payment data from the Accounts Payable Excellence System (APEX) to form the cost proportions for the Intra-P&DC and Intra-District account categories, as the OIG recommended, but determined that APEX data does not contain the information necessary on vehicle capacity necessary to apportion payments between the four transportation/route types. *Id.*

Second, the Postal Service proposes using the rural cost distribution key (CS10, component 260) to attribute CDS costs to products. *Id.* at 6. The Postal Service states ''that both operational protocols and field observations support the hypothesis that similar mail volumes are delivered on CDS routes and rural routes.'' *Id.* Furthermore, the Postal Service contends that ''support for the similarities between CDS contractors and rural carriers is found in the process that exists for the conversion of CDS routes to rural routes in comparable offices.'' *Id.* at 7.

Impact. The Postal Service states that applying an initial update to the Intra-P&DC and Intra-District cost proportions, the first proposed revision, would result in an increase in volume variable highway costs by 0.03 percent. *Id.* at 9. The Postal Service reports that applying the rural cost distribution key to CDS costs, the second proposed change, would result in an increase ''by $33.7 M, or 0.9 percent'' in volume variable highway costs. *Id.*

The Postal Service states that implementing both of the proposed revisions would have resulted ''in a shift of $42.6 M, or 1.2 percent, in highway costs from institutional to volume variable costs'' using FY 2021 data. *Id.* at 11. The Postal Service reports that Competitive highway costs would decrease by 0.02 percent under this proposal while Market Dominant costs would increase by 2.5 percent. *Id.* The Postal Service acknowledges that highway costs for High Density and Saturation Flats/Parcels increase ''significantly'' on a percentage basis but states that the proposed changes result in less than a $0.01 increase on a unit cost basis. *Id.* The Postal Service states that the proposed methodology would result in approximately 0.2 percent of the volume variable costs for highway transportation being attributed to Total Domestic Market Dominant Services. *Id.*

III. Notice and Comment

The Commission establishes Docket No. RM2022–11 for consideration of matters raised by the Petition. More information on the Petition may be accessed via the Commission's website at *http://www.prc.gov.* Interested persons may submit comments on the Petition and Proposal Five no later than September 20, 2022. Pursuant to 39 U.S.C. 505, Almaroof Agoro is designated as an officer of the Commission (Public Representative) to represent the interests of the general public in this proceeding.

IV. Ordering Paragraphs

It is ordered:

1. The Commission establishes Docket No. RM2022–11 for consideration of the matters raised by the Petition of the United States Postal Service for the Initiation of a Proceeding to Consider Proposed Changes in Analytical Principles (Proposal Five), filed July 29, 2022.

2. Comments by interested persons in this proceeding are due no later than September 20, 2022.

3. Pursuant to 39 U.S.C. 505, the Commission appoints Almaroof Agoro to serve as an officer of the Commission (Public Representative) to represent the interests of the general public in this docket.

4. The Secretary shall arrange for publication of this order in the **Federal Register**.

By the Commission.

Jennie L. Jbara,

Alternate Certifying Officer.

[FR Doc. 2022–16879 Filed 8–5–22; 8:45 am]

BILLING CODE 7710–FW–P

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 372

[EPA–HQ–TRI–2022–0262; FRL–2425.1–04–OCSPP]

RIN 2025–AA17

Addition of Diisononyl Phthalate Category; Community Right-to-Know Toxic Chemical Release Reporting

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed rulemaking; supplemental notice.

SUMMARY: On September 5, 2000, in response to a petition filed under the Emergency Planning and Community Right-to-Know Act (EPCRA), EPA issued a proposed rule to add a diisononyl phthalate (DINP) category to the list of toxic chemicals subject to the reporting requirements under EPCRA and the Pollution Prevention Act (PPA). EPA proposed to add this chemical category to the EPCRA toxic chemical list based on its preliminary conclusion that this category met the EPCRA toxicity criterion. EPA has updated its hazard assessment for DINP and is proposing to add DINP as a category defined to include branched alkyl di-esters of 1,2 benzenedicarboxylic acid in which alkyl ester moieties contain a total of nine carbons. The updated hazard assessment demonstrates that the proposed DINP category meets the EPCRA toxicity criterion because the members of the category can reasonably be anticipated to cause cancer and serious or irreversible chronic health effects in humans; specifically, developmental, kidney, and liver toxicity. EPA is proposing to add the DINP category to the toxic chemical list on this basis and is requesting comment on the updated DINP hazard assessment and associated updated economic analysis.

DATES: Comments must be received on or before October 7, 2022.

ADDRESSES: Submit your comments, identified by docket identification (ID) number EPA–HQ–TRI–2022–0262, using the Federal eRulemaking Portal at *https://www.regulations.gov.* Follow the online instructions for submitting comments. Do not submit electronically any information you consider to be Confidential Business Information (CBI) or other information whose disclosure is restricted by statute. Additional instructions on commenting and visiting the docket, along with more information about dockets generally, is available at *https://www.epa.gov/dockets.*

FOR FURTHER INFORMATION CONTACT:

For technical information contact: Daniel R. Bushman, Data Gathering and Analysis Division (7406M), Office of Pollution Prevention and Toxics, Environmental Protection Agency, 1200 Pennsylvania Ave. NW, Washington, DC 20460–0001; telephone number: (202) 566–0743; email: *bushman.daniel@epa.gov.*

For general information contact: The Emergency Planning and Community Right-to-Know Hotline; telephone numbers: toll free at (800) 424–9346 (select menu option 3) or (703) 348–5070 in the Washington, DC Area and International; or go to *https://www.epa.gov/home/epa-hotlines.*

SUPPLEMENTARY INFORMATION:

I. General Information

A. Does this action apply to me?

You may be potentially affected by this action if you own or operate a facility that manufactures, processes, or otherwise uses any chemicals in the proposed DINP category. The following list of North American Industrial Classification System (NAICS) codes is not intended to be exhaustive, but rather

provides a guide to help readers determine whether this document applies to them. Facilities subject to reporting under EPCRA section 313 include:

- Facilities included in the following NAICS manufacturing codes (corresponding to Standard Industrial Classification (SIC) codes 20 through 39): 311*, 312*, 313*, 314*, 315*, 316, 321, 322, 323*, 324, 325*, 326*, 327, 331, 332, 333, 334*, 335*, 336, 337*, 339*, 111998*, 211130*, 212324*, 212325*, 212393*, 212399*, 488390*, 511110, 511120, 511130, 511140*, 511191, 511199, 512230*, 512250*, 519130*, 541713*, 541715* or 811490*. *Exceptions and/or limitations exist for these NAICS codes.
- Facilities included in the following NAICS codes (corresponding to SIC codes other than SIC codes 20 through 39): 211130 (corresponds to SIC code SIC 1321, Natural Gas Liquids and SIC 2819, Industrial Inorganic Chemicals, Not Elsewhere Classified); or 212111, 212112, 212113 (corresponds to SIC code 12, Coal Mining (except 1241)); or 212221, 212222, 212230, 212299 (corresponds to SIC code 10, Metal Mining (except 1011, 1081, and 1094)); or 221111, 221112, 221113, 221118, 221121, 221122, 221330 (limited to facilities that combust coal and/or oil for the purpose of generating power for distribution in commerce) (corresponds to SIC codes 4911, 4931, and 4939, Electric Utilities); or 424690, 425110, 425120 (limited to facilities previously classified in SIC code 5169, Chemicals and Allied Products, Not Elsewhere Classified); or 424710 (corresponds to SIC code 5171, Petroleum Bulk Terminals and Plants); or 562112 (limited to facilities primarily engaged in solvent recovery services on a contract or fee basis (previously classified under SIC code 7389, Business Services, NEC)); or 562211, 562212, 562213, 562219, 562920 (limited to facilities regulated under the Resource Conservation and Recovery Act, subtitle C, 42 U.S.C. 6921 *et seq.*) (corresponds to SIC code 4953, *Ref*use Systems).
- Federal facilities.

A more detailed description of the types of facilities covered by the NAICS codes subject to reporting under EPCRA section 313 can be found at: *https://www.epa.gov/toxics-release-inventory-tri-program/tri-covered-industry-sectors.* To determine whether your facility would be affected by this action, you should carefully examine the applicability criteria in 40 CFR part 372, subpart B. Federal facilities are required to report under Executive Order 13834 (*https://www.govinfo.gov/content/pkg/FR-2018-05-22/pdf/2018-11101.pdf*) as explained in the Implementing Instructions from the Council on Environmental Quality (*https://www.sustainability.gov/pdfs/eo13834_instructions.pdf*). If you have questions regarding the applicability of this action to a particular entity, consult the person listed under **FOR FURTHER INFORMATION CONTACT**.

B. What action is the Agency taking?

In response to a petition, EPA is proposing to add DINP as a category to the list of toxic chemicals subject to the reporting requirements under section 313 of EPCRA. As discussed in more detail later in this document, EPA is proposing to conclude that the members of the DINP category meet the EPCRA section 313(d)(2)(B) criteria for listing.

C. What is the Agency's authority for taking this action?

This action is issued under EPCRA sections 313(d), 313(e)(1) and 328, 42 U.S.C. 11023(d), 11023(e)(1) and 11048. EPCRA is also referred to as Title III of the Superfund Amendments and Reauthorization Act of 1986.

EPCRA section 313, 42 U.S.C. 11023, requires owners/operators of certain facilities that manufacture, process, or otherwise use listed toxic chemicals in amounts above reporting threshold levels to report their facilities' environmental releases and other waste management information on such chemicals annually. These facility owners/operators must also report pollution prevention and recycling data for such chemicals, pursuant to PPA section 6607, 42 U.S.C. 13106.

Under EPCRA section 313(c), Congress established an initial list of toxic chemicals subject to EPCRA toxic chemical reporting requirements that was comprised of 308 individually listed chemicals and 20 chemical categories.

EPCRA section 313(d) authorizes EPA to add or delete chemicals from the list and sets criteria for these actions. EPCRA section 313(d)(2) states that EPA may add a chemical to the list if any of the listing criteria in EPCRA section 313(d)(2) are met. Therefore, to add a chemical, EPA must determine that at least one criterion is met, but need not determine whether any other criterion is met. Conversely, to remove a chemical from the list, EPCRA section 313(d)(3) dictates that EPA must determine that none of the criteria in EPCRA section 313(d)(2) are met. The listing criteria in EPCRA section 313(d)(2)(A)–(C) are as follows:

- The chemical is known to cause or can reasonably be anticipated to cause significant adverse acute human health effects at concentration levels that are reasonably likely to exist beyond facility site boundaries as a result of continuous, or frequently recurring, releases.
- The chemical is known to cause or can reasonably be anticipated to cause in humans: cancer or teratogenic effects, or serious or irreversible reproductive dysfunctions, neurological disorders, heritable genetic mutations, or other chronic health effects.
- The chemical is known to cause or can be reasonably anticipated to cause, because of its toxicity, its toxicity and persistence in the environment, or its toxicity and tendency to bioaccumulate in the environment, a significant adverse effect on the environment of sufficient seriousness, in the judgment of the Administrator, to warrant reporting under this section.

EPA often refers to the EPCRA section 313(d)(2)(A) criterion as the ''acute human health effects criterion;'' the EPCRA section 313(d)(2)(B) criterion as the ''chronic human health effects criterion;'' and the EPCRA section 313(d)(2)(C) criterion as the ''environmental effects criterion.''

Under EPCRA section 313(e)(1), any person may petition EPA to add chemicals to or delete chemicals from the list. EPA issued a statement of policy in the **Federal Register** of February 4, 1987 (52 FR 3479) providing guidance regarding the recommended content of and format for petitions. On May 23, 1991 (56 FR 23703), EPA issued guidance regarding the recommended content of petitions to delete individual members of the metal compounds categories reportable under EPCRA section 313. EPA published in the **Federal Register** of November 30, 1994 (59 FR 61432) (FRL–4922–2) a statement clarifying its interpretation of the EPCRA section 313(d)(2) and (d)(3) criteria for modifying the EPCRA section 313 list of toxic chemicals.

D. Why is the Agency taking this action?

EPA is taking this action in response to a petition submitted under EPCRA section 313(e)(1). EPA is required to respond to petitions by ether initiating a rulemaking to grant the petition or publishing an explanation of why the petition is denied. In this case, EPA is proposing to grant the petition to list DINP.

E. What are the estimated incremental impacts of this action?

EPA prepared an economic analysis for this action entitled, ''Economic Analysis for the Addition of Diisononyl Phthalate Category; Community Right-

to-Know Toxic Chemical Release Reporting'' which presents an analysis of the costs of the proposed addition of the DINP category (Reference (Ref.) 1). EPA estimates that this action would result in an additional 198 to 396 reports being filed annually. EPA estimates that the costs of this action will be approximately $920,938 to $1,839,925 in the first year of reporting and approximately $438,542 to $876,155 in the subsequent years. In addition, EPA has determined that of the 181 to 362 small businesses affected by this action, none are estimated to incur annualized cost impacts of more than 1%. Thus, this action is not expected to have a significant adverse economic impact on a substantial number of small entities.

F. What should I consider as I prepare my comments for EPA?

1. Submitting CBI. Do not submit CBI information to EPA through *https://www.regulations.gov* or email. Clearly mark the part or all of the information that you claim to be CBI. For CBI information in a disk or CD–ROM that you mail to EPA, mark the outside of the disk or CD–ROM as CBI and then identify electronically within the disk or CD–ROM the specific information that is claimed as CBI. In addition to one complete version of the comment that includes information claimed as CBI, a copy of the comment that does not contain the information claimed as CBI must be submitted for inclusion in the public docket. Information so marked will not be disclosed except in accordance with procedures set forth in 40 CFR part 2.

2. Tips for preparing your comments. When preparing and submitting your comments, see the commenting tips at *https://www.epa.gov/dockets/commenting-epa-dockets#tips.*

II. What is the petition and EPA's response?

A. Who submitted the petition and what was requested?

On February 29, 2000, EPA received a petition from the Washington Toxics Coalition (which is now called Toxic-Free Future) requesting that EPA add DINP to the list of toxic chemicals subject to reporting under EPCRA Section 313 and PPA section 6607 (Ref. 2). The petitioner indicated that the composition of DINP varies, and that DINP is known by at least three CAS numbers: 28553–10–0, 68515–48–0, and 71549–78–5. The petitioner asserted that DINP causes cancer, systemic toxicity, developmental toxicity, and endocrine disruption, and therefore should be added to the list of chemicals subject to reporting under EPCRA Section 313 and PPA section 6607. The petitioner also stated that DINP is a dangerous phthalate ester used as the principal plasticizer in toys and other products used by children and adults. The petitioner asserted that in all studies conducted to measure DINP exposure from children's use of plastic, DINP migrates from the plastic into saliva when the plastic item is chewed or put into the child's mouth. (Ref. 2)

B. How did EPA initially respond to the petition?

In response to the petition to add DINP to the EPCRA section 313 list of toxic chemicals, EPA published a proposed rule to add DINP as a category to the EPCRA section 313 list (65 FR 53681, September 5, 2000) (FRL–6722–3). The proposed rule was based on information contained in the hazard assessment for DINP that was developed in response to the petition. EPA proposed to list the DINP category based on cancer and serious or irreversible chronic health effects including liver, kidney, and developmental toxicity. In response to comments on the proposal, EPA revised its hazard assessment for DINP and issued a notice of data availability (NODA) requesting comments on the revised hazard assessment (70 FR 34437, June 14, 2005) (FRL–7532–4). In the NODA, EPA proposed to list DINP based on serious or irreversible chronic health effects including liver, kidney, and developmental toxicity but reserved judgment on whether cancer was an endpoint of concern for DINP.

C. How is EPA updating its response to the petition?

Note that a considerable amount of time has elapsed since the DINP petition was received and EPA published the 2000 proposal and 2005 NODA. Therefore, EPA has prepared an updated hazard assessment based on currently available information, including studies developed since 2005 (Ref. 3). EPA has also updated the economic analysis for the addition of the DINP category (Ref. 1). For the reasons more fully explained in the updated hazard assessment (Ref. 3), EPA is now proposing to list the DINP category based on our preliminary conclusion that it is reasonably anticipated to cause cancer and serious or irreversible chronic health effects including developmental, kidney, and liver toxicity.

This supplemental proposal provides the public an opportunity to comment on all aspects of the proposed addition of the DINP category to the EPCRA section 313 toxic chemical list. EPA specifically requests comments on all parts of the updated hazard assessment and updated economic analysis as well as any other issues related to the addition of the DINP category. Note that EPA does not intend to respond to comments received in response to its 2000 proposal to add the DINP category to the EPCRA toxic chemicals list or those received in response to the associated 2005 NODA. This supplemental proposal presents an updated hazard assessment for DINP and an updated economic analysis for the proposed action. As such, comments on the prior hazard assessment and prior economic analysis are not relevant to the current proposed action. If a commenter believes a previously submitted comment is relevant to this proposed action, the commenter should resubmit the comment to the docket for this supplemental proposal. Also note that DINP is also undergoing a risk evaluation required under section 6(b) of the Toxic Substances Control Act (TSCA) and that the scientific analyses used for this listing will undergo further analyses and review as part of the TSCA risk evaluation process. Having chemicals on the TRI list can be helpful to the TSCA risk evaluation process, as well as any related risk management activities, as TRI can provide information concerning releases and waste management activities. Such information can help inform what potential exposures are present, as well as help identify facilities that deal with a given chemical (*e.g.,* chemicals in the proposed TRI DINP category). Nevertheless, EPA is not requesting comment in response to this present Notice on any issues related to the TSCA 6(b) risk evaluation as part of this rulemaking; rather, only comments directly related to the TRI listing proposal are relevant to this action.

III. What is EPA's technical evaluation of the toxicity of DINP?

A. What is the chemistry and use of DINP?

The DINP category for purposes of this action is a category of chemicals that includes the branched alkyl di-esters of 1,2 benzenedicarboxylic acid in which the alkyl ester moieties contain a total of nine carbons. The DINP category is a family of di-ester phthalates widely used as plasticizers. These chemicals are colorless, oily liquids with high boiling points, low volatilities, and are poorly soluble in water (less than 10^{-4} milligrams per liter (mg/L)). Multiple Chemical Abstracts Service (CAS) numbers are associated with DINPs

including 28553–12–0, 71549–78–5, 14103–61–8 and 68515–48–0. There is no single generic CAS number that represents all DINPs. The chemicals represented by CAS numbers 28553–12–0 and 71549–78–5 consist of a mixture of isomers (compounds which have the same molecular formula but differ in the arrangement of their atoms). CAS number 14103–61–8 represents a single isomeric structure of DINP (bis(3,5,5-trimethylhexyl) phthalate). The alkyl ester moieties of the diisononyl phthalate esters represented by the three CAS numbers stated above are branched and contain a total of nine carbons. These alkyl ester moieties are represented by the molecular formula C_9H_{19}. The molecular formulas of these nine-carbon alkyl ester moieties are the same for these DINP isomers. They differ in structure mainly due to the variable location of the methyl group on the alkyl ester moieties. CAS number 68515–48–0 is also a DINP, but unlike the chemicals represented by the other three CAS numbers discussed above, 68515–48–0 consists of di-ester phthalates with nine-carbon alkyl ester moieties (approximately 70% by weight), mixed with lesser amounts of di-ester phthalates with eight- and ten-carbon alkyl ester moieties.

Of the chemicals represented by the four CAS numbers stated above, two (68515–48–0 and 28553–12–0) were reported by industry to EPA under the Chemical Data Reporting regulations at 40 CFR part 711 as having production volumes of greater than 25,000 pounds per year per manufacturing or importing site. While reviewing data for the hazard assessments, EPA noted that only a limited number of studies reported the CAS numbers for the DINP test chemical base stocks. When studies did report CAS numbers, the CAS numbers were either 68515–48–0 or 28553–12–0. These two CAS numbers represent the primary DINP products manufactured commercially in the United States. Again, these two CAS numbers represent a mixture of DINP isomers and not any one single specific DINP isomer. There was no literature available for review which identified a single specific DINP isomer as the test chemical. Please refer to EPA's updated hazard assessment (Ref. 3) for more details on the chemistry and environmental fate of DINP.

The principle use of DINP is as a plasticizer, particularly in the production of polyvinyl chloride (PVC) (Ref. 3). The treatment of plastics with DINP provides greater flexibility and softness to the final product. Some of the uses of DINP treated plastics are the production of coated fabrics, plastic toys, electrical insulation, and vinyl flooring. On October 27, 2017, the U.S. Consumer Product Safety Commission (CPSC) issued a final phthalates rule (82 FR 49938, 16 CFR part 1307) that made permanent the interim prohibition on children's toys that can be placed in a child's mouth and child care articles that contain concentrations of more than 0.1 percent of DINP.

B. What technical data supports EPA's proposed addition of the DINP category to the EPCRA section 313 list?

EPA reviewed the available data on human health and ecological effects associated with DINP and has presented this information in an updated hazard assessment document (Ref. 3). Based on EPA's evaluation of the available data, EPA is proposing to conclude that DINP satisfies the criteria for listing under EPCRA section 313(d)(2)(B) because the members of the category can reasonably be anticipated to cause cancer and serious or irreversible chronic health effects in humans; specifically, developmental, kidney, and liver toxicity. Brief summaries of the available human health information that support listing the DINP category under EPCRA section 313(d)(2)(B) are provided in this Unit. Readers should consult the updated hazard assessment document (Ref. 3) for more detailed information about the effects discussed here as well as other human health and ecological effects associated with DINP.

1. *What carcinogenicity data were found for DINP?* In the following subsections a–c, EPA discusses some of the available cancer data for DINP. Subsection d summarizes the cancer data that supports EPA's proposed conclusion that DINP can reasonably be anticipated to cause cancer in humans. Additional information is provided in the updated DINP hazard assessment (Ref. 3).

EPA's evaluation used a weight of the evidence (or weight-of-evidence (WoE)) approach, which means a comprehensive evaluation of evidence and information, taking into consideration the strengths, limitations, and uncertainties across streams of evidence within a discipline. This yields a qualitative, overall summary of the strength of each evidence stream and an overall judgment across all relevant evidence (Ref. 4).

a. *Liver Tumors.* Chronic dietary exposure to DINP induced liver tumors in male and female rats fed 12,000 parts per million (ppm) (Ref. 5), in male mice fed 4,000 ppm and above, and in female mice fed 1,500 ppm and above (Ref. 6) when tested in 2-year oral bioassays. An increased incidence of liver carcinoma was also observed in male rats fed 6,000 ppm in the 2-year bioassay conducted by Lington *et al.* (Ref. 7), although the response did not reach statistical significance. These data indicate that DINP is a liver carcinogen in rats and mice.

The mode of action (MOA) for induction of hepatic tumors in rodents by DINP is by inducing peroxisome proliferation. Peroxisome proliferators are a structurally diverse group of non-mutagenic chemicals that induce a broad range of responses via interaction with peroxisome proliferator activated receptors (PPAR). There is evidence to suggest that the liver tumors which develop in rats and mice chronically exposed to DINP are mechanistically related to activation of PPAR receptor subtype alpha (PPARα) (Refs. 8, 9 and 10). Transgenic mice that lack PPARα are generally resistant to the pleiotropic effects of peroxisome proliferators, such as peroxisome proliferation, liver enlargement, and liver cancer (Refs. 11 and 12). There have been no 2-year studies of DINP in transgenic mice that lack PPARα to determine whether tumors would develop in this scenario. However, there are long term studies (about 70 weeks) available that show, development of hepatocellular carcinomas in PPARα transgenic mice with human PPARα agonists (GW7647), suggesting that PPARA is indeed responsible for carcinogenesis albeit at a dimished level (~35–72%) to a rodent PPARα driven carcinogenesis (Refs. 13 and 14).

There are no adequate epidemiological studies on cancer in humans exposed to PPARα agonists. Humans and non-human primates express functional PPARα, and hypolipidemic drugs are known to act through PPARα in humans. However, *in vivo* studies of DINP in primates (*e.g.,* Refs. 15 and 16) and *in vitro* studies of cultured primate or human cells (Refs. 17 and 18) exposed to DINP or its metabolite mono-isononyl phthalate (MINP) suggest that primates (including humans) are resistant to the induction of peroxisome proliferation. The basis for the species differences in these studies is unknown but may be related to differences in the quantity of PPARα or to differences in the regulatory sequences of the rodent and primate genes (Ref. 18). Human and mouse adenoviral recombinant PPARα expressed in PPARα deficient mice fully restored the development of peroxisome proliferator-induced immediate pleiotropic responses, including peroxisome proliferation and enhanced expression of genes involved in lipid metabolism, suggesting that the human

PPARα is functionally competent and is equally as dose-sensitive as mouse PPARα in inducing peroxisome proliferation within the context of mouse liver environment (Ref. 19). Absolute levels of PPARα are generally thought to be lower in human compared with rodent liver. However, PPARα amount varies by an order of magnitude among individuals (Refs. 20 and 21); for example, one of the six human samples examined expressed levels comparable to the mouse in one study (Ref. 22).

New information has emerged from recent literature (post 2005), on the mechanism(s) by which multiple nuclear receptors are activated by chemicals producing certain carcinogenic responses in rodents, including advances in the understanding of the underlying genetic factors that mediate the biochemical and cellular responses to such chemicals (summarized in Refs. 23, 24, and 25). To study the question of whether peroxisome proliferating chemicals such as DINP are a hazard to humans considering this new information, several panels and workshops have been convened and charged with reviewing the state of the science on the relationship between peroxisome proliferation and hepatocarcinogenesis in rodents and the human relevance of PPARα-induced liver tumors. One of the first panels, composed of government, academic and industry scientists and organized by Toxicology Excellence for Risk Assessment (TERA), concluded that significant quantitative differences in PPARα-induced liver effects associated with hepatic tumor formation exist between humans and rodents (Ref. 24). Based on quantitative differences between species, most panel members felt that the PPARα MOA for liver tumorigenesis is ''not relevant to humans;'' however, several panel members concluded that it was more appropriate to conclude that the PPARα mode of action is ''unlikely to be relevant to humans.'' In a subsequent workshop sponsored by the Toxicology Forum, the human relevance of rodent PPARα and constitutive androstane receptor (CAR) mediated modes of action for liver tumors were considered by industry, academic, and government experts (Refs. 23 and 26). Similar to the first panel, most workshop participants concluded that the PPARα and CAR modes of action are not relevant to humans based on qualitative and quantitative differences. However, there is evidence to show that the mouse and human PPARα expression levels are almost similar (Rakhshandehroo et al Ref. 27) and the set of genes/pathways regulated are similar to one another.

In considering the role of PPARα in inducing liver tumors, the California Office of Environmental Health Hazard Assessment (OEHHA) classified DINP as a carcinogen under California's Proposition 65 based in part on evidence that DINP can induce liver tumors in mice and rats (Refs. 28 and 9) and concluded that there was sufficient evidence to suggest that ''PPAR alpha activation may not be causally related to DINP-induced liver tumors in rats and mice'' and that other mechanisms may be involved (Ref. 29). Similarly, Environment Canada and Health Canada concluded that the mechanisms of DINP-induced liver tumorigenesis have not been fully elucidated, but that there is sufficient evidence to suggest that multiple mechanisms, including PPARα-independent mechanisms, may be involved (Ref. 30). Based on this, Health Canada (Ref. 10) concluded that the phthalates in their evaluation (including DINP) pose a carcinogenic hazard to humans. While the relevance of PPARα-mediated carcinogenic MOA to humans is not entirely clear, evidence suggests that peroxisome proliferating chemicals such as DINP are a hazard to humans because of its ability to cause liver cancer.

b. *Kidney Tumors.* In the study conducted in rats by Moore (Ref. 5), renal tubule cell carcinoma was observed in 2/65 high-dose (12,000 ppm) males and 4/50 recovery males compared to 0/65 in the control group. The response in recovery males was statistically significant relative to the control group. In the Lington *et al.* study (Ref. 7), renal tubule cell carcinoma was observed in 1/80 low-dose (300 ppm) males and 2/80 high-dose males (6,000 ppm). No preneoplastic or neoplastic lesions were observed in females. Treatment-related histopathologic changes in the kidneys of rats were consistent with male rat-specific α2u-globulin nephropathy. Additional evidence for α2u-globulin nephropathy was obtained in the retrospective evaluation of archived kidney tissue from the Lington *et al.* study (Ref. 7) conducted by Caldwell *et al.* (Ref. 31).

As discussed in the updated hazard assessment (Ref. 3), the data obtained in these studies were evaluated against published criteria for male-specific α2u-globulin nephropathy and its relevance to kidney tumors in humans (USEPA (Ref. 32); International Agency for Research on Cancer (IARC) 1999 (Ref. 33)). The EPA criteria (Ref. 32) are: (1) Increase in number and size of hyaline (protein) droplets in kidney proximal tubule cells of treated male rats; (2) Immunohistochemical evidence of α2u-globulin accumulating protein in the hyaline droplets; and (3) Histopathological evidence of kidney lesions associated with α2u-globulin nephropathology. The IARC criteria (Ref. 33) are: (1) Tumors occur only in male rats; (2) Acute exposure exacerbates hyaline droplet formation; (3) α2u-Globulin accumulates in hyaline droplets; (4) Subchronic lesions include granular casts and linear papillary mineralization; (5) Absence of hyaline droplets and other histopathological changes in female rats and mice; and (6) Negative for genotoxicity. Additional IARC Supporting Evidence includes: (1) Reversible binding of chemical to α2u-globulin; (2) Increased sustained cell proliferation in proximal tubule (P2 segment) and (3) Dose-response relationship between hyaline droplet severity and renal tumor incidence. For DINP, the EPA criteria for the α2u-globulin MOA have been met. However, for DINP, only three of the IARC criteria were met (1, 3, and 6) the other three criteria (2, 4, and 5) were not met. The data for DINP do not meet any of the IARC supporting criteria. In addition, the evaluation noted that (1) kidney weight increases along with histopathological changes (increase tubule cell pigmentation) were identified in female rats and (2) exposure resulted in nephropathy in female mice. Thus, α2u-globulin accumulation in the renal tubules of male rats alone do not explain the MOA for renal tubule carcinomas observed in DINP-exposed rodents.

Based on this evaluation, EPA along with the California Environmental Protection Agency (CalEPA) (Ref. 9) and the Consumer Product Safety Commission (Refs. 34 and 35) have determined that DINP-induced kidney tumors are relevant to estimating cancer hazard to humans as part of WoE approach described in Unit III.B.1.

c. *Mononuclear Cell Leukemia (MNCL).* The incidence of MNCL was significantly elevated in male and female rats exposed to DINP in the diet when compared to study control animals and the corresponding spontaneous/background incidence in two independent chronic/carcinogenicity rat studies (Refs. 5 and 7). The key issue in use of these data to assess the hazard of DINP exposure is the relevance of MNCL to human health as part of the WoE to suggest the carcinogenic hazard of DINP to humans. As fully explained in the revised hazard assessment (Ref. 3), the WoE supports a finding that DINP can reasonably be anticipated to cause MNCL in humans.

MNCL, also referred to as large granular lymphocyte (LGL) leukemia or T (lymphocyte) leukemia, is a spontaneously occurring neoplasm of the hematopoietic system that is one of the most common tumor types in the Fischer-344 rat strain. MNCL is life threatening in Fischer rats and results in a decreased life span. In contrast, MNCL is rare in other strains of rats and does not occur in mice. Although MNCL is recognized as a common neoplasm in Fischer rats, the MOA for induction of MNCL is not completely understood. In addition, there are differing views on the existence of a close human correlate to MNCL (Refs. 31 and 36).

The increased mortality due to MNCL in DINP-treated rats suggests that DINP is associated with the elevated incidence, progression, and severity of MNCL. Findings indicate that the time to onset of tumor was decreased and the disease was more severe in treated than in control animals. On the basis of these data, the increase in severity of MNCL with increasing dose in male rats is indicative of a carcinogenic response to DINP. However, EPA notes that there are several sources of uncertainty in the interpretation of the experimental data. These include high and variable background rate and possible strain-specificity as well as incomplete information on the MOA for induction of MNCL. However, full details on MOA are not required to establish a cancer hazard unless there is evidence to suggest that the MOA is not applicable to an assessment of human cancer, which is not the case in the context of MNCL derived cancer hazard discussed here.

Overall, there is some scientific uncertainty as to the human significance of the MNCL observed in rats, and whether DINP can reasonably be anticipated to cause MNCL in humans. However, the WoE within the MNCL dataset supports a finding that DINP can reasonably be anticipated to cause MNCL in humans.

d. *Additional considerations and conclusions.* As discussed above in sections a through c and in full detail in the updated hazard assessment (Ref. 2), evidence for carcinogenicity of DINP is provided by multiple studies in rats and mice exposed chronically via oral route. Statistically significant increases in many tumor types were observed in rats and mice such as increase in hepatocellular tumors (Refs. 5 and 7), hepatocellular adenoma and carcinoma (Refs. 5, 6, and 37) mononuclear cell leukemia of the spleen (Refs. 5, 6, and 7), and renal tubular cell carcinomas (Refs. 5, 6, and 7). In addition, other non-significant increases in tumor types considered rare and/or uncommon were noted in DINP-treated animals, including renal tubular and transitional cell carcinoma (Refs. 5, 6, and 7), pancreatic islet cell carcinoma (Refs. 6 and 37), testicular interstitial (Leydig) cell carcinoma (Ref. 37), and uterine adenocarcinoma (Ref. 37). All the above enumerated significant and non-significant increases in tumor, carcinoma and adenomas were also evaluated by CPSC in 2001 and 2010 (Refs. 34 and 35).

To date, DINP has been classified as a human carcinogen by OEHHA of CalEPA, but not by any international agencies. OEHHA has published a document on the evidence on the carcinogenicity of DINP in which members of the Carcinogen Identification Committee (CIC) conclude that DINP has been clearly shown, through scientifically valid testing according to generally accepted principles, to cause cancer and should be listed under California's Proposition 65 as a carcinogen (Ref. 9). Accordingly, DINP was listed under California's Proposition 65 at the end of 2013 (Ref. 28). California OEHHA (Ref. 24) cites evidence from multiple studies in mice and rats to support the Proposition 65 listing of DINP, including identification of:

- Liver tumors in female SD rats;
- Liver tumors in male and female F344 rats;
- Liver tumors in male and female B6C3F1 mice;
- Mononuclear cell leukemia (MNCL) in male and female F344 rats;
- Renal tubular cell carcinomas, which are rare or uncommon, in male F344 rats;
- Renal transitional cell carcinomas, which are rare, in male F344 rats;
- Pancreatic islet cell carcinomas, which are rare, in male SD rats and female B6C3F1 mice;
- Testicular interstitial (Leydig) cell carcinomas, which are uncommon, in male SD rats; and
- Uterine adenocarcinomas, which are rare, in female SD rats.

DINP, similar to other phthalates, was negative in the limited number of genotoxic assays and ruled-out as a genotoxic carcinogen. However, that determination leaves non-genotoxic mechanisms for consideration as plausible carcinogenic mechanisms for DINP. DINP has been found to induce in vitro cell transformation in only one out of eight studies conducted with Balb/c-3T3 A31 mouse cells (Refs. 38 and 39). DINP binds to PPAR and activates both rodent and human PPARα and PPAR gamma but not PPAR beta receptors (Ref. 40). MINP, the metabolite of DINP, activated both the mouse and human PPARα and PPAR gamma receptors, but the degree of PPARα and PPAR gamma activation was greater for the mouse receptor than for the human receptor for both receptor types in the tested conditions (Ref. 40).

DINP has been shown to activate human CAR (hCAR2) and pregnane X receptor (PXR), and the metabolites of DINP, specifically MINP, activates hCAR2 isoform, suggesting that DINP and its metabolites have more than one MOA (Ref. 41). DINP has also been shown to promote and induce tumorigenesis in a variety of cell types through aryl hydrocarbon receptors (AhR)-mediated genomic and nongenomic pathways (Ref. 42). DINP induces several changes in rodent liver consistent with PPARα activation (Ref. 41). DINP induces some of these liver changes independently of PPARα activation as shown in PPARα-null mice (Ref. 12).

Tumor necrosis factor-alpha (TNF-α) plays a pivotal role in a number of cell signaling pathways involved in inflammation, cell proliferation, and apoptosis (Ref. 43). Although inconsistently reported with DINP treatment, TNF-α functional perturbation contributes to carcinogenesis (Ref. 43). In studies conducted in a human promonocyte cell line, DINP reduced phagocytosis in a dose-dependent manner and increased TNF-α levels (Ref. 44). DINP is shown to inhibit hepatic gap junctional intercellular communication (GJIC), and the inhibition of GJIC has been proposed as a non-genotoxic carcinogenic mechanism in rodents exposed to DINP for 2 or 4 weeks (Refs. 45 and 46).

In considering the structure activity relationships (*i.e.,* the read-across approach) between similar phthalates, DINP is structurally similar to di(2-ethylhexyl)phthalate (DEHP). Both the phthalates have phthalic acid as the common structure with different branched alkyl chains for the ester portion. DEHP has an eight carbon alkyl chain with an ethyl branch at the 2 position and DINP has a nine carbon alkyl chain with a methyl group at various positions. One of the commercially available DINP mixtures (CAS number 68515–48–0) contains ~70% nine-carbon alkyl ester chains with the rest being eight- and ten-carbon alky ester chains. Analog searches with AIM (*https://www.epa.gov/tsca-screening-tools/analog-identification-methodology-aim-tool*) and GenRA (*https://comptox.epa.gov/genra*), identified DEHP as the analog to DINP. DEHP and DINP are carcinogenic in rodents, are metabolized via similar

detoxification pathways, and have similar modes of action (*e.g.,* PPARα is believed to play a role in liver tumorigenesis for most phthalates (Refs. 23 and 24). Due to these similarities, DEHP carcinogenicity data is useful for a read-across approach to DINP. DEHP has been classified by IARC as a Group 2B (possibly carcinogenic to humans) carcinogen (Refs. 47 and 48); by EPA as a Class B2 (Probable human carcinogen) carcinogen (Ref. 49); by the National Toxicology Program (NTP) to be reasonably anticipated to be a human carcinogen (Ref. 50); and is listed by CalEPA under California's Proposition 65 as causing cancer (Ref. 51). These previous assessments indicate DEHP is a carcinogenic hazard to humans. Based on available toxicity data for DINP in multiple species (mouse and rats) and adverse effects on multiple tissues (liver, kidney, uterus and testicular), with similar mechanism of action (MOA), through activation of multiple toxicity pathways by multiple nuclear receptors (such as PPARα/γ, CAR, AhR), leading to cancer in multiple organs and structural similarities between DEHP and DINP, it is reasonable to assume that DINP would be a carcinogenic hazard to humans.

In summary, the available literature as discussed above and in the updated hazard assessment (Ref. 3), provides evidence that DINP can be reasonably anticipated to cause cancer in humans. EPA proposes to conclude that the available cancer data provides a sufficient basis for listing DINP on the EPCRA section 313 toxic chemicals list pursuant to EPCRA section 313(d)(2)(B)(i) because it demonstrates that DINP can reasonably be anticipated to cause cancer in humans.

2. *What chronic developmental toxicity data were found for DINP?* In this section, EPA discusses the available developmental toxicity data that supports EPA's proposed conclusion that DINP can reasonably be anticipated to cause serious or irreversible developmental effects in humans. Additional information is provided in the updated hazard assessment (Ref. 3).

The available data for developmental toxicity (see Table 22 of Ref. 3) generally shows a consistent pattern of effects within the window of exposure (*in utero,* prenatal, and post natal exposure). The results of the one- and two-generation reproductive studies indicate that DINP affects post natal growth, as evident from significantly reduced pup growth at doses of 143–285 milligrams per kilogram per day (mg/kg/day) (during gestation and lactation (Refs. 52 and 53)). The results of two developmental toxicity studies on DINP (Refs. 52 and 53) are also consistent. In both studies, DINP exposure in utero resulted in increased incidences of rudimentary lumbar and/or supernumerary cervical ribs and adverse renal effects in fetuses. Hellwig *et al.* (Ref. 52) identified a no-observed-adverse-effect level (NOAEL) and a lowest-observed-adverse-effect level (LOAEL) of 200 and 1,000 mg/kg/day, respectively, for these developmental effects. EPA has identified lower NOAEL and LOAEL values of 100 and 500 mg/kg/day, respectively, based on effects observed in the developmental study conducted by Waterman *et al.* (Ref. 53). DINP causes malformations of the reproductive tract and alterations in fetal testicular testosterone production and content in male offspring of rats exposed to 750 mg/kg/day during gestation (Refs. 54 and 55).

In a study of male sexual development, timed pregnant Crl:CD Sprague-Dawley rats were administered the test substance in corn oil via oral gavage at target doses of 0 (vehicle), 50, 250, or 750 mg/kg/day (corresponding to mean analytical doses of 0, 47, 242, or 760 mg/kg/day) from gestation days (GDs) 12–19 (Ref. 56). The maternal NOAEL and LOAEL were determined to be 47 and 242 mg/kg/day based on increased liver weights in dams. The developmental NOAEL and LOAEL were determined to be 47 and 242 mg/kg/day based on induction of multinucleated gonocytes (MNGs) and reduced testosterone in fetal testes.

In a prenatal developmental toxicity study, timed pregnant female Sprague-Dawley rats (20/group, 24 controls) were administered the test substance in the diet at target concentrations of 0 (base diet), 760, 3,800, or 11,400 ppm (target doses of 0, 50, 250, or 750 mg/kg/day, respectively) from GD 12 through post natal day (PND) 14 (Ref. 57). The study identified a LOAEL for maternal effects of 11,400 ppm (~750 mg/kg/day) based on reduced body weight, body weight gain, and food consumption during gestation and lactation; the NOAEL was 3,800 ppm (~250 mg/kg/day). The developmental LOAEL was 3,800 ppm (~250 mg/kg/day) for effects seen in male pups, including reduced pup weight and increased MNGs at greater than 3,800 ppm and decreased anogenital distance (AGD) and increased Leydig cell (LC) aggregation at 11,400 ppm. The developmental NOAEL was found to be 760 ppm (~50 mg/kg/day).

The WoE from the available reproductive and developmental toxicity studies that were considered and presented in Table 22 of the hazard assessment (Ref. 3) demonstrates that DINP causes serious or irreversible developmental effects in animals. The adverse effects include decreased body weight of pups during lactation in a rat two-generation reproductive toxicity study and in a multi-dose perinatal exposure study (Refs. 53 and 54); adverse renal and skeletal effects observed in two rat developmental toxicity studies (Refs. 52 and 58); altered sexual differentiation observed in a single dose gavage study (750 mg/kg/day) of perinatally-exposed male rats (Ref. 55); and occurrence of histological lesions in the ovaries and testes of male and female rats exposed perinatally via the diet (1,164–2,656 mg/kg/day) (Ref. 59).

Reduction in the mean body weight of pups exposed to DINP either for one generation, two generations, or perinatally is a sensitive indicator of developmental toxicity, in part because it is a continuous variable. The Agency believes that the weight of evidence indicates reduced pup body weight is a serious effect because (1) the observed responses were statistically significant; (2) the responses were dose-related, (3) the reductions ranged from 9–43% below control values (a range that is consistent with biological significance); (4) the magnitude of the response tended to increase with DINP exposure over time via lactation exposure during the post-natal period; (5) the reductions were observed in both sexes and in both F1 and F2 generations of the two-generation study; (6) the weight reductions were noted in both one- and two-generation and perinatal exposure studies; and (7) the response may have long-term consequences. Although there is always a question as to whether weight reduction is a permanent or transitory effect, little is known about the long-term consequences of short-term fetal or neonatal weight changes; however, a previous study has shown that exposure to chemicals during organogenesis that reduced pup birth weight also permanently reduced adult mouse weight with about 50% of the chemicals (about 40 tested) (Ref. 60), and there is growing epidemiological evidence of the long-term consequences of low birth weight in humans (Ref. 61). Therefore, EPA has concerns for potentially serious developmental effects of DINP in humans.

The kidney and skeletal variations observed in rats treated with DINP are serious because they are structural effects that indicate that development has been disrupted. The observed renal effects and skeletal variations occurred in the absence of or at minimal maternal toxicity. In particular, the occurrence of extra cervical ribs may be of serious

health consequence. As noted by National Toxicology Program Center for the Evaluation of Risks to Human Reproduction (Ref. 62), supernumerary cervical ribs are an uncommon finding, and their presence may indicate a disruption of gene expression leading to this structural anomaly. In addition, there is concern that cervical ribs may interfere with normal nerve function and blood flow.

The effects on sexual differentiation observed in male rats by Gray *et al.* (Ref. 54) are serious because they represent gross morphological malformations not normally seen in development of this species. The discrepancy between the antiandrogenic effects observed in the perinatal exposure study (Ref. 54) and the absence of similar effects in the two-generation reproductive study conducted by Waterman *et al.* (Ref. 53) may be explained, in part, by the dose (750 mg/kg) used by Gray *et al.* (Ref. 54) and by differences in the protocol used for each study. Exposures during gestation in the two-generation study did not reach the dose that was used in the Gray *et al.* (Ref. 54) perinatal exposure study during gestation (approximately 560 mg/kg/day vs. 750 mg/kg/day, respectively) and the reproductive parameters affected in the study by Gray *et al.* (Ref. 54), including nipple retention, anogenital distance, age at testes descent, and age at preputial separation, were not measured in the two-generation reproductive study.

Furthermore, the number of F1 animals examined by Waterman *et al.* (Ref. 53) was not sufficient to detect the low (7.7%) but statistically significant incidence of malformations observed by Gray *et al.* (Ref. 54). The perinatal exposure study reported by Masutomi *et al.* (Ref. 59) did not detect the same type of alterations reported by Gray *et al.* (Ref. 54), although the administered dietary concentrations resulted in doses (306.7–656.7 mg/kg/day and 1,164–2,657 mg/kg/day) that bracketed the single gavage dose of 750 mg/kg/day administered by Gray *et al.* (Ref. 54). However, Masutomi *et al.* (Ref. 59) examined fewer litters (5 vs. 14), examined fewer pups (number of pups and developmental endpoints examined prior to culling were not reported) and did not report use of the same type of detailed internal and external examinations used by Gray *et al.* (Ref. 54) to detect areolas, retained nipples, and other developmental effects. In addition, the differing routes of administration (gavage vs. diet) used in these studies may have resulted in different peak blood concentrations of DINP.

Although the study by Gray *et al.* (Ref. 54) used a single dose and a NOAEL/LOAEL could not be established, the observed effects indicate that DINP has the potential for antiandrogenic effects in neonatal male rats when tested at 750 mg/kg/day. The effects of DINP on sexual differentiation were characterized by the study authors as malformations for the tested species and are therefore believed to be permanent (*i.e.,* not transient or reversible) and adverse. The observed effects may have resulted from inhibition of fetal testis hormone production during sexual differentiation, a process that is critical in all mammals including humans. It has been demonstrated that several other structurally related phthalate esters (dibutyl phthalate (DBP), DEHP, and benzyl butyl phthalate (BBP)) also alter sexual differentiation and do so by altering fetal testis testosterone production and/or content (Refs. 63 and 64) and insulin-like hormone 3 (Insl3) production (Ref. 65), resulting in malformations of male reproductive tissues that require these hormones for development. The results of a recent study by Borch *et al.* (Ref. 55), which showed decreased fetal testis production and content of testosterone in offspring of female rats treated with DINP during gestation, are consistent with this pattern and increase the WoE for disruption of testosterone synthesis as a potential MOA for the observed effects on the male reproductive system. Although information is currently lacking on (1) the precise mechanism(s) responsible for DINP-induced malformations and its relevance to humans, and (2) the critical window of susceptibility for these effects during reproductive development, based upon the WoE, EPA concludes that humans can reasonably be anticipated to be affected if exposed to sufficient concentrations of DINP or its metabolites at critical stages of reproductive development.

In summary, the available literature as discussed above and in the updated hazard assessment (Ref. 3), provides evidence that DINP can be reasonably anticipated to cause developmental toxicity in humans. EPA proposes to conclude that the available developmental toxicity data provides a sufficient basis for listing DINP on the EPCRA section 313 toxic chemicals list pursuant to EPCRA section 313(d)(2)(B)(ii) because it demonstrates that DINP can reasonably be anticipated to cause serious or irreversible chronic developmental toxicity.

3. *What chronic kidney toxicity data were found for DINP?* In this section, EPA discusses the available kidney toxicity data that supports EPA's proposed conclusion that DINP can reasonably be anticipated to cause chronic kidney toxicity in humans. Additional information is provided in the updated hazard assessment (Ref. 3).

The kidney is both a cancer and a non-cancer target organ of DINP in chronic toxicity studies in rats and mice. In rats, increased relative kidney weights were seen in a 21-day (Ref. 66) and three 2-year rodent studies of DINP (Refs. 5, 6, and 7). In the 2-year study conducted by Lington *et al.* (Ref. 7), exposure to dietary levels of 152 and 307 mg/kg/day increased relative kidney weights of both male and female rats. An increase in tubular cell pigment was also noted in the tubular epithelium of high-dose males at 18 months. In the 2-year study reported by Moore (Ref. 5), increased relative kidney weights occurred in rats receiving dietary doses greater than 359 mg/kg/day for males and 442 mg/kg/day for females. Urinalysis findings from the chronic studies included significant increases in urine output and corresponding decreases in electrolyte levels in high-dose males, suggesting compromised ability to concentrate urine in the renal tubule epithelium. These effects occurred at the same dosages that produced changes in kidney weights. In the Moore (Ref. 5) study, serum urea levels (a marker of kidney toxicity) were significantly increased in rats exposed to 359 mg/kg/day and higher during the second half of the study. Increases in urine volume and kidney lesions were observed in the recovery group exposed to 733 mg/kg/day.

In the Moore (Ref. 5) study, male rats with increased kidney weights also had increased mineralization of renal papillae. However, it is unlikely that the histological effects reported (mineralization of renal papillae in male rats and pigmentation of kidney tubule cells) account for the increased weights of the kidneys because routine histological observations do not account for observations of mineralizations and pigmentations in the kidney.

The kidney was also a target organ for DINP toxicity in the chronic study in mice (Ref. 6). Kidney weights were significantly decreased at doses of 1,500 ppm (276 mg/kg/day) and above in male mice. This decrease in kidney weight correlated with clinical chemistry findings of higher urine volumes accompanied by lower osmolarity (with lower concentrations of sodium, potassium and chlorides) in the highest dose group and recovery groups of both sexes. The urinalysis findings suggest compromised ability to concentrate urine in the renal tubule epithelium.

Histopathology findings included a DINP-induced increase in the incidence of chronic progressive nephropathy in females of the highest dose group (but not in males). Granular pitted/rough kidneys were observed in female mice receiving the 8,000 ppm diet (1,888 mg/kg/day) and corresponded to increased incidence/severity of treatment-related nephropathy. The recovery group had a decreased incidence of chronic progressive nephropathy, suggesting that the effects of DINP were partially reversible upon cessation of DINP treatment or that cessation of treatment prevented exacerbation of existing lesions. Kidney changes in female mice (increased incidence and severity of nephrotoxicity) occurred at 8,000 ppm (1,888 mg/kg/day) and in male and female rats (increased kidney weights, compromised ability to concentrate urine) at 6,000 ppm (359 and 442 mg/kg/day, respectively). Such changes are indicative of kidney toxicity. Although effects in male rats appear to be due to α2u-globulin nephropathy, the toxic kidney effects in female mice and increased kidney weights in female rats cannot be explained by an α2u-globulin MOA.

In summary, the available literature as discussed above and in the updated hazard assessment (Ref. 3), provides evidence that DINP can be reasonably anticipated to cause chronic kidney toxicity in humans. EPA proposes to conclude that the available kidney toxicity data provides a sufficient basis for listing DINP on the EPCRA section 313 toxic chemicals list pursuant to EPCRA section 313(d)(2)(B)(ii) because it demonstrates that DINP can reasonably be anticipated to cause serious or irreversible chronic effects on the kidney.

4. *What chronic liver toxicity data were found for DINP?* In this section, EPA discusses the available liver toxicity data that supports EPA's proposed conclusion that DINP can reasonably be anticipated to cause chronic liver toxicity in humans. Additional information is provided in the updated hazard assessment (Ref. 3).

Adverse liver effects were noted in rats following chronic DINP exposure in three independent studies (Refs. 5, 6, and 7). Spongiosis hepatis, also called cystic or microcystic degeneration, has been identified as the most sensitive non-neoplastic response resulting from DINP exposure and is thus considered the critical non-cancer effect. The incidence of spongiosis hepatis was dose-related, and significantly elevated in male rats chronically treated with DINP in three studies conducted by different laboratories (Refs. 5, 6, and 7). In the Lington *et al.* (1997) study (Ref. 7), the LOAEL for spongiosis hepatis was 152 mg/kg/day, while the LOAEL in the Moore study (Ref. 5) was 359 mg/kg/day; the NOAELs were 15 and 88 mg/kg/day, respectively. A Histopathology Peer Review and Pathology Working Group (Ref. 67) independently evaluated the liver slides from rats chronically treated with DINP (Refs. 5 and 7) and confirmed that the incidence of spongiosis hepatis was increased in male rats in each study.

There is general agreement that spongiosis hepatis develops from the perisinusoidal (Ito) cells of the liver. The existing data support the conclusion that the increased incidence of spongiosis hepatis in dosed rats is clearly related to DINP treatment. In evaluating the data for hepatic spongiosis, EPA considered (1) the possibility that occurrence of spongiosis hepatis and induction of peroxisome proliferation were related; (2) the possibility that the occurrence of spongiosis hepatis was a consequence of MNCL; (3) the relationship of spongiosis hepatis to hepatocellular cancer; and (4) the human relevance of hepatis spongiosis.

The occurrence of spongiosis hepatis and peroxisome proliferation in the livers of rats exposed to DINP are likely to be unrelated due to two different MOAs. Although peroxisome proliferation appeared to occur in both sexes of rats and mice, the incidence of spongiosis hepatis was increased only in male rats. In addition, spongiosis hepatis occurred in control animals and in treated animals at doses that did not induce peroxisome proliferation. These data indicate that induction of peroxisome proliferation per se is not a prerequisite for induction of spongiosis hepatis.

The increased incidence of spongiosis hepatis observed in rats exposed to DINP is not due to MNCL. This conclusion is based on the findings of the Experimental Pathology Laboratories (Ref. 67), which noted that only about 50% of the animals with spongiosis hepatis also had MNCL and that the incidence of spongiosis hepatis increased in some rats that did not show signs of MNCL.

Spongiosis hepatis may be associated with or located within foci of cellular alteration or hepatocellular neoplasms. This association has prompted questions regarding the relationship of this lesion to carcinogenic processes in the liver. EPA considers the relationship between spongiosis hepatis and hepatic carcinogenesis to be two independent events. There does not appear to be strong correlation between the induction of spongiosis hepatis and the occurrence of hepatocellular neoplasms in rats treated with DINP. In addition, 4 of the 12 studies reviewed by Karbe and Kerlin (Ref. 68) reported spongiosis hepatis in the absence of hepatocellular neoplasms while a fifth study observed hepatocellular cancer in females only.

Spontaneous and induced spongiosis hepatis lesions have been observed in fish as well as rats, but the existence of the lesion in humans and other species is less well supported (Ref. 68). It is unknown whether human Ito cells are capable of developing spongiosis hepatis as observed in rats. In the absence of information that clearly indicates a species-specific MOA for development of spongiosis hepatis, the occurrence of this lesion in rats is assumed to be relevant to humans (Ref. 68).

Based on the available data, the WoE indicates that the spongiosis hepatis is a treatment-related lesion in rats treated with DINP and that the occurrence of this lesion in animals is relevant to human health. EPA has identified NOAEL and LOAEL values of 15 and 152 mg/kg/day, respectively, for the Lington study (Ref. 7) and 88 and 359 mg/kg/day, respectively, for the Moore study (Ref. 5) based on indications of serious liver damage (*i.e.,* a statistically significant increased incidence of spongiosis hepatis and increased liver weight and liver enzyme activities) in male rats chronically exposed to DINP for 2 years.

In summary, the available literature as discussed above and in the updated hazard assessment (Ref. 3), provides evidence that DINP can be reasonably anticipated to cause chronic liver toxicity in humans. EPA proposes to conclude that the available liver toxicity data provides a sufficient basis for listing DINP on the EPCRA section 313 toxic chemicals list pursuant to EPCRA section 313(d)(2)(B)(ii) because it demonstrates that DINP can reasonably be anticipated to cause serious or irreversible chronic effects on the liver.

IV. What is EPA's rationale for listing the DINP category?

Based on EPA's review of the available carcinogenicity data, EPA proposes to conclude that DINP can reasonably be anticipated to cause cancer in humans. In addition, based on EPA's review of the available chronic toxicity data, EPA proposes to conclude that DINP can reasonably be anticipated to cause serious or irreversible chronic human health effects at moderately low to low doses including developmental effects, kidney toxicity, and liver toxicity. The data for DINP

demonstrates that DINP has moderately high to high human health toxicity based on the available animal studies. Therefore, EPA proposes to conclude that, based on the available toxicity data summarized above and in the updated hazard assessment, DINP meets the criteria in EPCRA section 313(d)(2)(B) for listing on the EPCRA section 313 toxic chemicals list.

EPA is proposing to add DINP to the EPCRA section 313 list as a chemical category under the name ''Diisononyl Phthalates (DINP): Includes branched alkyl di-esters of 1,2 benzenedicarboxylic acid in which alkyl ester moieties contain a total of nine carbons.'' As explained in Unit III.A., DINP includes the branched alkyl di-esters of 1,2 benzenedicarboxylic acid in which the alkyl ester moieties contain a total of nine carbons and there is no single generic CAS number that represents all DINPs. This category includes the four CAS numbers that represent the DINP esters identified in Unit III.A., as well as any other branched alkyl di-ester of 1,2-benzenedicarboxylic acid in which the alkyl ester moieties contain a total of nine carbons. As EPA has explained in the past (see 59 FR 61442–61443, November 30, 1994)(FRL–4922–2), EPCRA allows the Agency, in its discretion, to add a chemical category to the list, where EPA identifies the toxic effect of concern for at least one member of the category and then shows why that effect can reasonably be expected to be caused by all other members of the category. Given the structural similarities of the members of the proposed DINP category, it is reasonable to anticipate that all members of the DINP category as described will exhibit similar toxicity. For this reason, creating a category of DINP is the most appropriate way to list this class of chemicals.

EPA has concluded that it is not appropriate to consider exposure for chemicals that are moderately high to highly toxic based on a hazard assessment when determining if a chemical should be added for chronic human health effects pursuant to EPCRA section 313(d)(2)(B) (see 59 FR 61440–61442). Therefore, in accordance with EPA's standard policy on the use of exposure assessments (see November 30, 1994 (59 FR 61432, FRL–4922–2), an exposure assessment is neither necessary nor appropriate for determining whether DINP meets the criteria of EPCRA section 313(d)(2)(B).

V. References

The following is a listing of the documents that are specifically referenced in this document. The docket includes these documents and other information considered by EPA, including documents that are referenced within the documents that are included in the docket, even if the referenced document is not itself physically located in the docket. For assistance in locating these other documents, please consult the person listed under **FOR FURTHER INFORMATION CONTACT**.

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2. Letter to EPA Administrator Carol M. Browner, Re: Petition to Add Diisononyl Phthalate (DINP) to the Emergency Planning and Community Right-to-Know Act Section 313 List of Toxic Chemicals. From Laurie Valeriano, Policy Director, Wastington Toxics Coalition. February 24, 2000.
3. USEPA. Technical Review of Diisononyl Phthalate (*i.e.,* updated hazard assessment). Office Pollution Prevention and Toxics Data Gathering and Analysis Division and Existing Chemicals Risk Assessment Division. April 11, 2022.
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VI. Statutory and Executive Order Reviews

Additional information about these statutes and Executive Orders can be found at *https://www.epa.gov/laws-regulations/laws-and-executive-orders.*

A. Executive Order 12866: Regulatory Planning and Review and Executive Order 13563: Improving Regulation and Regulatory Review

This action is not a significant regulatory action and was therefore not submitted to the Office of Management and Budget (OMB) for review under Executive Orders 12866 (58 FR 51735, October 4, 1993) and 13563 (76 FR 3821, January 21, 2011).

B. Paperwork Reduction Act (PRA)

This action does not impose any new information collection burden under the PRA, 44 U.S.C. 3501 *et seq.* Burden is defined in 5 CFR 1320.3(b). OMB has previously approved the information collection activities contained in the existing regulations and has assigned OMB control numbers 2070–0212 and 2050–0078. Currently, the facilities subject to the reporting requirements under EPCRA section 313 and PPA section 6607 may use either EPA Toxic Chemicals Release Inventory Form R (EPA Form 9350–1), or EPA Toxic Chemicals Release Inventory Form A (EPA Form 9350–2). The Form R must be completed if a facility manufactures, processes, or otherwise uses any listed chemical above threshold quantities and meets certain other criteria. For the Form A, EPA established an alternative threshold for facilities with low annual reportable amounts of a listed toxic chemical. A facility that meets the appropriate reporting thresholds, but estimates that the total annual reportable amount of the chemical does not exceed 500 pounds per year, can take advantage of an alternative manufacture, process, or otherwise use threshold of 1 million pounds per year of the chemical, provided that certain conditions are met, and submit the Form A instead of the Form R. In addition, respondents may designate the specific chemical identity of a substance as a trade secret pursuant to EPCRA section 322, 42 U.S.C. 11042, 40 CFR part 350.

OMB has approved the reporting and recordkeeping requirements related to Forms A and R, supplier notification, and petitions under OMB Control number 2070–0212 (EPA Information Collection Request (ICR) No. 2613.02) and those related to trade secret designations under OMB Control 2050–0078 (EPA ICR No. 1428). As provided in 5 CFR 1320.5(b) and 1320.6(a), an Agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. The OMB control numbers relevant to EPA's regulations are listed in 40 CFR part 9 and displayed on the information collection instruments (*e.g.,* forms, instructions).

C. Regulatory Flexibility Act (RFA)

I certify that this action will not have a significant economic impact on a substantial number of small entities under the RFA, 5 U.S.C. 601 *et seq.* The small entities subject to the requirements of this action are small manufacturing facilities. The Agency has determined that of the 198 to 396 entities estimated to be impacted by this action, 181 to 362 are small businesses; no small governments or small organizations are expected to be affected by this action. All small businesses affected by this action are estimated to incur annualized cost impacts of less than 1%. Thus, this action is not expected to have a significant adverse economic impact on a substantial number of small entities. A more detailed analysis of the impacts on small entities is located in EPA's economic analysis (Ref. 1).

D. Unfunded Mandates Reform Act (UMRA)

This action does not contain an unfunded mandate of $100 million or more as described in UMRA, 2 U.S.C. 1531–1538, and does not significantly or uniquely affect small governments. This action is not subject to the requirements of UMRA because it contains no regulatory requirements that might significantly or uniquely affect small governments. EPA did not identify any small governments that would be impacted by this action. EPA's economic analysis indicates that the total industry cost of this action is

estimated to be $920,938 to $1,839,925 in the first year of reporting and $438,542 to $876,155 in subsequent years (Ref. 1).

E. Executive Order 13132: Federalism

This action does not have federalism implications as specified in Executive Order 13132 (64 FR 43255, August 10, 1999). It will not have substantial direct effects on the States, on the relationship between the national government and the States, or on the distribution of power and responsibilities among the various levels of government.

F. Executive Order 13175: Consultation and Coordination With Indian Tribal Governments

This action does not have tribal implications as specified in Executive Order 13175 (65 FR 67249, November 9, 2000). This action relates to toxic chemical reporting under EPCRA section 313, which primarily affects private sector facilities. Thus, Executive Order 13175 does not apply to this action.

G. Executive Order 13045: Protection of Children From Environmental Health Risks and Safety Risks

EPA interprets Executive Order 13045 (62 FR 19885, April 23, 1997) as applying only to those regulatory actions that concern environmental health or safety risks that EPA has reason to believe may disproportionately affect children, per the definition of ''covered regulatory action'' in section 2–202 of the Executive Order. This action is not subject to Executive Order 13045 because it does not concern an environmental health risk or safety risk.

H. Executive Order 13211: Actions Concerning Regulations That Significantly Affect Energy Supply, Distribution, or Use

This action is not subject to Executive Order 13211, because it is not a significant regulatory action under Executive Order 12866.

I. National Technology Transfer and Advancement Act (NTTAA)

This rulemaking does not involve technical standards. As such, NTTAA section 12(d), 15 U.S.C. 272 *note,* does not apply to this action.

J. Executive Order 12898: Federal Actions To Address Environmental Justice in Minority Populations and Low-Income Populations

Executive Order 12898 (59 FR 7629, February 16, 1994) directs federal agencies, to the greatest extent practicable and permitted by law, to make environmental justice part of their mission by identifying and addressing, as appropriate, disproportionately high and adverse human health or environmental effects of their programs, policies, and activities on minority populations (people of color) and low-income populations. The EPA believes that this type of action does not directly concern human health or environmental conditions and therefore cannot be evaluated with respect to potentially disproportionate and adverse effects on people of color, low-income populations and/or indigenous peoples. This regulatory action adds an additional chemical category to the EPCRA section 313 reporting requirements; it does not have any impact on human health or the environment. This action does not address any human health or environmental risks and does not affect the level of protection provided to human health or the environment. This action adds an additional chemical category to the EPCRA section 313 reporting requirements which provides information that government agencies and others can use to identify potential problems, set priorities, and help inform activities.

List of Subjects in 40 CFR Part 372

Environmental protection, Community right-to-know, Reporting and recordkeeping requirements, and Toxic chemicals.

Dated: August 2, 2022.

Michal Freedhoff,

Assistant Administrator, Office of Chemical Safety and Pollution Prevention.

Therefore, for the reasons set forth in the preamble, EPA proposes that 40 CFR chapter I be amended as follows:

PART 372—TOXIC CHEMICAL RELEASE REPORTING: COMMUNITY RIGHT-TO-KNOW

■ 1. The authority citation for part 372 continues to read as follows:

Authority: 42 U.S.C. 11023 and 11048.

■ 2. In § 372.65, adding in alphabetical order an entry to Table 3 in paragraph (c) for ''Diisononyl Phthalates (DINP)'' to read as follows:

§ 372.65 Chemicals and chemical categories to which this part applies.

* * * * *

(c) * * *

TABLE 3 TO PARAGRAPH (c)

Category name	Effective date
* * * * * * *	
Diisononyl Phthalates (DINP): Includes branched alkyl di-esters of 1,2 benzenedicarboxylic acid in which alkyl ester moieties contain a total of nine carbons. (This category includes but is not limited to the chemicals covered by the CAS numbers and names listed here)	1/1/2024
28553–12–0 Diisononyl phthalate.	
71549–78–5 Branched dinonyl phthalate.	
14103–61–8 Bis(3,5,5-trimethylhexyl) phthalate.	
68515–48–0 Di(C8-10, C9 rich) branched alkyl phthalates.	
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