBP, DIBP, BBP, DCHP, DINP), 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.

c. 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. EPA anticipates that the exposure methodologies demonstrated in the Draft Risk Evaluation for DIDP will be applicable to DINP exposure scenarios.

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 (*i.e.*, DEHP, DBP, DIBP, BBP, DCHP, DINP), 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.

d. In light of comments on charge question 1.c.i, please comment on the weight of scientific evidence and its conclusions for the environmental exposure assessment (Sections 6 and 7 of Draft Environmental Exposure Assessment). Please include in these comments a discussion of the clarity and transparency of the data used, hazard values, and EPA's interpretation of the results.
e. 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. EPA anticipates that the exposure methodologies demonstrated in the Draft Risk Evaluation for DIDP will be applicable to DINP exposure scenarios.
    i. For environmental release assessments, please comment on the strengths and uncertainties of using EU PV % to estimate production volumes for DIDP.
    ii. For the remaining phthalates (*i.e.*, DEHP, DBP, DIBP, BBP, DCHP, DINP), EPA anticipates potentially needing to refine the environmental release 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.

2. Ecological hazard
    a. 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.
    b. 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.
3. Human health hazard

a. 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.
b. 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.

DINP Hazard Assessment

1. Ecological hazard
    a. 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.
2. Human health hazard
    a. 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 ($BMDL_5$ 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.
    b. In Section 4.1.3 of 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.
    c. In the Draft Cancer Human Health Hazard Assessment for DINP, EPA considered MNCL (Section 3.2.2), kidney tumors (Section 3.2.3), 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.

d. 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 alpha (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.
e. 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 will adequately account for all chronic toxicity, including carcinogenicity. Please comment on the strengths and uncertainties of this preliminary conclusion.