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Pollution Prevention

Cancer Human Health Hazard Assessment for Di(2-ethylhexyl) Phthalate (DEHP), Dibutyl Phthalate (DBP), Butyl Benzyl Phthalate (BBP), Diisobutyl Phthalate (DIBP), and Dicyclohexyl Phthalate (DCHP)

Technical Support Document for the Risk Evaluations

CASRNs: 117-81-7 (DEHP), 84-74-2 (DBP), 85-68-7 (BBP), 84-69-5 (DIBP), 84-61-7 (DCHP)

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KEY ABBREVIATIONS AND ACRONYMS

2-EH	2-Ethylhexanol
ADME	Adsorption, distribution, metabolism, and excretion
AhR	Aryl hydrocarbon receptor
ANKCL	Aggressive natural killer cell leukemia
ATSDR	Agency for Toxic Substances and Disease Registry (U.S.)
BBP	Butyl benzyl phthalate
BMD	Benchmark dose
BMDL	Benchmark dose lower confidence limit
CAR	Constitutive androstane receptor
CASRN	Chemical Abstracts Service Registry Number
CHO	Chinese hamster ovary
CI	Confidence interval
CPSC	Consumer Product Safety Commission (U.S.)
DBP	Dibutyl phthalate
DEHP	Di(2-ethylhexyl) phthalate
DIBP	Diisobutyl phthalate
DIDP	Diisodecyl phthalate
DINP	Diisononyl phthalate
EC50	Effect concentration at which 50 percent of test organisms exhibit an effect
ECB	European Chemicals Bureau
ECHA	European Chemicals Agency
EFSA	European Food Safety Authority
EPA	Environmental Protection Agency (U.S.)
F344	Fischer 344 (rat)
GD	Gestation day
HR	Hazard ratio
IARC	International Agency for Research on Cancer
IL-1α	Interleukin 1-alpha
IL-1β	Interleukin 1-beta
IRIS	Integrated Risk Information System
KE	Key event
LGL	Large granular lymphocyte
LOAEL	Lowest-observable-adverse-effect level
MBP	Monobutyl phthalate
MBzP	Monobenzyl phthalate
MECPP	Mono(2-ethyl-5-carboxypentyl) phthalate
MEHP	Mono(2-ethylhexyl) phthalate
MEHHP	Mono(2-ethyl-5-hydroxyhexyl) phthalate
MEOHP	Mono(2-ethyl-5-oxohexyl) phthalate
MIBP	Monoisobutyl phthalate

MNCL	Mononuclear cell leukemia
MOA	Mode of action
MTD	Maximum tolerable dose
NASEM	National Academies of Sciences, Engineering, and Medicine (formerly National Research Council [NRC]
NF-κB	Nuclear factor kappa B
NHANES	National Health and Nutrition Examination Survey
NICNAS	National Industrial Chemicals Notification and Assessment Scheme
NOAEL	No-observed-adverse-effect level
NTP	National Toxicology Program (U.S.)
OCSPP	Office of Chemical Safety and Pollution Prevention (EPA)
OECD	Organisation for Economic Co-operation and Development
OEHHA	Office of Environmental Health Hazard Assessment
OPPT	Office of Pollution Prevention and Toxics (EPA)
OR	Odds ratio
PACT	Pancreatic acinar cell tumor
PBOX	Peroxisomal β-oxidation
PECO	Population, exposure, comparator, and outcome
PESS	Potentially exposed or susceptible subpopulation(s)
PND	Postnatal day
POD	Point of departure
PPARα	Peroxisome proliferator activated receptor alpha
PPRTV	Provisional Peer-Reviewed Toxicity Value
PVC	Polyvinyl chloride
PXR	Pregnane X receptor
ReCAAP	Rethinking Chronic Toxicity and Carcinogenicity Assessment for Agrochemicals Project
SACC	Science Advisory Committee on Chemicals
SCE	Sister chromatid exchange
SD	Sprague Dawley (rat)
SIR	Standard incidence ratio
TNFα	Tumor necrosis factor alpha
TSCA	Toxic Substances Control Act
TSD	Technical support document
U.S.	United States
WY	WY 14,643 (also known as prinixic acid)

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Docket
Supporting information can be found in the public dockets Docket IDs (EPA-HQ-OPPT-2018-0504, EPA-HQ-OPPT-2018-0434, EPA-HQ-OPPT-2018-0503, EPA-HQ-OPPT-2018-0433, and EPA-HQ-OPPT-2018-0501).

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SUMMARY

This technical support document (TSD) accompanies the TSCA risk evaluations for di(2-ethylhexyl) phthalate (DEHP) (U.S. EPA, 2025s), butyl benzyl phthalate (BBP) (U.S. EPA, 2025p), dibutyl phthalate (DBP) (U.S. EPA, 2025q), diisobutyl phthalate (DIBP) (U.S. EPA, 2025t), and dicyclohexyl phthalate (DCHP) (U.S. EPA, 2025r). This document summarizes the genotoxicity and cancer hazards associated with exposure to DEHP, BBP, DBP, DIBP, and DCHP. The genotoxicity and cancer hazards of diisononyl phthalate (DINP) and diisodecyl phthalate (DIDP) have been evaluated by EPA previously (U.S. EPA, 2025a, 2024a), but are briefly summarized in this TSD to support genotoxicity and cancer hazard comparisons and read-across for the seven total phthalate diesters evaluated under TSCA.

Available studies indicate that DEHP, BBP, DBP, DIBP, DCHP, DINP, and DIDP are not direct acting genotoxicants or mutagens (Section 3). Rodent cancer bioassays are available for DEHP, BBP, DBP, DINP and DIDP. EPA has previously concluded that DIDP is *not likely to be carcinogenic to humans* (U.S. EPA, 2024a). For DEHP, BBP, and DBP, EPA has also concluded that these phthalates are *not likely to be carcinogenic to humans* (Sections 4.3.1.4, 4.3.2.4, 4.3.3.3). For DINP (Section 4.3.4), dose-related increases in hepatocellular adenomas and/or carcinomas have been consistently observed in rats and mice of both sexes. EPA has previously concluded that DINP causes liver tumors in rodents through a peroxisome proliferator activated receptor alpha (PPARα) mode of action (MOA) (U.S. EPA, 2025a). Notably, this conclusion was supported by the Science Advisory Committee on Chemicals (SACC) during its July 2024 peer review meeting (U.S. EPA, 2024d) of DINP and DIDP. However, EPA has previously concluded that DINP is *not likely to be carcinogenic to humans* at doses below levels that do not result in PPARα activation (U.S. EPA, 2025a).

No chronic toxicity or cancer bioassays are reasonably available for DIBP or DCHP. Therefore, EPA used elements of the Rethinking Chronic Toxicity and Carcinogenicity Assessment for Agrochemicals Project (ReCAAP) weight of evidence framework (Hilton et al., 2022) as an organizational tool to evaluate the extent to which the lack of carcinogenicity studies imparts significant uncertainty on the human health risk assessments for DIBP and DCHP (Section 5). Human health hazards and toxicokinetic properties of DIBP and DCHP were evaluated and compared to DEHP, BBP, DBP, DINP, and DIDP. Overall, based on the weight of scientific evidence, EPA concludes that the lack of chronic toxicity data and carcinogenicity bioassays for DIBP and DCHP do not suggest that there are significant remaining scientific uncertainties in the qualitative and quantitative risk characterization for either phthalate. EPA has further concluded that the non-cancer points of departure (PODs) for DIBP and DCHP are health-protective—including for potentially exposed or susceptible subpopulation(s) (PESS).

The PODs for DIBP and DCHP are based on effects on the developing male reproductive system consistent with a disruption of androgen action and phthalate syndrome that were selected for characterizing risk from acute, intermediate, and chronic exposure to both phthalates. These conclusions are based on several key weight of scientific evidence considerations (Section 5). First, for DEHP, BBP, DBP, and DINP, effects on the developing male reproductive system are a more sensitive and robust endpoint for deriving PODs for use in characterizing risk for acute, intermediate, and chronic exposure scenarios than PPARα-mediated effects on the liver. The one exception was for deriving a chronic POD for DINP, in which chronic non-cancer liver effects were identified as a more sensitive outcome than effects on the developing male reproductive system. Second, EPA determined that quantitative cancer risk assessment is not needed for DEHP, BBP, DBP, DINP, and DIDP.

This TSD was released as a draft for public comment in 2025 and peer reviewed by the SACC during their August 2025 meeting. Following external SACC peer review and public comment, this TSD was revised to incorporate recommendations from the SACC and public.

1 INTRODUCTION AND SCOPE

In December 2019, EPA designated di(2-ethylhexyl) phthalate (DEHP, Chemical Abstracts Service Registry Number [CASRN] 117-81-7 [1]), butyl benzyl phthalate (BBP, CASRN 85-68-7), dibutyl phthalate (DBP, CASRN 84-74-2), diisobutyl phthalate (DIBP, CASRN 85-69-5), and dicyclohexyl phthalate (DCHP, CASRN 84-61-7) as high-priority substances for risk evaluation under the Toxic Substances Control Act (TSCA) (U.S. EPA, 2019a, b, c, d, e). Additionally, on May 24, 2019, EPA received requests from industry, pursuant to 40 CFR 702.37, to conduct risk evaluations for diisononyl phthalate (DINP, CASRNs 28553-12-0 and 68515-48-0) (ACC HPP, 2019b) and diisodecyl phthalate (DIDP, CASRNs 26761-40-0 and 68515-49-1) (ACC HPP, 2019a). The Agency determined that the requests met the applicable regulatory criteria and requirements, as prescribed under 40 CFR 702.37, and granted the manufacturer-requested risk evaluations for DIDP and DINP on December 2, 2019. As one of the first steps in the risk evaluation process, EPA published the final scope documents for DEHP (U.S. EPA, 2020b), BBP (U.S. EPA, 2020a), DBP (U.S. EPA, 2020d), DIBP (U.S. EPA, 2020c), and DCHP (U.S. EPA, 2020e) in August 2020, fulfilling requirements under TSCA section 6(b)(4)(D) and as described in 40 CFR 702.41(c)(8). In August 2021, EPA published the final scope documents for DINP (U.S. EPA, 2021b) and DIDP (U.S. EPA, 2021a).

Following publication of the final scope documents, one of the next steps in the TSCA risk evaluation process is to identify and characterize the human health hazards and conduct dose-response assessments. Non-cancer hazards associated with exposure to DEHP, BBP, DBP, DIBP, DCHP, DINP, and DIDP are summarized elsewhere in non-cancer human health hazard TSDs (U.S. EPA, 2025a, e, f, g, h, i, j, 2024a). This assessment summarizes the genotoxicity and cancer hazards associated with DEHP, BBP, DBP, DIBP, DCHP, DINP, and DIDP. As discussed further in Section 3 through Section 5, varying amounts of genotoxicity, human epidemiologic, and animal cancer bioassays are available for DEHP, BBP, DBP, DIBP, DCHP, DINP, and DIDP. Furthermore, DEHP, BBP, DBP, DINP, and DIDP have the most robust databases that include multiple genotoxicity studies and animal cancer bioassays, while DIBP and DCHP have been evaluated for genotoxicity in a limited number of studies and have not been evaluated for carcinogenicity in any 2-year cancer bioassays. Therefore, data for DEHP, BBP, DBP, DIBP, DCHP, DINP, and DIDP is summarized in this TSD to support read-across and weight of scientific evidence conclusions across the phthalates being evaluated under TSCA.

Genotoxicity and cancer hazards associated with exposure to DINP and DIDP have been summarized previously by EPA as part of the finalized human health hazard assessments and risk evaluations for DIDP (U.S. EPA, 2024a, c) and DINP (U.S. EPA, 2025a, j, u). Conclusions from these assessments of DIDP and DINP are also briefly summarized and discussed in this TSD to support read-across and weight of scientific evidence conclusions for DEHP, BBP, DBP, DIBP, and DCHP.

The remainder of this assessment is organized as follows:

- Section 2 describes EPA's approach for identifying the genotoxicity, epidemiologic, and animal cancer studies discussed throughout this TSD.
- Section 3 summarizes available genotoxicity data for DEHP, BBP, DBP, DIBP, DCHP, DINP, and DIDP.

[1] DEHP (like other phthalates) has several chemical names (accessed December 3, 2025) for CASRN 117-81-7 (see also U.S. EPA, 2025k). Although "diethylhexyl phthalate" is predominantly used in the draft and final DEHP risk evaluations, TSDs, and supplemental files, the use of "di(2-ethylhexyl) phthalate" is retained from the draft to this final TSD.

- Section 4 summarizes available human and animal evidence for the carcinogenicity of DEHP, BBP, DBP, DINP, and DIDP. This section includes information pertaining to MOA analysis and EPA's weight of scientific evidence conclusions and cancer classifications for each phthalate.
- Section 5 describes application of a read-across framework—known as the Rethinking Chronic Toxicity and Carcinogenicity for Agrochemicals Project, or the ReCAAP Framework (OECD, 2024; Hilton et al., 2022)—for DIBP and DCHP.
- Appendix A provides additional details on the extensive data on genotoxicity for DEHP.
- Appendix B provides additional details on rodent carcinogenicity studies for DEHP and BBP.
- Appendix C provides discussion of scientific uncertainties related to incidence of mononuclear cell leukemia (MNCL) and Leydig cell tumors in Fischer (F344) rats.
- Appendix D provides additional details on studies of DEHP investigating peroxisome proliferator activated receptor alpha (PPARα) activation in *in vivo* experimental animal models.
- Appendix E provides a comparison of the DEHP non-cancer POD to the lowest identified thresholds for liver, pancreas, and testis tumorigenesis and PPARα activation.

2 APPROACH TO IDENTIFYING EPIDEMIOLOGY AND LABORATORY ANIMAL DATA

EPA utilized a similar approach to identifying and integrating human epidemiologic, genotoxicity, experimental animal cancer bioassays, and mechanistic information for DEHP, BBP, DBP, DIBP, DCHP, DINP, and DIDP—as previously described in EPA's non-cancer human health hazard assessments for DEHP, BBP, DBP, DIBP, DCHP, DINP, and DIDP (U.S. EPA, 2025a, e, f, g, h, i, j, 2024a). EPA first reviewed existing assessments of DEHP, BBP, DBP, DIBP, DCHP, DINP, and DIDP conducted by various regulatory and authoritative agencies. Existing assessments reviewed by the Agency are provided in the bulleted summary. The purpose of this review was to identify information relevant to assessing carcinogenicity, as well as conclusions pertaining to the genotoxicity and carcinogenicity of these phthalates by various authoritative and regulatory agencies. In addition to the information identified through review of existing phthalate assessments, EPA also considered population, exposure, comparator, and outcome (PECO)-relevant literature identified through the 2019 TSCA literature searches, as well as studies submitted to the dockets for each phthalate by the SACC and by public commenters in 2025. These are described in the systematic review protocols for DEHP (U.S. EPA, 2025z), BBP (U.S. EPA, 2025w), DBP (U.S. EPA, 2025x), DIBP (U.S. EPA, 2025aa), DCHP (U.S. EPA, 2025y), DINP (U.S. EPA, 2025ab), and DIDP (U.S. EPA, 2024e) in assessing the carcinogenicity of these phthalates.

- *Integrated Risk Information System (IRIS), Chemical Assessment Summary, Dibutyl Phthalate; CASRN 84-74-2* (U.S. EPA, 1987);
- *Integrated Risk Information System (IRIS), Chemical Assessment Summary, Butyl Benzyl Phthalate; CASRN 85-68-7* (U.S. EPA, 1988a);
- *Integrated Risk Information System (IRIS), Chemical Assessment Summary, Di(2-ethylhexyl)phthalate (DEHP); CASRN 117-81-7* (U.S. EPA, 1988b);
- *Provisional Peer Reviewed Toxicity Values for Butyl Benzyl Phthalate* (U.S. EPA, 2002);
- *Toxicological Profile for Di-b-phthalate* (ATSDR, 2001);
- *Toxicological Profile for Di(2-Ethylhexyl)Phthalate (DEHP)* (ATSDR, 2022);
- *Toxicity Review of Di-n-butyl Phthalate (DBP)* (U.S. CPSC, 2010b);
- *Toxicity Review for Benzyl-n-butyl Phthalate (BBP)* (U.S. CPSC, 2010a);
- *Toxicity Review of Dicyclohexyl Phthalate (DCHP)* (U.S. CPSC, 2010e);
- *Toxicity Review of Di(isodecyl) Phthalate (DIDP)* (U.S. CPSC, 2010d);
- *Toxicity Review of Di(2-ethylhexyl) Phthalate (DEHP)* (U.S. CPSC, 2010c);
- *Toxicity Review of Diisononyl Phthalate (DINP*) (U.S. CPSC, 2010f);
- *Toxicity Review of Diisobutyl Phthalate (DiBP, CASRN 84-69-5)* (U.S. CPSC, 2011);
- *Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives* (U.S. CPSC, 2014);
- *NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Di-isodecyl Phthalate (DIDP)* (NTP-CERHR, 2003b);
- *NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Di-n-Butyl Phthalate (DBP)* (NTP-CERHR, 2003d);

- *NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Butyl Benzyl Phthalate (BBP)* (NTP-CERHR, 2003a);
- *NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Di-isononyl Phthalate (DINP)* (NTP-CERHR, 2003c);
- *NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Di(2-ethylhexyl) Phthalate (DEHP)* (NTP-CERHR, 2006);
- *Safe Drinking Water and Toxic Enforcement Act of 1986 Proposition 65. Initial Statement of Reasons. Title 27, California Code of Regulations. Proposed amendment to Section 25805(b), Specific Regulatory Levels: Chemicals Causing Reproductive Toxicity. Butyl Benzyl Phthalate (Oral Exposure)* (OEHHA, 1986);
- *Proposition 65 Maximum Allowable Dose Level (MADL) for Reproductive Toxicity for Di(n-butyl)phthalate (DBP)* (OEHHA, 2007);
- *Evidence on the Carcinogenicity of Butyl Benzyl Phthalate* (OEHHA, 2013b);
- *Chemical Listed Effective December 20, 2013 as Known to the State of California to Cause Cancer: Diisononyl Phthalate (DINP)* (OEHHA, 2013a);
- *Application of Systematic Review Methods in an Overall Strategy for Evaluating Low-dose Toxicity from Endocrine Active Chemicals* (NASEM, 2017);
- *Bis(2-ethylhexyl) Phthalate* (Environment Canada, 1994);
- *Canadian Environmental Protection Act Priority Substances List Assessment Report: Dibutyl Phthalate* (EC/HC, 1994);
- *Canadian Environmental Protection Act Priority Substances List Assessment Report: Butylbenzylphthalate* (Environment Canada, 2000);
- *Supporting Documentation: Carcinogenicity of Phthalates – Mode of Action and Human Relevance* (Health Canada, 2015);
- *State of the Science Report: Phthalate Substance Grouping: Medium-chain Phthalate Esters: Chemical Abstracts Service Registry Numbers: 84-61-7; 84-64-0; 84-69-5; 523-31-9; 5334-09-8;16883-83-3; 27215-22-1; 27987-25-3; 68515-40-2; 71888-89-6* (EC/HC, 2015b);
- *State of the Science Report: Phthalates Substance Grouping: Long-chain Phthalate Esters. 1,2-Benzenedicarboxylic Acid, Diisodecyl Ester (Diisodecyl Phthalate; DIDP) and 1,2-Benzenedicarboxylic Acid, Diundecyl Ester (Diundecyl Phthalate; DUP). Chemical Abstracts Service Registry Numbers: 26761-40-0, 68515-49-1; 3648-20-2* (EC/HC, 2015c);
- *State of the Science Report: Phthalate Substance Grouping 1,2-Benzenedicarboxylic Acid, Diisononyl Ester; 1,2-Benzenedicarboxylic Acid, di-C8-10-branched Alkyl Esters, C9-rich (Diisononyl Phthalate; DINP). Chemical Abstracts Service Registry Numbers: 28553-12-0 and 68515-48-0* (EC/HC, 2015a);
- *Supporting Documentation: Evaluation of Epidemiologic Studies on Phthalate Compounds and their Metabolites for Hormonal Effects, Growth and Development and Reproductive Parameters* (Health Canada, 2018b);
- *Supporting Documentation: Evaluation of Epidemiologic Studies on Phthalate Compounds and their Metabolites for Effects on Behaviour and Neurodevelopment, Allergies, Cardiovascular*

Function, Oxidative Stress, Breast Cancer, Obesity, and Metabolic Disorders (Health Canada, 2018a);

- *Screening Assessment - Phthalate Substance Grouping* (ECCC/HC, 2020);
- *European Union Risk Assessment Report, vol 36: 1,2-Benzenedicarboxylic Acid, Di-C9-11-Branched Alkyl Esters, C10-Rich and Di-"isodecyl"phthalate (DIDP)* (ECB, 2003a);
- *European Union Risk Assessment Report: 1,2-Benzenedicarboxylic Acid, di-C8-10-Branched Alkyl Esters, C9-rich - and Di-"isononyl" Phthalate (DINP)* (ECB, 2003b);
- *European Union Risk Assessment Report: Dibutyl Phthalate with Addendum to the Environmental Section* (ECB, 2004);
- *European Union Risk Assessment Report: Benzyl Butyl Phthalate (BBP)* (ECB, 2007);
- *European Union Risk Assessment Report: Bis(2-ethylhexyl)phthalate (DEHP)* (ECJRC, 2008);
- *Substance Name: Benzyl Butyl Phthalate, EC Number: 201-622-7, CAS Number: 85-68-7: Member State Committee Support Documentation for Identification of Benzyl Butyl Phthalate (BBP) as a Substance of Very High Concern* (ECHA, 2008);
- *Evaluation of New Scientific Evidence Concerning the Restrictions Contained in Annex XVII to Regulation (EC) No 1907/2006 (REACH): Review of New Available Information for Dibutyl Phthalate (DBP) CAS No 84-74-2 Einecs No 201-557-4* (ECHA, 2010a);
- *Evaluation of New Scientific Evidence Concerning the Restriction Contained in Annex XVII to Regulation (EC) No. 1907/2006 (REACH): Review of New Available Information for Benzyl Butyl Phthalate (BBP) CAS No. 85-68-7 Einecs no. 201-622-7* (ECHA, 2010b);
- *Annex XV Restriction Report: Proposal for a Restriction, Version 2. Substance Name: Bis(2-ehtylhexyl)phthlate (DEHP), Benzyl Butyl Phthalate (BBP), Dibutyl Phthalate (DBP), Diisobutyl Phthalate (DIBP)* (ECHA, 2011);
- *Committee for Risk Assessment (RAC) Opinion on an Annex XV Dossier Proposing Restrictions on Four Phthalates* (ECHA, 2012b);
- *Committee for Risk Assessment (RAC) Committee for Socio-economic Analysis (SEAC): Background Document to the Opinion on the Annex XV Dossier Proposing Restrictions on Four Phthalates* (ECHA, 2012a);
- *Evaluation of New Scientific Evidence Concerning DINP and DIDP in Relation to Entry 52 of Annex XVII to REACH Regulation (EC) No 1907/2006* (ECHA, 2013);
- *Committee for Risk Assessment RAC Opinion Proposing Harmonised Classification and Labelling at EU Level of Dicyclohexyl Phthalate, EC Number: 201-545-9, CAS Number: 84-61-7* (ECHA, 2014);
- *Opinion on an Annex XV Dossier Proposing Restrictions on Four Phthalates (DEHP, BBP, DBP, DIBP)* (ECHA, 2017b);
- *Annex to the Background Document to the Opinion on the Annex XV Dossier Proposing Restrictions on Four Phthalates* (DEHP, BBP, DBP, DIBP) (ECHA, 2017a);
- *Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC) Related to Di-isodecylphthalate (DIDP) for Use in Food Contact Materials* (EFSA, 2005e);

- *Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC) on a Request from the Commission Related to Di-isononylphthalate (DINP) for Use in Food Contact Materials* (EFSA, 2005a);
- *Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC) Related to Butylbenzylphthalate (BBP) for Use in Food Contact Materials* (EFSA, 2005c);
- *Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials In Contact With Food (AFC) Related to Bis(2-ethylhexyl)phthalate (DEHP) for Use in Food Contact Materials* (EFSA, 2005b);
- *Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC) Related to Di-Butylphthalate (DBP) for Use in Food Contact Materials* (EFSA, 2005d);
- *Update of the Risk Assessment of Di-butylphthalate (DBP), Butyl-benzyl-phthalate (BBP), Bis(2-ethylhexyl)phthalate (DEHP), Di-isononylphthalate (DINP) and Di-isodecylphthalate (DIDP) for Use in Food Contact Materials* (EFSA, 2019);
- *Existing Chemical Hazard Assessment Report: Diisobutyl Phthalate* (NICNAS, 2008a);
- *Phthalates Hazard Compendium: A Summary of Physicochemical and Human Health Hazard Data for 24 Ortho-phthalate Chemicals* (NICNAS, 2008c);
- *Priority Existing Chemical Draft Assessment Report: Diethylhexyl Phthalate* (NICNAS, 2010);
- *Priority Existing Chemical Assessment Report no. 35: Diisononyl Phthalate* (NICNAS, 2012);
- *Priority Existing Chemical Assessment Report no. 36: Dibutyl Phthalate* (NICNAS, 2013);
- *Priority Existing Chemical Assessment Report no. 40: Butyl Benzyl Phthalate* (NICNAS, 2015a);
- *Priority Existing Chemical Draft Assessment Report: Diisodecyl Phthalate & Di-n-octyl Phthalate* (NICNAS, 2015b);
- *C4-6 Side Chain Transitional Phthalates: Human Health Tier II Assessment* (NICNAS, 2016);
- *Phthalate Exposure and Male Reproductive Outcomes: A Systematic Review of the Human Epidemiological Evidence* (Radke et al., 2018);
- *Phthalate Exposure and Female Reproductive and Developmental Outcomes: A Systematic Review of the Human Epidemiological Evidence* (Radke et al., 2019b);
- *Phthalate Exposure and Metabolic Effects: A Systematic Review of the Human Epidemiological Evidence* (Radke et al., 2019a);
- *Phthalate Exposure and Neurodevelopment: A Systematic Review and Meta-analysis of Human Epidemiological Evidence* (Radke et al., 2020); and
- *Hazards of Diisobutyl Phthalate (DIBP) Exposure: A Systematic Review of Animal Toxicology Studies* (Yost et al., 2019).

3 GENOTOXICITY HAZARD IDENTIFICATION

Understanding the carcinogenic MOA of a chemical substance is an important consideration in determining the most appropriate approach for cancer dose-response assessment, including use of a linear vs. nonlinear approach. Consistent with EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), chemical substances with anticipated mutagenic MOAs are assessed with a linear approach. In this section, EPA reviews available genotoxicity and mutagenicity data for DEHP (Section 3.1), BBP (Section 3.2), DBP (Section 3.3), DIBP (Section 3.4), DCHP (Section 3.5), DINP (Section 3.6), and DIDP (Section 3.7).

3.1 Di(2-ethylhexyl) Phthalate (DEHP)

The genotoxicity of DEHP and its major metabolites (*e.g.,* mono(2-ethylhexyl) phthalate [MEHP] and 2-ethylhexanol [2-EH]) have been evaluated extensively in various *in vitro* and *in vivo* test systems. Available genotoxicity studies have been reviewed by several authoritative and regulatory agencies. The U.S. Consumer Product Safety Commission (U.S. CPSC) (U.S. CPSC, 2010c), European Chemicals Agency (ECHA) (ECHA, 2017a, b), European Food Safety Authority (EFSA) (EFSA, 2019), and Australia National Industrial Chemicals Notification and Assessment Scheme (NICNAS) (NICNAS, 2010) have concluded that the overall evidence supports the conclusion that DEHP is non-genotoxic and non-mutagenic. Similarly, the European Chemicals Bureau (ECB) (ECJRC, 2008) and Environment Canada (1994) concluded that DEHP and its major metabolites (*i.e.,* MEHP and 2-EH) are not genotoxic or mutagenic.

More recently, the database of *in vitro* and *in vivo* genotoxicity studies of DEHP was reviewed by the Agency for Toxic Substances and Disease Registry (ATSDR) (ATSDR, 2022) and National Toxicology Program (NTP) (NTP, 2021b). ATSDR reviewed *in vitro* and *in vivo* genotoxicity studies of DEHP (76 *in vitro* studies and 39 *in vivo* studies) and MEHP (36 *in vitro* studies and 5 *in vivo* studies), which are summarized in Table_Apx A-1, Table_Apx A-2, Table_Apx A-3, and Table_Apx A-4. Overall, ATSDR concluded:

> DEHP has been extensively tested in a variety of genotoxicity assays. Evidence suggests that DEHP is not mutagenic to bacterial or mammalian cells; however, there is limited evidence that it may damage DNA and/or result in chromosomal abnormalities (either directly or indirectly via oxidative stress mechanisms), and it has been shown to induce morphological transformation. The weight of evidence from these assays indicates that DEHP is not a potent genotoxin but may lead to genotoxic effects secondary to oxidative stress.

Similarly, NTP (2021b) has tested DEHP in a range of *in vitro* and *in vivo* genotoxicity studies, some of which were not considered as part of the ATSDR assessment and generally found negative results (see Table_Apx A-5). Overall, NTP concluded "The consensus from published data is that DEHP shows limited evidence of genotoxic potential, and for the sporadic positive results that have been reported, the response is either weak, not reproducible, obtained in a nonstandard test system, or qualified to some degree by the authors."

Herein, EPA did not independently re-evaluate the extensive database of *in vitro* and *in vivo* genotoxicity studies of DEHP and its major metabolites. However, a summary of available genotoxicity studies considered most recently by ATSDR (2022) and conducted by NTP (2021b) are provided in Appendix A. *Overall, EPA agrees with the conclusions of ATSDR, NTP, and other authoritative and regulatory agencies that available evidence indicates that DEHP and its metabolites are not mutagenic,*

but that there is some limited evidence that DEHP may be weakly genotoxic, inducing effects such as deoxyribonucleic acid (DNA) damage and/or chromosomal aberrations. As noted by ATSDR, these effects may be secondary to oxidative stress.

3.2 Butyl Benzyl Phthalate (BBP)

BBP has been evaluated for genotoxicity in a number of *in vitro* and *in vivo* test systems (see Table 3-1 for a summary of available assays). BBP did not demonstrate mutagenic activity in four *in vitro* bacterial reverse mutation assays or in two *in vitro* mouse lymphoma assays with or without metabolic activation. No increases in sister chromatid exchanges (SCE) or chromosomal aberrations were observed in studies of Chinese hamster ovary (CHO) cells treated with BBP with or without metabolic activation (NTP, 1997b). BBP did not induce cell transformation in one study of Balb/c-3T3 A31 mouse cells (Monsanto, 1985). In a second study of Syrian hamster ovary cells, BBP did not induce a significant increase in transformed foci when cells were incubated for 24 hours, while an increase in transformed foci was observed after 7 days of incubation with BBP, albeit without a clear dose-response relationship (no increase in foci was observed at the highest dose) (Leboeuf et al., 1996).

In *in vivo* studies, BBP did not induce sex-linked recessive lethal mutations in feed or injection studies with *Drosophila melanogaster* (NTP, 1997b) and was negative in dominant lethal assays of B6C3F1 and CD-1 mice (Bishop et al., 1987). BBP did not induce micronuclei formation in one study of female Sprague Dawley (SD) rats exposed to BBP via drinking water, albeit at an extremely low dose (*i.e.*, 182.6 µg/kg) (Ashby et al., 1997). In contrast, BBP did induce a significant increases in micronuclei formation in male B6C3F1 mice, but only at a very high dose (*i.e.*, increased micronuclei observed at 5,000 mg/kg, but not at doses of 1,250−3,750 mg/kg), and only in trials in which cells were harvested 17 hours post-exposure, but not in the trial in which cells were harvested 36 hours post-exposure (NTP, 1997b). Similarly, treatment with high doses of BBP (1,250−5,000 mg/kg) resulted in a weakly positive response in increased SCEs in male B6C3F1 mice in two trials conducted by NTP (1997b). However, in one of the two trials, the positive trend (no statistically significant pairwise comparisons to the control) in increased SCEs was observed only after data from the high-dose group was removed from the analysis because there was no apparent increase in SCE in the high-dose animals.

Overall, available data support the conclusion that BBP is not likely to be mutagenic. Although BBP was weakly positive for increased SCEs and chromosomal aberrations *in vivo*, the effects were only weakly positive and only observed at extremely high doses of BBP (*i.e.*, 5,000 mg/kg). Notably, EPA's conclusion is consistent with the conclusions of other authoritative and regulatory agencies. The ECB (ECB, 2007), ECHA (2017a, b), and Australia NICNAS (2015a) concluded that BBP is not mutagenic, whereas EFSA (2019) concluded that available data for BBP do not give rise to a concern for genotoxicity. Similarly, Environment Canada (2000) concluded "although the weight of evidence of genotoxicity is clearly negative, available data are inadequate to conclude unequivocally that BBP is not clastogenic, although in available studies it has induced, at most, weak activity." Finally, while U.S. CPSC (2010a) did not draw any specific conclusion on the genotoxicity of BBP, U.S. CPSC (2014) did conclude that phthalate esters as a class are not genotoxic.

Table 3-1. Summary of Genotoxicity Studies of BBP

Test Type	Test System (Species / Strain / Sex)	Dose / Duration	Metabolic Activation	Result	Reference(s)
In vitro – gene mutation studies					
Reverse mutation assay	*S. typhimurium* strains TA 98, 100, 1535, 1537	100–10,000 µg/plate	± Aroclor-induced rat or hamster liver S9	Negative for mutagenicity	(NTP, 1997b)
Reverse mutation assay	*S. typhimurium* strains TA 98, 100, 1535, 1537	333–11,550 µg/plate	± Aroclor-induced rat or hamster liver S9	Negative for mutagenicity	(NTP, 1997b)
Reverse mutation assay	*S. typhimurium* strains TA 98, 100, 1535, 1537, 1538; *S. cerevisiae* strain D4	0.1–10 µL/plate	± Aroclor-induced rat liver S9	Negative for mutagenicity	(Monsanto, 1976a) as reported in (ECB, 2007)
Reverse mutation assay	*S. typhimurium* strains TA 98, 100, 1535, 1537, 1538	0.001–10 µL/plate	± Aroclor-induced rat liver S9	Negative for mutagenicity	(Monsanto, 1976b)
Mouse lymphoma mutation assay	L5178Y+/- mouse lymphoma cells	0, 5, 10, 20, 30, 40, 60 nL/mL	± Aroclor-induced rat liver S9	Negative for mutagenicity	(NTP, 1997b)
Mouse lymphoma mutation assay	L5178Y+/- mouse lymphoma cells	0, 0.06, 0.16, 0.32, 0.65, 1.25, 2.5, 5 µL/mL	± Aroclor-induced mouse liver S9	Negative for mutagenicity	(Monsanto, 1976c) as reported in (ECB, 2007)
In vitro – cytogenetic studies					
SCE	CHO cells	Trial 1: 0, 0.4, 1.25, 4.0 µg/mL	Without S9	Trial 1: Equivocal (trend in increased SCE) (Trial 1); Trial 2: Negative for SCE *Overall: Negative for SCE*	(NTP, 1997b)
		Trial 2: 0, 0.4, 1.25, 4.0, 12.5 µg/mL	Without S9		
		Trial 3: 0, 125, 400, 1250 µg/mL	With induced liver S9	Negative for SCE	
Chromosomal aberrations	CHO cells	0, 125, 400, 1250 µg/mL	± Aroclor-induced liver S9	Negative for chromosomal aberrations	(NTP, 1997b)
In vitro – other genotoxicity assays					

Test Type	Test System (Species / Strain / Sex)	Dose / Duration	Metabolic Activation	Result	Reference(s)
In vitro cell transformation	Syrian hamster embryo cells	Cells treated with 0, 25, 50, 100, 150, 250 µg/mL BBP for 24 hours	Not specified	No significant increase in transformed foci	(Leboeuf et al., 1996)
		Cells treated with 0, 1, 2, 5, 10, 20 µg/mL BBP for 7 days	Not specified	Increased in transformed foci at 2, 5, and 10, but not 20 µg/mL dose groups	
In vitro cell transformation	Balb/c-3T3 A31 mouse cells	0.49–8000 nL/mL	No	No significant increase in transformed foci	(Monsanto, 1985)
In vivo studies					
Sex-linked recessive lethal mutations	*Drosophila melanogaster*	0, 10,000 ppm in feed	NA	No induction of sex-linked recessive lethal mutations	(NTP, 1997b)
		0, 10,000 ppm in feed	NA		
		0, 500 ppm (injection)	NA		
Mouse dominant lethal assay	B6C3F1 mice	Male mice given subcutaneous injections of 400 to 4560 mg/kg BBP on days 1, 5, and 10 and then mated with untreated females. Fetuses examined 17 days after start of mating period.	Negative	Negative	(Bishop et al., 1987)
	CD-1 mice		Negative	Negative	
Chromosomal aberrations in femoral bone marrow cells	Female Alpk:AP$_f$SD rats	Dams exposed to 0 or ≈182.6 µg/kg-day BBP via drinking water during gestation and lactation.	NA	Negative for micronuclei	(Ashby et al., 1997)
Chromosomal aberrations in femoral bone marrow cells	Male B6C3F1 mice	Trial 1: Mice (10/dose) received intraperitoneal injections of 0 (corn oil), 1250, 2500, 5000 mg/kg BBP. Cells harvested 17 hours post-exposure.	NA	Positive for micronuclei (highest dose only)	(NTP, 1997b)
		Trial 2: Mice (10/dose) received intraperitoneal injections of 0 (corn oil), 1250, 3750, 5000 mg/kg BBP. Cells harvested 17 hours post-exposure.	NA	Positive for micronuclei (highest dose only)	
		Trial 3: Mice (10/dose) received intraperitoneal injections of 0 (corn oil), 1250, 2500, 5000 mg/kg BBP. Cells harvested 36 hours post-exposure.	NA	Negative for micronuclei	

Test Type	Test System (Species / Strain / Sex)	Dose / Duration	Metabolic Activation	Result	Reference(s)
SCE in femoral bone marrow	Male B6C3F1 mice	Mice (5/dose) received intraperitoneal injections of 0 (corn oil), 1250, 2500, 5000 mg/kg BBP. Cells harvested 23 hours post-exposure.	NA	Weakly positive response (positive trend in increased SCEs when highest dose excluded)	(NTP, 1997b)
		Mice (5/dose) received intraperitoneal injections of 0 (corn oil), 1250, 2500, 5000 mg/kg BBP. Cells harvested 42 hours post-exposure.	NA	Weakly positive response by trends analysis	
BBP = butyl benzyl phthalate; CHO = Chinese hamster ovary; NA = not applicable; ppm = parts per million; SCE = sister chromatid exchange					

3.3 Dibutyl Phthalate (DBP)

The mutagenic and genotoxic potential of DBP has been evaluated in 20 studies (Table 3-2). Available studies include two *in vivo* micronucleus tests in mice, two *in vitro* chromosomal aberration assays, one *in vitro* SCE assay, two *in vitro* mouse lymphoma assays, six bacterial mutation assays, two gene mutation assays (one in *Escherichia coli* and one in *Saccharomyces cerevisiae*), one *in vitro* cell transformation assay, and two comet assays with primary human cells.

DBP did not induce clastogenic effects or micronuclei formation in two *in vivo* studies of mice (NTP, 1995; BASF, 1990) or induce unscheduled DNA repair in *E. coli* or *Bacillus subtilis* (Omori, 1976; Kurata, 1975). DBP induced DNA strand breaks in comet assays of primary human lymphocytes, oropharyngeal cells, and mucosal cells (Kleinsasser et al., 2000b; Kleinsasser et al., 2000a). Exposure to DBP did not cause an increase in cell transformation in one *in vitro* study of Balb/c-3T3 A31 mouse cells (Litton Bionetics, 1985). DBP showed no mutagenic activity in gene mutation assays with *E. coli* and *S. cerevisiae* (Shahin and Von Borstel, 1977; Omori, 1976; Kurata, 1975). DBP was negative for mutagenic activity both with and without metabolic activation in four out of five reverse mutation assays with several strains of *S. typhimurium* (NTP, 1995; Zeiger et al., 1985; Kozumbo et al., 1982; Florin et al., 1980; Omori, 1976; Kurata, 1975). Equivocal results were obtained in one bacterial reverse mutation assay of *S. typhimurium* strains TA 100 and TA 1535 that included doses of 100 to 2,000 µg DBP per plate (Agarwal et al., 1985).

In TA 1535, a mild increase (<2×) in the number of revertant colonies was observed at the two highest doses in the absence of S9. In TA 100, an increase in the number of reversions was observed in the absence of S9, with a maximum response (<3×) occurring in the low-dose group. However, the response was not dose-dependent, was less than a factor of 2 at 200 µg DBP per plate, and the effect plateaued at higher doses. No mutagenic activity was observed with metabolic activation in TA 100 or TA 1535, and no mutagenic activity was observed in other strains with or without metabolic activation. A marginally positive response was also observed in an 8-azaguanine resistance assay with *S. typhimurium* strain TA 100 in the absence of metabolic activation (Seed, 1982). A marginal increase (<2×) in mutagenic activity was observed at doses of 0.09 and 0.18 mM DBP, which were also cytotoxic (all doses tested in the study resulted in ≈50% cytotoxicity in the absence of S9). No mutagenic activity was apparent with metabolic activation.

Positive results have been obtained across two *in vitro* mouse lymphoma mutation assays (Barber et al., 2000; NTP, 1995; Hazleton, 1986). In the first study, a significant increase in mutagenic activity was observed in the absence of metabolic activation, but only at concentrations that caused a marked decrease in cell survival (*i.e.*, at doses of 46 µg/mL and greater) (NTP, 1995). In the second *in vitro* mouse lymphoma mutation assay, which tested DBP with and without S9, no mutagenic activity was present in the absence S9, while a significant increase in mutant frequency was noted in the presence of S9 at high-concentrations that were above the solubility limit and coincided with a marked decrease in cell survival (Barber et al., 2000; Hazleton, 1986).

DBP did not induce chromosomal aberrations in one *in vitro* assay with CHO cells (Abe and Sasaki, 1977), while an equivocal result was obtained in a second poorly-reported study with Chinese hamster lung fibroblasts (Ishidate and Odashima, 1977). Ishidate and Odashima report a 6 percent increase in chromosomal aberrations, which study authors characterized as a “suspicious result.” However, no statistical analysis was performed, and it is unclear if the small increase in chromosomal aberrations would be concentration-dependent by trend test, statistically significantly different than the concurrent control, or outside the distribution of historical control data, which are criteria for considering if an *in*

vitro mammalian chromosomal aberration test is positive under current OECD 473 guidelines (OECD, 2016). Finally, treatment with DBP induced a slight (<2×) but statistically significant increase in SCE in one study of CHO cells; however, the increase in SCEs was not concentration-dependent.

Available genotoxicity data for DBP has been evaluated by numerous authoritative and regulatory agencies. Based on the weight of evidence, Health Canada (EC/HC, 1994), the ECB (2004), ECHA (2017a, b), Australia NICNAS (2013), and EFSA (2019) concluded that DBP is not genotoxic or mutagenic. U.S. CPSC (2010b) did not draw any specific conclusion on the genotoxicity of DBP; however, U.S. CPSC (2014) did conclude that phthalate esters as a class are not genotoxic. In contrast, ATSDR (2001) concluded that results from available studies "suggest that di-*n*-butyl phthalate may be weakly mutagenic *in vitro*. The significance of these findings to the intact mammalian organism is not known because *in vivo* genotoxicity studies have not been conducted." However, in drawing this conclusion, ATSDR did not take into consideration the two *in vivo* studies of mice that were both negative for micronuclei formation.

Overall, available data support the conclusion that DBP is not likely to be mutagenic. Although DBP was positive for mutagenicity in two *in vitro* mouse lymphoma assays, the effects were only apparent at high concentrations that were reported to be above the limit of solubility in one study and that coincided with marked decreases in cell survival in both studies. Furthermore, as discussed in Section 4.3.3, DBP shows equivocal evidence of carcinogenic activity in male rats (based on a slight increase in pancreatic acinar cell tumors [PACTs]), but no evidence of carcinogenic activity in female rats or mice of either sex.

Table 3-2. Summary of Genotoxicity Studies of DBP

Test Type	Test System (Species/ Strain/ Sex)	Dose/ Duration	Metabolic Activation	Result	Reference(s)
In vivo studies					
Micronucleus test	Male and Female B6C3F1/N mice	1,250–20,000 ppm DBP in the diet for 3 months (equivalent to 163–4,278 mg/kg-day)	NA	Negative for micronuclei formation in peripheral blood erythrocytes	(NTP, 1995)
Micronucleus test	Male and Female NMRI mice	Mice gavaged once with 333, 1,000, or 3,000 mg/kg DBP in olive oil	NA	Negative for micronuclei formation in femoral erythrocytes	(BASF, 1990)
In vitro gene mutation studies					
Bacterial reverse mutation assay	*S. typhimurium* strains TA 98, 100, 1535, 1537	100–10,000 µg/plate	± Aroclor-induced rat or hamster liver S9	Negative for mutagenicity	(NTP, 1995; Zeiger et al., 1985)
Bacterial reverse mutation assay	*S. typhimurium* strains TA 98, 100, 1535, 1537	3 µmol/plate	± Aroclor-induced rat liver S9	Negative for mutagenicity (precipitation of DBP occurred)	(Florin et al., 1980)
Bacterial reverse mutation assay	*S. typhimurium* strains TA 98, TA 100	Up to 1,000 µg/plate	± Aroclor-induced rat liver S9	Negative for mutagenicity	(Kozumbo et al., 1982)
Bacterial reverse mutation assay	*S. typhimurium* strain TA 100	10,000 µg/plate	+ Aroclor-induced rat liver S9	Negative for mutagenicity	(Omori, 1976; Kurata, 1975)
Bacterial reverse mutation assay	*S. typhimurium* strains TA 98, 100, 1535, 1537, 1538, 2637	100–2,000 µg/plate	No	Equivocal in TA 100 and TA 1535, but not in other strains [a]	(Agarwal et al., 1985) [a]
			+ Aroclor-induced liver S9 (species not specified)	Negative for mutagenicity	
Bacterial forward mutation assay	*S. typhimurium* strain TA 100	0.045, 0.09, or 0.18 mM	No	Marginally positive (weak increases [<2×] at cytotoxic doses)	(Seed, 1982)
			+ Aroclor-induced rat liver S9	Negative for mutagenicity	
Gene mutation assay	*Escherichia coli* (uvrA-)	10,000 µg/plate	No	Negative for mutagenicity	(Omori, 1976; Kurata, 1975)
Gene mutation assay	*S. cerevisiae* (Xv 185-14C)	10, 20, 100 µL/mL	± Aroclor-induced mouse liver S9	Negative for mutagenicity	(Shahin and Von Borstel, 1977)

Test Type	Test System (Species/ Strain/ Sex)	Dose/ Duration	Metabolic Activation	Result	Reference(s)
Mouse lymphoma mutation assay	L5178Y+/- mouse lymphoma cells	Trial 1: 0, 12, 24, 36, 48, 60 µg/mL	No	Positive (increased mutant fraction at 48 µg/mL; coincided with 11–16% relative growth compared to control; lethal at 60 µg/mL)	(NTP, 1995)
		Trial 2: 0, 30, 38, 46, 54, 62, 70 µg/mL	No	Positive (increased mutant fraction at ≥46 µg/mL; coincided with 5–37% relative growth compared to control; lethal at 70 µg/mL)	
		Trial 3: 0, 38, 46, 54, 62, 70 µg/mL	No	Positive (increased mutant fraction at ≥54 µg/mL; coincided with 1–19% relative growth compared to control)	
Mouse lymphoma mutation assay	L5178Y+/- mouse lymphoma cells	0.015, 0.030, 0.040, 0.50, 0.06 µL/mL (-S9) 0.0125, 0.050, 0.075, 0.100, 0.150 µL/mL (+S9)	No	Negative for mutagenicity	(Barber et al., 2000) (Hazleton, 1986)
			+ Aroclor-induced rat liver S9	Positive for mutagenicity at two highest doses (above the solubility limit; coincided with 7–25% relative growth compared to control)	
In vitro cytogenetics assays					
Chromosomal aberrations	Chinese hamster lung fibroblast cells	0.03–1.1 mg/mL for 24 hours	No	Marginally positive for chromosomal aberrations	(Ishidate and Odashima, 1977)
Chromosomal aberrations	CHO cells	0.0001–0.001 M	No	Negative for chromosomal aberrations	(Abe and Sasaki, 1977)
SCE	CHO cells	0.0001–0.001 M	No	Marginally positive for SCE (<2x increase, no concentration-dependent - relationship)	(Abe and Sasaki, 1977)
Other genotoxicity assays					
Bacterial test (indirect DNA-repair)	*Escherichia coli* (pol A-, rec A-)	10,000 µg/plate	No	Negative	(Omori, 1976; Kurata, 1975)

Test Type	Test System (Species/ Strain/ Sex)	Dose/ Duration	Metabolic Activation	Result	Reference(s)
Bacterial test (indirect DNA-repair)	*Bacillus subtilis* (Rec A-)	10,000 µg/plate	No	Negative	(Omori, 1976; Kurata, 1975)
Cell transformation assay	Balb/c-3T3 A31 mouse cells	0, 3.4, 13.7, 27.5, 55, 82.3 nL/mL	No	Negative	(Litton Bionetics, 1985)
Comet assay	Human: oropharyngeal and nasal mucosa cells from 40 and 30 patients, respectively	Cells incubated with 354 µmol/mL DBP for 60 minutes	No	↑ DNA strand breaks in both cell types	(Kleinsasser et al., 2000a)
Comet assay	Human: mucosal cells and lymphocytes from 60 patients	Cells incubated with 354 µmol/mL DBP for 60 minutes	No	↑ DNA strand breaks in both cell types	(Kleinsasser et al., 2000b)

DBP = dibutyl phthalate; CHO = Chinese hamster ovary; NA = not applicable; ppm = parts per million; SCE = sister chromatid exchange
[a] For TA 100, treatment with DBP increased the number of revertant colonies per plate at all concentrations; however, the response was not concentration-dependent (estimated mean # of revertants/plate at 0, 100, 200, 500, 750, 1,000, 1,500, 2,000 µg/plate: 125, 275, 200, 175, 200, 160, 175, 200, respectively). For TA 1535, a mild (<2×), but statistically significant, increase in mean number of revertant colonies per plate was observed in the 2 highest dose concentrations.

3.4 Diisobutyl Phthalate (DIBP)

Limited genotoxicity testing of DIBP has been conducted (Table 3-3). DIBP was negative for mutagenicity in four bacterial reverse mutation assays conducted with several strains of *S. typhimurium* both with and without metabolic activation (Sato et al., 1994; Zeiger et al., 1985; Seed, 1982; Simmon et al., 1977). In contrast, DIBP induced DNA strand breaks in several *in vitro* comet assays with human mucosal cells and lymphocytes (Kleinsasser et al., 2001; Kleinsasser et al., 2000b; Kleinsasser et al., 2000a).

Due to limited data, most previous assessments of DIBP have determined that there is insufficient information to determine the genotoxic potential of DIBP (Yost et al., 2019; EC/HC, 2015b; U.S. CPSC, 2011; NICNAS, 2008a). In contrast, ECHA (2017a, b) considered genotoxicity data of four phthalates (*i.e.*, DEHP, BBP, DBP, DIBP), whereas Australia NICNAS (2016) considered data for eight phthalates (*i.e.*, DIBP, DCHP, DBP, BBP, dihexyl phthlate, di(methoxyethyl) phthalate, dialkyl(C7-11-branched and linear) phthalate, diisoheptyl phthlate). Based on the weight of evidence for all phthalates under consideration, ECHA (2017a, b) concluded that DIBP is not mutagenic in *in vitro* tests, while NICNAS (2016) concluded that DIBP is not expected to have mutagenic or genotoxic potential in humans.

As discussed further in Section 3.8, though limited genotoxicity testing of DIBP has been conducted, *EPA does not consider DIBP likely to be genotoxic or mutagenic to humans based on read-across from DEHP, BBP, DBP, DINP and DIDP*.

Table 3-3. Summary of Genotoxicity Studies of DIBP

Test Type	Test System (Species/ Strain/Sex)	Dose/Duration	Metabolic Activation	Result	Reference
In vitro gene mutation assays					
Reverse mutation	*S. typhimurium* TA 98, TA 100, TA 1535, TA 1537	0, 100, 333, 1,000, 3,333, 10,000 µg/plate	± Aroclor-induced rat or hamster liver S9	Negative for mutagenicity	(Zeiger et al., 1985; Zeiger et al., 1982)
Reverse mutation	*S. typhimurium* TA 98	0.25−500 µmol/plate	± Aroclor-induced rat liver S9	Negative for mutagenicity	(Sato et al., 1994)
Reverse mutation [a]	*S. typhimurium* TA 100	Not reported [a]	± S9 [a]	Negative for mutagenicity	(Seed, 1982)
Reverse mutation [b]	*S. typhimurium* TA 98, TA 100, TA 1538, TA 1537, TA 1535	Not reported [b]	± Aroclor-induced rat liver S9	Negative for mutagenicity	(Simmon et al., 1977)
Other genotoxicity assays					
In vitro comet assay	Human: oropharyngeal and nasal mucosa cells from 40 and 30 patients, respectively	Cells incubated with 354 µmol/mL DIBP for 60 minutes	No	↑ DNA strand breaks in both cell types	(Kleinsasser et al., 2000a)
In vitro comet assay	Human: mucosal cells and lymphocytes from 60 patients	Cells incubated with 354 µmol/mL DIBP for 60 minutes	No	↑ DNA strand breaks in both cell types	(Kleinsasser et al., 2000b)

In vitro comet assay	Human: oropharyngeal mucosa cells and lymphocytes from 132 and 49 patients, respectively	Cells incubated with 354 µmol/mL DIBP for 60 minutes	No	↑ DNA strand breaks in both cell types	(Kleinsasser et al., 2001)

[a] Seed (1982) tested bacteria for mutations to azaguanine resistance and reversion to histidine prototrophy. Tested concentrations of DIBP were not reported. The maximal concentration tested was determined by either the solubility limit or cytotoxicity exceeding 90% of control values. Study authors report that experiments were conducted with S9 mix; however, assay results for DIBP are reported as negative, and it is unclear if this negative result was for studies with or without S9 mix.
[b] Simmon et al. (1977) report that a "wide range of doses was tested up to 5 mg/plate or a dose which gave a toxic response, whichever was lower."

3.5 Dicyclohexyl Phthalate (DCHP)

Limited genotoxicity testing of DCHP has been conducted (Table 3-4). Reasonably available information includes one bacterial reverse mutation study. DCHP was negative for mutagenicity in the one available bacterial reverse mutation assay that was conducted with several strains of *S. typhimurium* both with and without metabolic activation (Zeiger et al., 1985).

EPA also identified several additional genotoxicity studies of DCHP reported in the ECHA Dossier Publication for DCHP (accessed December 3, 2025)). In the Dossier, registrants report that DCHP was negative for mutagenicity in one study that adhered to OECD Guideline No. 471 (Bacterial Reverse Mutation Test), was negative for induction of chromosomal aberrations in one study that adhered to OECD Guideline No. 473 (*In Vitro* Mammalian Chromosomal Aberration Test), and was negative for mutagenicity in one study that adhered to OECD Guideline No. 476 (*In Vitro* Mammalian Cell Gene Mutation Test). However, original study reports were not reasonably available to EPA for independent review, so the results of these studies are not considered further.

Given the limited genotoxicity testing that has been conducted for DCHP, Health Canada and U.S. CPSC refrained from drawing any conclusions regarding the genotoxicity of DCHP (EC/HC, 2015b; U.S. CPSC, 2010e). However, U.S. CPSC (2014) has more generally concluded that phthalate esters as a class are not genotoxic. As discussed further in Section 3.8, though limited genotoxicity testing of DCHP has been conducted, *EPA does not consider DCHP likely to be genotoxic or mutagenic to humans based on read-across from DEHP, BBP, DBP, DINP and DIDP*.

Table 3-4. Summary of Genotoxicity Studies of DCHP

Test Type	Test System (Species/ Strain/Sex)	Dose/Duration	Metabolic Activation	Result	Reference
Reverse mutation	*S. typhimurium* TA 98, TA 100, TA 1535, TA 1537	0, 100, 333, 1,000, 3,333, and 10,000 µg/plate	± Aroclor-induced rat or hamster liver S9	Negative for mutagenicity	(Zeiger et al., 1985)

3.6 Diisononyl Phthalate (DINP)

EPA has previously evaluated the mutagenic and genotoxic potential of DINP and concluded that the weight of scientific evidence supports the conclusion that DINP is not likely to be genotoxic or mutagenic (U.S. EPA, 2025a). This conclusion is based on results from 20 studies, including two *in vivo*

micronucleus tests in rodents, one *in vitro* chromosomal aberration assay, two *in vitro* mouse lymphoma assays, five bacterial reverse mutation assays, one *in vitro* unscheduled DNA synthesis assay, and nine *in vitro* cell transformation assays. Across available studies, DINP was negative for genotoxicity and mutagenicity.

Notably, the SACC supported EPA's conclusions regarding the genotoxicity and mutagenicity of DINP during the July 2024 peer review meeting of DIDP and DINP (U.S. EPA, 2024d). Consistently, Health Canada, ECHA, Australia NICNAS, U.S. CPSC, and EFSA have also concluded that DINP is not genotoxic nor is it likely to be genotoxic (ECCC/HC, 2020; EC/HC, 2015a; ECHA, 2013; NICNAS, 2012; U.S. CPSC, 2010f; EFSA, 2005a; ECB, 2003c; U.S. CPSC, 2001).

Readers are directed to EPA's *Cancer Human Health Hazard Assessment for Diisononyl Phthalate (DINP)* (U.S. EPA, 2025a) for further discussion of available genotoxicity data for DINP.

3.7 Diisodecyl Phthalate (DIDP)

EPA has previously evaluated the mutagenic and genotoxic potential of DIDP and concluded that the weight of scientific evidence supports the conclusion that DIDP is not likely to be genotoxic or mutagenic (U.S. EPA, 2024a). This conclusion is based on results from five studies, including two bacterial reverse mutation assays, two *in vitro* mouse lymphoma assays, and one *in vivo* mouse micronucleus test. Across available studies, DIDP was negative for genotoxicity and mutagenicity. Consistently, existing assessments of DIDP by ECB (2003a), ECHA (2013), Australia NICNAS (2015b, 2008b, c), Health Canada (EC/HC, 2015c), and U.S. CPSC (2014, 2010d) have also concluded that DIDP is not genotoxic or is not likely to be genotoxic.

Readers are directed to EPA's *Human Health Hazard Assessment for Diisodecyl Phthalate (DIDP)* (U.S. EPA, 2024a) for further discussion of available genotoxicity data for DIDP.

3.8 Conclusions on Genotoxicity

Overall, available data support the conclusion that BBP (Section 3.2), DBP (Section 3.3), DINP (Section 3.6), and DIDP (Section 3.7) are not likely to be genotoxic or mutagenic. As discussed earlier in this section, U.S. CPSC (2014, 2010a, d, f, 2001), Canada (ECCC/HC, 2020; EC/HC, 2015a, c; Environment Canada, 2000), Australia NICNAS(2015a, b, 2012, 2008b, c), ECHA (2017a, b, 2013), EFSA (2019, 2005a), and the European Chemical's Bureau (2007, 2003a, c) have all reached similar conclusions regarding the genotoxicity of BBP, DINP, and DIDP.

For DEHP, EPA did not independently evaluate the extensive database of *in vitro* and *in vivo* genotoxicity studies of DEHP and its major metabolites (Section 3.1). However, EPA agrees with the conclusions of ATSDR (2022), NTP (2021b), U.S. CPSC (2010c), Health Canada (1994), Australia NICNAS (2010), ECHA (2017a, b), EFSA (2019), and the European Chemical's Bureau (ECJRC, 2008), and EPA did not identify any new data that would impact the conclusions of these existing assessments. Overall, available data indicate that DEHP and its metabolites are not mutagenic, but that there is some limited evidence that DEHP may be weakly genotoxic inducing effects such as DNA damage and/or chromosomal aberrations. As noted by ATSDR (2022), these effects may be secondary to oxidative stress.

Limited genotoxicity testing has been conducted for DIBP (Section 3.4) and DCHP (Section 3.5). DIBP showed no mutagenic activity in four bacterial reverse mutation assays with or without metabolic activation, while DCHP showed no mutagenic activity in one bacterial reverse mutation assay with or without metabolic activation. However, for the phthalates evaluated herein, data supports the conclusion

that phthalates are either not genotoxic or mutagenic (as is the case for BBP, DINP, and DIDP) or at most weakly genotoxic based on some limited data (as is the case for DEHP and DBP). Overall, based on read-across from BBP, DINP, DIDP, DEHP, and DBP, EPA does not consider DIBP or DCHP likely to be genotoxic or mutagenic to humans. This conclusion is consistent with that of other assessments, which have also generally concluded phthalate esters as a class are not likely to be genotoxic or mutagenic (ECHA, 2017a, b; NICNAS, 2016; U.S. CPSC, 2014). Overall, EPA agrees with the conclusions of other phthalate assessments, that phthalate esters (*i.e.*, DEHP, BBP, DBP, DIBP, DCHP, DINP, DIDP) are not likely to be mutagenic.

4 CANCER HAZARD IDENTIFICATION, CHARACTERIZATION, AND MODE OF ACTION

Section 4.1 summarizes available human epidemiologic data, while Section 4.2 summarizes available cancer bioassays of experimental animal models. Section 4.3 summarizes EPA's cancer hazard characterization, including MOA information and EPA's cancer classifications. No cancer bioassays are available for DIBP or DCHP. Lack of this data for DIBP and DCHP is addressed in Section 5 using read-across and elements from the ReCAAP weight of evidence framework (Hilton et al., 2022) as an organizational tool to evaluate the extent to which the lack of carcinogenicity studies imparts significant uncertainty on the human health risk assessments for DIBP and DCHP.

4.1 Summary of Available Epidemiological Studies for DEHP, BBP, DBP, DIBP, DCHP, DINP and DIDP

This section summarizes available human epidemiologic studies of DEHP, BBP, DBP, DIBP, DCHP, DINP, and DIDP that investigate the association between phthalate exposure and cancer outcomes. Section 4.1.1 provides a summary of conclusions from existing cancer hazard assessments of phthalates by Health Canada (2018a), ATSDR (2022), and IARC (2013), while Section 4.1.2 provides a summary of new epidemiologic studies published between 2018 and 2019 evaluating the association between phthalates (DEHP, BBP, DBP, DIBP, DCHP, DINP, and DIDP) and cancer outcomes in humans. Finally, Section 4.1.3 summarizes EPA's conclusions regarding the association between phthalate exposure and cancer outcomes in humans based on available epidemiologic evidence.

4.1.1 Previous Epidemiologic Assessments of Phthalates

EPA reviewed and summarized conclusions from previous assessments that investigated the association between exposure to DEHP, BBP, DBP, DIBP, DCHP, DINP, and DIDP and cancer outcomes in humans—including those by Health Canada (2018a), ATSDR (2022), and IARC (2013). The outcomes evaluated by each assessment are shown in Table 4-1.

Table 4-1. Summary of Existing Epidemiologic Assessments of Phthalates Investigating Cancer Outcomes

Previous Assessment	Phthalates in Assessment	Outcomes Evaluated
Health Canada (2018a)	DIBP and its metabolites	• Breast cancer
ATSDR (2022)	DEHP and its metabolites	• Breast cancer • Prostate cancer • Thyroid cancer
IARC (2013)	DEHP and its metabolites	• Breast cancer • Cancer mortality • Respiratory cancer mortality • Testicular cancer • Pancreatic cancer • Multiple Myeloma

4.1.1.1 Health Canada (2018a)

Health Canada evaluated two case-control studies (Martinez-Nava et al., 2013; Lopez-Carrillo et al., 2010) that looked at the relationship between urinary monoisobutyl phthalate (MIBP), a metabolite of DIBP, and breast cancer outcomes in populations of reproductive-aged women. Lopez-Carrillo et al.

(2010) found no significant association between urinary MIBP and breast cancer. Martinez-Nava et al. (2013), who evaluated the association between urinary MIBP and breast cancer by PPARGC1B Ala203Pro alleles, reported a significant negative association between urinary MIBP and breast cancer risk in carriers of the PPARGC1B Ala203Pro G allele, but not the $PPAR_{\gamma}$ Pro12Ala C allele.

Overall, Health Canada found inconsistent results for MIBP and breast cancer. Health Canada did not observe any positive associations, exposure-response relationships, and temporality was not established. Therefore, *Health Canada concluded that there was inadequate evidence*[2] for the association between urinary MIBP and risk of breast cancer. Health Canada did not evaluate studies of the association between cancer outcomes and other phthalates (*e.g.*, DINP, DIDP, BBP, DBP, DEHP).

4.1.1.2 ATSDR (2022)

ATSDR evaluated the epidemiological evidence for an association between exposure to DEHP (based on urinary levels of DEHP metabolites) and cancer outcomes. The epidemiological studies evaluated by ATSDR included one population-based study (Morgan et al., 2016) and nine case-control studies. Six studies evaluated breast cancer outcomes (Reeves et al., 2019; Mérida-Ortega et al., 2016; Morgan et al., 2016; Holmes et al., 2014; Martinez-Nava et al., 2013; Lopez-Carrillo et al., 2010); one evaluated prostate cancer (Chuang et al., 2020); and three evaluated thyroid cancer (Liu et al., 2020; Miao et al., 2020; Marotta et al., 2019). The population based study by Morgan and colleauges did not find an association between urinary DEHP metabolite levels and breast cancer in the general U.S. population using National Health and Nutrition Examination Survey (NHANES) data from 2003 through 2010 (Morgan et al., 2016). The remaining nine case-control studies evaluated exposure to DEHP after the outcome, cancer, was observed.

Overall, ATSDR (2022) concluded that "There is no information (qualitative or quantitative) on exposures prior to incidence/diagnosis that could have been involved in tumor induction. Furthermore, cancer treatments could increase exposure to, and excretion of, phthalates from medical equipment. Thus, these studies are not useful for evaluating the carcinogenicity of DEHP."

4.1.1.3 IARC (2013)

The IARC workgroup identified one occupational study by Thiess et al. (1978), one case control study by Lopez-Carrillo et al. (2010), one cohort study by Hagmar et al. (1995; 1990) that looked at the association between exposure to DEHP (and other phthalates being evaluated under TSCA) and cancer outcomes in humans.

A case-control study was carried out in northern Mexico by Lopez-Carrillo et al. (2010) to assess the association between breast cancer and urine levels of nine phthalate metabolites, including four metabolites of DEHP (*i.e.*, MEHP, mono(2-ethyl-5-hydroxyhexyl) phthalate [MEHHP], mono(2-ethyl-5-oxohexyl) phthalate [MEOHP], mono(2-ethyl-5-carboxypentyl) phthalate [MECPP]), one metabolite of DIBP (*i.e.*, MIBP), one metabolite of DBP (monobutyl phthalate [MBP]), and one metabolite of BBP (*i.e.*, monobenzyl phthalate [MBzP). Because there was no information on individual habits with respect to phthalate exposure, exposure evaluation was dependent on the measurement of urinary metabolite levels. No significant associations between urine levels of MBP or MIBP and breast cancer were observed after adjusting for current age, age of menarche, parity, menopause status, and other phthalate metabolites. A significant negative association between urine levels of MBzP and breast cancer was observed after adjusting for current age, age of menarche, parity, menopause status, and other phthalate

[2] Health Canada defines *inadequate evidence* as "the available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of an association."

metabolites. For DEHP, neither the sum of urinary DEHP metabolites nor individual metabolites showed a significant association with breast cancer, except for MECPP. Urinary levels of MECPP were significantly associated with increased breast cancer after adjusting for current age, age of menarche, parity, menopause status and other phthalate metabolites ($p = 0.047$). Although the IARC workgroup concluded that the study design was appropriate, there were issues with the timing of the exposure assessment. Biological samples were taken to measure DEHP metabolites in the urine after cancer cases were diagnosed, but before any treatment was administered. It is unknown whether the disease status had an impact on the levels of these metabolites. No measures of urinary phthalate exposure were measured prior to diagnosis. This study was limited by the lack of a dose-response for all urinary metabolites, the timing of the exposure assessment that precludes conclusions related to temporality, and inconsistent associations of the four DEHP metabolites that were evaluated.

The mortality of 2,031 Swedish employees at a polyvinyl chloride (PVC) processing plant that made floor tiles, thick and thin film floor sheeting, and pipes from PVC was documented in a cohort study by Hagmar et al. (1995; 1990). The products were made from PVC containing phthalic acid esters, with DEHP, BBP, and DIDP being the main plasticizer used at the plant. Cumulative exposures to plasticizers were estimated as the time-weighted average breathing zone levels of total phthalic acid esters among various types of worker class and were therefore not specific to any individual phthalate, including DEHP. The PVC-processing workers had a significant excess of respiratory cancer morbidity (standard incidence ratio [SIR], 2.13; 95% confidence interval [CI]: 1.27−3.47; 17 cases) and total cancer morbidity SIR, 1.28; 95% CI: 1.01−1.61; 75 cases), but there was no statistically significant association between cumulative exposure to plasticizers and respiratory cancer morbidity.

The workgroup also evaluated seven case-control studies of workers potentially exposed to DEHP, unspecified combinations of phthalates, or PVC plastics and cancer outcomes in workers (Westberg et al., 2005; Hardell et al., 2004; Ohlson and Hardell, 2000; Hansen, 1999; Hardell et al., 1997; Selenskas et al., 1995; Heineman et al., 1992). Three population-based, case-control studies examined the relationship between testicular cancer and occupational exposure to PVC plastics or products (exposure assessment did not evaluate exposure to any specific phthalate) (Westberg et al., 2005; Hansen, 1999; Hardell et al., 1997). Two of these studies were conducted in Sweden (Westberg et al., 2005; Hardell et al., 2004) and one in Denmark (Hansen, 1999). Men who had ever been exposed to mostly PVC (odds ratio [OR], 0.7; 95% CI: 0.5−1.2) or plastics in general (OR, 1.0; 95% CI: 0.8−1.2) did not have an increased risk of testicular cancer, according to a larger Danish study; however, exposure to DEHP or any other phthalate was not directly evaluated (Hansen, 1999). The exposure assessment of these studies were centered on PVC in general rather than exposure to any specific chemical, which reduces the likelihood of identifying a phthalate-related effect.

A nested case-control study of pancreatic cancer was carried out by Selenskas et al. (1995) on a group of employees working at a plastic production and research and development facility in New Jersey, where occupational exposure was assessed by employment history and department of work (Dell and Teta, 1995). The manufacturing of flexible plastics may have potentially exposed workers to DEHP, which was identified as being used at this plant. However, only workers who processed vinyl and polyethylene showed a significant increased risk for pancreatic cancer (relative risk, 7.15; 95% CI: 1.28−40.1). The exposure assessment did not quantitatively evaluate exposure to any specific phthalate.

In a population-based case-control study of Danish men, the association between exposure to unspecified combinations of phthalates (and other occupational agents) and multiple myeloma was assessed (Heineman et al., 1992). Larger but non-significant ORs for multiple myeloma were linked to phthalate exposure: the risk estimate for probable exposure was larger (OR, 2.0; 95% CI: 0.9−4.4; 11

cases and 21 controls) than the risk estimates for possible exposure (OR, 1.3; 95% CI: 0.9−2.0; 34 cases and 94 controls).

Overall, while IARC did find some association between exposure to DEHP and cancers such as breast cancer, cancer mortality, respiratory cancer mortality, testicular cancer, and multiple myeloma, the results were generally not statistically significant. The limitations of the studies and/or possible explanations for non-significant results include the following: small number of workers exposed to site-specific cancer fatalities or cases; possible confounding by tobacco use or other risk factors; and imprecise exposure estimates.

4.1.2 Epidemiologic Studies of Phthalates and Cancer Outcomes (2018−2019) Evaluated by EPA

EPA also evaluated new epidemiologic studies published between 2018 and 2019 evaluating the association between phthalates (DEHP, BBP, DBP, DIBP, DCHP, DINP, and DIDP) and cancer outcomes in humans. EPA identified five epidemiology studies that evaluated the association between phthalates such as DINP, DIDP, BBP, DBP, DEHP, and DIBP and cancer outcomes, including breast cancer, colorectal cancer, and breast cancer mortality (Trasande et al., 2021; Ahern et al., 2019; Ennis et al., 2019; Reeves et al., 2019; Parada et al., 2018). Results of these studies are discussed further below.

4.1.2.1 Di(2-ethylhexyl) Phthalate (DEHP)

Five studies evaluated the association between DEHP and its metabolites and breast cancer and colorectal cancer outcomes. These included one high-confidence study (Ahern et al., 2019) and three medium-confidence studies (Trasande et al., 2021; Reeves et al., 2019; Parada et al., 2018) that evaluated breast cancer outcomes and one low-confidence study (Ennis et al., 2019) that evaluated colorectal adenocarcinoma. There were no statistically significant findings from the high- or low-confidence studies that evaluated exposure to DEHP and breast cancer risk. There were significant results from two of the medium-confidence studies (Reeves et al., 2019; Parada et al., 2018). One medium-confidence study (Parada et al., 2018) reported a significant inverse association in multivariable adjusted hazard ratios (HRs) between urinary MEHP in the 4th and 5th quintiles of breast cancer specific mortality (HR = 0.47, 95% CI: 0.25−0.89; and HR = 0.54, 95% CI: 0.28−1.04), respectively, compared to the lowest quintile (quintile 1; HR = 1) among participants in the Long Island Breast Cancer Study Project who were diagnosed with breast cancer in 1996 through 1997 and followed for 18 or more years. Additionally, there was an inverse relationship between breast cancer specific mortality and continuous ln-transformed concentrations of MEHP ($HR_{Ln(MEHP)}$ = 0:79, 95% CI: 0.64−0.98). Statistical significance was not maintained for other quintiles, and no statistically significant results were reported for breast cancer incidence. This study also reported the odds of new breast cancer cases among participants in the Long Island Breast Cancer Study Project for the 3rd vs. 1st quintile of MECPP. Statistical significance was not maintained for other quintiles or when analyzed continuously.

The other medium-confidence study (Reeves et al., 2019) reported significantly decreased odds of breast cancer in a Women's Health Initiative study among participants with positive endocrine receptor and progesterone receptor status for the 3rd vs. 1st quartile of MEHHP. In non-stratified analyses, no statistically significant results were reported for MEHHP. This study also reported significant inverse association between MEOHP and odds of breast cancer with positive estrogen receptor and progesterone receptor status for the 3rd vs. 1st quartile of MEOHP. In non-stratified analyses, no statistically significant results were reported for MEOHP. In the third study by Trasande and colleagues who looked at the association between DEHP and mortality from all causes as well as cardiovascular disease and cancer (Trasande et al., 2021), no significant association between exposure to DEHP and cancer mortality was found.

4.1.2.2 Butyl Benzyl Phthalate (BBP)

Five studies evaluated the association between BBP and breast cancer and cancer mortality outcomes. One high-confidence study (Ahern et al., 2019), three medium-confidence studies (Trasande et al., 2021; Reeves et al., 2019; Parada et al., 2018) evaluated breast cancer outcomes, and one low-confidence study (Ennis et al., 2019) evaluated colorectal adenocarcinoma and BBP exposure. There were no significant results from the high- or low-confidence studies. The three medium-confidence studies (Trasande et al., 2021; Reeves et al., 2019; Parada et al., 2018) had some significant results. One medium-confidence study (Parada et al., 2018) of adult women on Long Island reported a significant inverse association between urinary MBzP measured shortly after diagnosis and odds of breast cancer (OR [95% CI] in the 2nd quintile compared to the 1st quintile of MBzP exposure = 0.64 [0.45, 0.91], and in the 4th quintile compared to the 1st quintile of MBzP exposure = 0.59 [0.41, 0.84]). No significant findings were reported for other quintiles of MBzP or for continuous measurements of MBzP. The other medium-confidence study (Reeves et al., 2019) of postmenopausal women in the United States reported a significant inverse association between urinary MBzP and odds of breast cancer (OR [95% CI] for Q3 vs. Q1 of MBzP exposure = 0.57 [0.39, 0.84], p-value for trend across quartiles = 0.03; and in women without estrogen and progesterone hormone receptors for Q3 vs. Q1 of MBzP exposure = 0.23 [0.05, 0.97]). The final medium-confidence study (Trasande et al., 2021) reported a significant positive association between urinary MBzP and cancer mortality in U.S. adults (HR (95% CI) per ln-µmol/L increase in MBzP = 1.19 [1.04, 1.36]). No significant findings were reported for tertiles of MBzP.

4.1.2.3 Dibutyl Phthalate (DBP)

The same five studies evaluated the association between DBP and breast cancer and colorectal cancer outcomes (Trasande et al., 2021; Ahern et al., 2019; Ennis et al., 2019; Reeves et al., 2019; Parada et al., 2018). There were no significant results from the low-confidence study, but there were significant results from the high-confidence study (Ahern et al., 2019), and one of the medium-confidence studies (Parada et al., 2018). The high-confidence study of Danish women (Ahern et al., 2019) reported a significant positive association between DBP from phthalate-containing oral medications and risk of invasive breast cancer in Swedish women with estrogen-receptor positive cancers (HR [95% CI] for medication-related DBP ≥10,000 mg vs. unexposed; all breast cancer = 2.0 [1.1, 3.6]; estrogen receptor-positive breast cancer = 1.9 [1.1, 3.5]). The medium-confidence study (Parada et al., 2018) reported significant inverse associations between urinary MnBP obtained shortly after diagnosis and breast cancer (OR [95% CI] of breast cancer for Q4 vs. Q1 of urinary MnBP = 0.65 [0.45, 0.93]).

4.1.2.4 Diisobutyl Phthalate (DIBP)

The same five studies evaluated the association between DIBP and breast cancer and colorectal cancer outcomes (Trasande et al., 2021; Ahern et al., 2019; Ennis et al., 2019; Reeves et al., 2019; Parada et al., 2018). There were no significant results from the high- or low-confidence studies that evaluated breast cancer outcomes. However, there was some significant results from one of the medium-confidence studies (Parada et al., 2018). The medium-confidence study (Parada et al., 2018) of adult women on Long Island reported a significant inverse association between urinary MIBP obtained shortly after diagnosis and odds of breast cancer (OR [95% CI] in the 4th quintile compared to 1st quintile of MIBP exposure = 0.69 [0.48, 0.99]). No significant findings were reported for other quintiles of MIBP or for continuous measurements of MIBP.

4.1.2.5 Dicyclohexyl Phthalate (DCHP)

EPA did not identify any studies evaluating the association between DCHP (or its metabolites) exposure and any cancer outcomes.

4.1.2.6 Diisononyl Phthalate (DINP)

Three medium-confidence studies (Trasande et al., 2021; Reeves et al., 2019; Parada et al., 2018) evaluated the associations between DINP and breast cancer and breast cancer mortality outcomes. Of these, only one study (Parada et al., 2018) reported significant results. The highest vs. lowest quintiles of MCOP were associated with breast cancer ORs ranging from 0.71 to 0.73. The highest (vs. lowest) quintiles of MCOP were associated with breast cancer-specific mortality HR of 0.55 (95% CI: 0.23, 1.35). MCOP concentrations differed by stage (*in situ* vs. invasive) based on statistically significant mean differences derived from generalized linear models regressing each of the ln-transformed creatinine-corrected phthalate metabolite concentrations on age and the covariate. Continuous ln-transformed MCOP were associated with HRs of breast cancer-specific mortality of 0.54 (95% CI: 0.33, 0.89), though estimates were imprecise. In follow-up analyses, MCOP had one of the largest inverse associations for which the highest quintiles were associated with HRs of breast cancer-specific mortality of 0.55 (95% CI: 0.23, 1.35) relative to the lowest quintiles. The estimate for MCOP was imprecise due to availability of data for the 320 women with breast cancer.

4.1.2.7 Diisodecyl Phthalate (DIDP)

Three medium-confidence studies evaluated the association between DIDP and breast cancer and breast cancer mortality outcomes (Trasande et al., 2021; Reeves et al., 2019; Parada et al., 2018). Of those studies only one study (Parada et al., 2018) had some significant results. Parada et al.(2018) reported a significant inverse association between urinary MCNP and odds of breast cancer (OR [95% CI]), in the highest vs. lowest quintile of MCNP; (OR = 0.51 [0.28, 0.92] of adult women in the Long Island Breast Cancer Study Project (LIBCSP) who were diagnosed with first primary *in situ* or invasive breast cancer during the years 1996 to 1997. Breast cancer-specific mortality HRs with multivariable adjustment were not statistically significant.

4.1.3 Conclusion

In conclusion, Health Canada and ATSDR, determined that the evidence was inadequate to support an association between phthalate exposure and cancer outcomes, whereas IARC found no statistically significant associations between DEHP exposure and cancer outcomes.

Overall, there are a number of sources of uncertainty associated with the available human epidemiologic studies of phthalates and cancer outcomes, including uncertainty associated with exposure characterization of individual phthalates, source of phthalate exposure, timing of phthalate exposure (exposure is typically measured after the outcome is reported, meaning temporality cannot be established), as well as co-exposure to multiple phthalates, which can confound results. Another uncertainty is that many of the available epidemiologic studies evaluated phthalate exposure after cancer diagnosis and cancer treatment had been initiated, which can confound study results because cancer treatment can increase phthalate exposure from plastic medical equipment. Overall, EPA agrees with the conclusions of Health Canada and ATSDR. Given the limitations and uncertainties, the Agency concludes that the epidemiologic evidence is insufficient to identify an association between phthalate exposure and subsequent cancer outcomes.

4.2 Overview of Laboratory Animals Studies

Of the seven phthalate diesters being evaluated under TSCA, DEHP, BBP, DBP, DINP, and DIDP have been evaluated for carcinogenicity in experimental animal models (see Table 4-2 for a summary of available cancer bioassays). No studies of experimental animal models evaluating carcinogenicity are available for DIBP or DCHP; however, the potential carcinogenicity of DIBP and DCHP is further considered in Section 5 based on read-across from DEHP, BBP, DBP, DINP and DIDP. As can be seen in Table 4-3, statistically significant increases in several tumor types have been observed in

experimental animal models following chronic oral exposure to DEHP, BBP, DBP, DINP and DIDP. Observed tumor types include the following:

- hepatocellular adenomas and/or carcinomas following exposure to DEHP, DINP, and DIDP;
- pancreatic acinar cell tumors (PACTs) following exposure to DEHP, BBP, and DBP;
- testicular Leydig cell adenomas following exposure to DEHP;
- MNCL in F344 rats following exposure to DEHP, BBP, DINP and DIDP;
- renal tubular cell carcinomas following exposure to DINP; and
- uterine adenoma, adenocarcinoma, squamous cell carcinoma, or squamous cell papilloma following exposure to DEHP.

Evidence for each of these tumor types for DEHP, BBP, and DBP—including EPA's weight of scientific evidence conclusions, cancer classifications, and, when applicable, MOA analyses—are summarized in Sections 4.3. EPA's weight of scientific evidence conclusions and cancer classifications for DIDP and DINP have been summarized previously in EPA's *Cancer Human Health Hazard Assessment for Diisononyl Phthalate (DINP)* (U.S. EPA, 2025a) and *Human Health Hazard Assessment for Diisodecyl Phthalate (DIDP)* (U.S. EPA, 2024a). However, a brief summary of carcinogenic findings, weight of scientific evidence conclusions, and cancer classifications for DINP and DIDP are provided in Sections 4.3.4 and 4.3.5, respectively, to facilitate comparisons across phthalates, including EPA's read-across assessment for DIBP and DCHP in Section 5.

Table 4-2. Summary of Database of Available Rodent Carcinogenicity Studies Considered

Phthalate	Experimental Model	Exposure Route (Method)	Exposure Duration	# of Studies	Notes	Reference(s)
DEHP	F344/N rat (both sexes)	Oral (diet)	2 years	2		(David et al., 2000b; David et al., 1999; NTP, 1982a)
	F344 rat (male only)	Oral (diet)	95−108 weeks	2		(Rao et al., 1990; Rao et al., 1987)
	SD rat (male only)	Oral (diet)	≤159 weeks	1	Lifetime exposure study	(Voss et al., 2005)
	SD rat (both sexes)	Oral (diet)	2 years	1	Perinatal and post-weaning exposure	(NTP, 2021b)
	SD rat (both sexes)	Oral (diet)	2 years	1	Post-weaning exposure only	(NTP, 2021b)
	B6C3F1/n mice (both sexes)	Oral (diet)	2 years	2		(David et al., 2000a; David et al., 1999; NTP, 1982a)
	Syrian golden hamster (both sexes)	Inhalation	17−23 months	1	Lifetime exposure study	(Schmezer et al., 1988)
	Syrian golden hamster (both sexes)	IP injection	17−23 months	1	Lifetime exposure study	(Schmezer et al., 1988)
	Wild-type & RasH2 mice (both sexes)	Oral (diet)	26 weeks	1		(Toyosawa et al., 2001)
	Tg.AC mice (both sexes)	Oral (diet)	26 weeks	1		(Eastin et al., 2001)
	Xpa$^{-/-}$, wild-type, & *Xpa*$^{-/-}$/*p53*$^{+/-}$ mice (both sexes)	Oral (diet)	39 weeks	1		(Mortensen et al., 2002)
	Wild-type & *Ppara*-null mice (males only)	Oral (diet)	22 months	1		(Ito et al., 2007a)
	Tg.AC mice (both sexes)	Dermal	28 weeks	1		(Eastin et al., 2001)
BBP	F344/N rat (both sexes)	Oral (diet)	2 years	2		(NTP, 1997b, 1982b)
	F344/N rat (both sexes)	Oral (diet)	24−32 months	3	*Ad libitum* and diet restricted studies	(NTP, 1997a)
	B6C3F1 mice (both sexes)	Oral (diet)	2 years	1		(NTP, 1982b)
DBP	SD rat (both sexes)	Oral (diet)	2 years	1	Perinatal and post-weaning exposure	(NTP, 2021a)
	B6C3F1 mice (both sexes)	Oral (diet)	2 years	1		(NTP, 2021a)
DIBP	*No carcinogenicity studies available*					
DCHP	*No carcinogenicity studies available*					

Phthalate	Experimental Model	Exposure Route (Method)	Exposure Duration	# of Studies	Notes	Reference(s)
DINP	F344 rat (both sexes)	Oral (diet)	2 years	2		(Covance Labs, 1998c; Lington et al., 1997)
	SD rat (both sexes)	Oral (diet)	2 years	1		(Bio/dynamics, 1987)
	B6C3F1 mice (both sexes)	Oral (diet)	2 years	1		(Covance Labs, 1998a)
DIDP	F344 rat (both sexes)	Oral (diet)	2 years	1		(Cho et al., 2008)
	Wild-type and RasH2 mice (both sexes)	Oral (diet)	26 weeks	1		(Cho et al., 2011)

Table 4-3. Summary of Tumor Types Observed Following Chronic Oral Exposure to Phthalates in Experimental Rodent Models[a]

Phthalate	Hepatocellular Adenoma and/or Carcinoma		Pancreatic Acinar Cell Tumors (PACTs)		Leydig Cell Tumors		Renal Tubular Carcinoma		Uterine Adenoma, Adenocarcinoma, Squamous Cell Carcinoma, or Squamous Cell Papilloma		Mononuclear Cell Leukemia (MNCL)	
	Rat	Mouse	Rat	Mouse	Rat	Mouse	Rat	Mouse	Rat	Mouse	Rat	Mouse
DEHP	Yes	Yes	Yes	No	Yes [c]	No	No	No	Yes	No	Yes [e]	No
BBP	No	No	Yes	No	No	No	No	No	No	No	Yes [e]	No
DBP	No	No	Yes	No	No	No	No	No	No	No	No	No
DIBP	*No carcinogenicity studies available*											
DCHP	*No carcinogenicity studies available*											
DINP	Yes	Yes	No	No	No	No	Yes [d]	No	No	No	Yes [e]	No
DIDP	No	Yes [b]	No	No	No	No	No	No	No	No	Yes [e]	No

[a] "Yes" indicates that a statistically significant increase in the tumor type has been observed in at least one of the available studies, while "No" indicates that no statistically significant increase in the tumor type has been observed in any of the available studies.
[b] Hepatocellular adenomas observed following chronic dietary exposure to DIDP in male rasH2 mice only (discussed further in Section 4.3.5).
[c] Statistically significant increases in Leydig cell tumors have been observed only in male SD rats. As discussed in Appendix C, this tumor type occurs at a high spontaneous background rate in F344 rats, which decreases the utility of this strain to detect treatment-related increases in this tumor.
[d] Renal tubular cell carcinomas observed only in male F344 rats following chronic dietary exposure to DINP (discussed further in Section 4.3.4).

Phthalate	Hepatocellular Adenoma and/or Carcinoma		Pancreatic Acinar Cell Tumors (PACTs)		Leydig Cell Tumors		Renal Tubular Carcinoma		Uterine Adenoma, Adenocarcinoma, Squamous Cell Carcinoma, or Squamous Cell Papilloma		Mononuclear Cell Leukemia (MNCL)	
	Rat	Mouse	Rat	Mouse	Rat	Mouse	Rat	Mouse	Rat	Mouse	Rat	Mouse
[e] MNCL has been observed only in F344 rats, which have a high background rate of MNCL in control rats. As discussed further in Appendix C, there are a number of scientific uncertainties associated with MNCL in F344 rats. Consistent with the recommendations of the SACC (U.S. EPA, 2024d), EPA is not further considering MNCL as a factor in the determination of the cancer classifications for phthalates.												

4.3 Cancer Hazard Characterization, Mode of Action and Conclusions for DEHP, BBP, DBP, DINP, and DIDP

This section characterizes the cancer hazards of DEHP (Section 4.3.1), BBP (Section 4.3.2), and DBP (Section 4.3.3), including MOA information and EPA's cancer classifications. Cancer hazards of DINP and DIDP have been evaluated by EPA previously (U.S. EPA, 2025a, 2024a) but are briefly summarized in Section 4.3.4 and 4.3.5, respectively, to support cancer hazard comparisons and read-across. No cancer bioassays are available for DIBP or DCHP. Lack of this data for DIBP and DCHP is addressed in Section 5 using read-across and elements from the ReCAAP weight of evidence framework (Hilton et al., 2022) as an organizational tool to evaluate the extent to which the lack of carcinogenicity studies imparts significant uncertainty on the human health risk assessments for DIBP and DCHP.

4.3.1 Di(2-ethylhexyl) Phthalate (DEHP)

DEHP has been evaluated for carcinogenicity by a number of authoritative and regulatory agencies. As summarized in Table 4-4, DEHP has been classified by IARC as Group 2B (possibly carcinogenic to humans) (IARC, 2013), by U.S. EPA as Group B2 (probable human carcinogen) (U.S. EPA, 1988b), by NTP as *reasonably anticipated to be a human carcinogen* (NTP, 2016), and is listed by OEHHA under California's Proposition 65 as causing cancer (OEHHA, 2022). Despite these cancer listings, DEHP has not been evaluated quantitatively for cancer risk in assessments by ECB (2008), ECHA (2017a, b), Australia NICNAS (2010), Health Canada (ECCC/HC, 2020), or U.S. CPSC (2014).

Table 4-4. Summary of Cancer Classifications and Listings for DEHP

Agency	Cancer Classification/Listing
NTP (2016)	Reasonably anticipated to be a human carcinogen
IARC (2013)	Group 2B (possibly carcinogenic to humans)
California OEHHA (2022)	Listed as carcinogen under Proposition 65
U.S. EPA (IRIS) (1988b)	Group B2 (probable human carcinogen)
IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; NTP = National Toxicology Program; OEHHA = Office of Environmental Health Hazard Assessment	

In 1988, EPA concluded that DEHP is a *Probable human carcinogen – based on sufficient evidence of carcinogenicity in animal*s. Consistent with the guidelines available at the time of the assessment (*i.e.*, *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1986)), DEHP was assessed under an assumption of low-dose linearity. However, since the 1988 Integrated Risk Information System (IRIS) assessment of DEHP, the science has evolved, and EPA's current *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005) emphasize a data-first approach, rather than use of default options, stating the following:

> Rather than viewing default options as the starting point from which departures may be justified by new scientific information, these cancer guidelines view a critical analysis of all of the available information that is relevant to assessing the carcinogenic risk as the starting point from which a default option may be invoked if needed to address uncertainty or the absence of critical information.

Moreover, TSCA requires EPA to use the "best available science"; thus, the cancer classification and risk assessment approach for DEHP has been re-evaluated.

DEHP has been evaluated extensively for carcinogenicity in experimental rodent models, including seven chronic dietary studies of rats, two chronic dietary studies of mice, five chronic dietary studies of transgenic mice, one chronic inhalation study of hamsters, and one chronic intraperitoneal injection study of hamsters. Available studies and neoplastic findings from each study are summarized in Table 4-5, while study summaries are provided in Appendix B.1. Across available studies, significant dose-related increases in hepatocellular adenomas and carcinomas have been consistently observed in seven chronic studies of male rats, four chronic studies of female rats, and both chronic studies of male and female B6C3F1 mice (Table 4-5 and Table 4-6). PACTs have been observed in three studies of male SD or F344 rats, while equivocal evidence for PACTs was observed in two studies of female SD rats (but not in 2 studies of female F344 rats), and no evidence of PACTs was reported in two studies of male or female B6C3F1 mice (Table 4-5 and Table 4-6).

Significant testicular Leydig cell tumors have been observed in one lifetime dietary exposure study of SD rats (Voss et al., 2005), while equivocal evidence of Leydig cell tumors was observed in another 2-year study of SD rats by NTP (2021b). Leydig cell tumors were not observed in 4 studies of male F344 rats or two studies of male B6C3F1 mice; however, as noted in Appendix C, there is a high spontaneous background rate of this tumor type in F344 rats, making this difficult to detect treatment-related changes in Leydig cell tumors in this F344 rats. Finally, there is some limited evidence for uterine tumors in female SD rats in two recent studies by NTP (2021b); however, uterine tumors were not observed in two studies of female F344 rats or two studies of female B6C3F1 mice. MNCL has been observed in one study of male F344 rats (David et al., 2000b; David et al., 1999), but has not been observed in any studies of SD rats or B6C3F1 mice. In contrast to studies of rats and mice, no significant increase in tumors were observed in inhalation and intraperitoneal injection studies of hamsters (Schmezer et al., 1988).

The remainder of this section includes a summary of evidence for each of these tumor types for DEHP, including EPA's weight of scientific evidence conclusions and information on MOA, as well as EPA's cancer classification. The remainder of the section is organized as follows:

- Section 4.3.1.1 summaries evidence of liver, pancreatic, and testicular tumors (sometimes referred to as the "tumor triad") following chronic oral exposure to DEHP in experimental rodent models. Information pertaining to MOA for induction of each of these tumor types is provided in Sections 4.3.1.1.1 through 4.3.1.1.3. Section 4.3.1.1.4 provides information pertaining to hypolipidemic drugs that are known peroxisome proliferator-activated receptor alpha (PPARα) activators and also cause the tumor triad in rats, but not humans. Evidence from these hypolipidemic drugs support inferences for DEHP-induced liver, pancreatic, and testicular tumors. Finally, Sections 4.3.1.1.5 and 4.3.1.1.6 summarize information for remaining areas of uncertainty and EPA's conclusions regarding the tumor triad.
- Section 4.3.1.2 summaries evidence of uterine tumors following chronic oral exposure to DEHP in experimental rodent models.
- Section 4.3.1.3 summaries evidence of MNCL following chronic oral exposure to DEHP in experimental rodent models.
- Section 4.3.1.4 summarizes EPA's cancer classification for DEHP.

Table 4-5. Summary of Available Carcinogenicity Studies of DEHP in Rodents

Brief Study Description	Tumor Type(s) Observed
Studies of rats	
Male and female F344 rats (50/sex/dose) fed diets containing 0, 6,000, or 12,000 ppm DEHP for 103 weeks (equivalent to ≈322 and 674 mg/kg-day [males]; 394 and 774 mg/kg-day [females]) (NTP, 1982a) (see Appendix B.1.2.1 for study details).	- Hepatocellular carcinomas and neoplastic nodules (both sexes)
Male and female F344 rats (55−80/sex/dose) were administered diets containing 0, 100, 500, 2,500, or 12,500 ppm DEHP for up to 104 weeks (equivalent to 6, 29, 147, and 780 mg/kg-day [males]; 7, 36, 182, and 939 mg/kg-day [females]) (David et al., 2000b; David et al., 1999) (see Appendix B.1.2.2 for study details).	- Hepatocellular carcinomas and adenomas (both sexes) - PACTs (males only) - MNCL (males only)
Male F344 rats (8−10 rats/group) were fed diets containing 0 or 2% DEHP for 95 weeks (Rao et al., 1987) (see Appendix B.1.2.3 for study details).	- Hepatocellular carcinomas and neoplastic nodules
Male F344 rats (10−14 rats/group) were fed diets containing 0 or 2% DEHP for 108 weeks (Rao et al., 1990) (see Appendix B.1.2.4 for study details).	- Hepatocellular carcinomas and neoplastic nodules
Male SD rats were fed diets containing 0 (N = 390), 600 (N = 180), 1,897 (N = 100), or 6,000 (N = 60) mg DEHP/kg diet. Rats were fed 5 g diet/100 g rat/day for 6 days/week and received DEHP-free food on the 7th day only after the rest of their DEHP diet had been consumed (received doses: 0, 30, 95, and 300 mg/kg-day over the entire lifetime of rats [up to 159 weeks]) (Voss et al., 2005) (see Appendix B.1.2.5 for study details).	- Hepatocellular carcinomas and adenomas (males only) - Leydig cell adenomas (males only)
Time-mated SD rats (45/dose) fed diets containing 0, 300, 1,000, 3,000, or 10,000 ppm DEHP on GD 6–PND 21 (weaning). Dams allowed to deliver litters naturally, and at weaning (PND 21), F1 offspring (50/sex/dose) were continued on the same respective diets for 2 years (received dose during 2-year phase of study: 18, 58, 189, and 678 mg/kg-day [males]; 18, 62, 196, and 772 mg/kg-day [females]) (NTP, 2021b) (see Appendix B.1.2.6 for study details)	- Hepatocellular carcinomas and adenomas (both sexes) - PACTs (Males) (Females: low, statistically non-significant increase in females was considered by NTP to be treatment-related) - Uterine adenocarcinoma and combined uterus adenoma, adenocarcinoma, squamous cell carcinoma, or squamous cell papilloma (equivocal finding)
Male and female SD rats (50/sex/dose) were fed diets containing 0, 300, 1,000, 3,000, or 10,000 ppm DEHP for 2 years (equivalent to: 17, 54, 170, and 602 mg/kg-day [males]; 17, 60, 177, and 646 mg/kg-day [females]) (NTP, 2021b) (see Appendix B.1.2.7 for study details)	- Hepatocellular carcinomas and adenomas (both sexes) - PACTs (Males) (Females: low, statistically non-significant increase in females was considered by NTP to be treatment-related) - Leydig cell adenomas (equivocal finding)

Brief Study Description	Tumor Type(s) Observed
	- Uterine adenocarcinoma and combined uterus adenoma, adenocarcinoma, squamous cell carcinoma, or squamous cell papilloma (Females)
Studies of mice	
Male and female B6C3F1 mice (50/sex/dose) fed diets containing 0, 3,000, or 6,000 ppm DEHP for 103 weeks (equivalent to ≈673 and 1,325 mg/kg-day [males]; 799 and 1,821 mg/kg-day [females]) (NTP, 1982a) (see Appendix B.1.1.1 for study details)	- Hepatocellular carcinomas and adenomas (both sexes)
Male and female B6C3F1 mice (65−70/sex/dose) fed diets containing 0, 100, 500, 1,500, or 6,000 ppm DEHP for 104 weeks (equivalent to: 19, 99, 292, and 1,266 mg/kg-day [males]; 24, 117, 354, and 1,458 mg/kg-day [females]) (David et al., 2000a; David et al., 1999) (see Appendix B.1.1.2 for study details)	- Hepatocellular carcinomas and adenomas (both sexes)
Studies of hamsters	
Male and female Syrian golden hamsters (80/sex for the control; 65/sex for treatment group) were exposed to vapor concentrations of 0 or 15 ± 5 μg/m^3 DEHP for 24 hours/day, 5 days/week from 12 weeks of age until natural death (around 23 months for males and 17 months for females) (Schmezer et al., 1988) (see Appendix B.1.3.1 for study details)	- None
Male and female Syrian golden hamsters (25/sex/group) were administered 0 or 3,000 mg DEHP per kg body weight via intraperitoneal injection once per week, once every 2 weeks, or once every 4 weeks for life (Schmezer et al., 1988) (see Appendix B.1.3.2 for study details)	- None
Studies of transgenic mice	
Male and female transgenic CB6F1-rasH2 mice (15/sex/dose) were fed diets containing 0, 1,500, 3,000, or 6,000 ppm DEHP for 26 weeks, while wild-type mice (15/sex/dose) were fed diets containing 0 or 6,000 ppm DEHP for 26 weeks (Toyosawa et al., 2001) (see Appendix B.1.4.1 for study details)	- Hepatocellular adenomas (rasH2 males only)
Male and female transgenic Tg.AC mice (15/sex/dose) were fed diets containing 0, 1,500, 3,000, or 6,000 ppm DEHP for 26 weeks (equivalent to 252, 480, and 1,000 mg/kg-day [males]; 273, 545, and 1,143 mg/kg-day [females]) (Eastin et al., 2001) (see Appendix B.1.4.2 for study details)	- None

Brief Study Description	Tumor Type(s) Observed
Male and female transgenic Tg.AC mice (15/sex/dose) were topically administered doses of 0, 100, 200, or 400 mg/kg DEHP to a clipped area of dorsal skin 5 days per week for 28 weeks (Eastin et al., 2001) (see Appendix B.1.4.2 for study details)	- None
Male and female *Xpa*$^{-/-}$ mice (15/sex/dose) fed diets containing 0, 1,500, 3,000, or 6,000 ppm DEHP (equivalent to: 204, 408, and 862 mg/kg-day [males]; 200, 401, and 827 mg/kg-day [females]) for 39 weeks. Male and female wild-type and *Xpa*$^{-/-}$/*p53*$^{+/-}$ mice (15/sex/dose) fed diets containing 0 and 6,000 ppm DEHP for 39 weeks (equivalent to 879 [male] and 872 [female] mg/kg-day for wild-type mice; 896 [male] and 796 [female] mg/kg-day for *Xpa*$^{-/-}$/*p53*$^{+/-}$ mice) (Mortensen et al., 2002) (see Appendix B.1.4.3 for study details)	- None
Male wild-type and *PPARα*-null mice fed diets containing 0, 0.01, or 0.05% DEHP for 22 months. (Ito et al., 2007a) (see Appendix B.1.4.4 for study details)	- Hepatocellular adenoma, carcinoma, and cholangiocellular carcinoma (combined) (*PPARα*-null mice)

Table 4-6. Summary of Observed Tumors and Effect Levels (LOAEL, mg/kg-day) Across Carcinogenicity Studies of DEHP[a]

Study Details (Strain; Sexes Evaluated; N; Duration; Doses (mg/kg-day); Table with Tumor Incidence data; Reference[s])	Hepatocellular Adenomas and/or Carcinomas		Pancreatic Acinar Cell Tumors (PACTs)		Testicular Leydig Cell Adenomas [b]	Uterine Adenoma, Adenocarcinoma, Squamous Cell Carcinoma, Squamous Cell Papilloma	MNCL [c]	
	Male	Female	Male	Female	Male	Female	Male	Female
Studies of rats								
F344; M/F; 50/sex/dose; 2-year; 0, 322, 674 (M); 0, 394, 774 (F); Table_Apx B-3; (NTP, 1982a)	↑ (674)	↑ (394)	Not observed	Not observed	Not observed	Not observed	Not observed	Not observed
F344; M/F; 55−80/sex/dose; 2-year; 0, 6, 29, 147, 780 (M); 0, 7, 36, 182, 939 (F); Table_Apx B-4; (David et al., 2000b; David et al., 1999)	↑ (147)	↑ (939)	↑ (780)	Not observed	Not observed	Not observed	↑ (780)	Not observed
SD; M only; 60−390/dose; lifetime (up to 159 weeks); 0, 30, 95, 300; Table_Apx B-6 and Table_Apx B-7; (Voss et al., 2005)	↑ (300)	Not evaluated	Not observed	Not evaluated	↑ (300)	Not evaluated	Not observed	Not evaluated
SD; M/F; 45/sex/dose; 2-year (perinatal and postweaning); 0, 18, 58, 189, 678 (M); 0, 18, 62, 196, 772 (F); Table_Apx B-9 to Table_Apx B-11; (NTP, 2021b)	↑ (678)	↑ (196)	↑ (189)	Equivocal [d]	Not observed	Equivocal	Not observed	Not observed
SD; M/F; 50/sex/dose; 2 years; 0, 17, 54, 170, 602 (M); 0, 17, 60, 177, 646 (F); Table_Apx B-12 to Table_Apx B-15; (NTP, 2021b)	↑ (602)	↑ (646)	↑ (170)	Equivocal [d]	Equivocal	↑ (646)	Not observed	Not observed
Studies of mice								
B6C3F1; M/F; 50/sex/dose; 2-year; 0, 673, 1,325 (M); 0, 799, 1,821 (F); Table_Apx B-1; (NTP, 1982a)	↑ (673)	↑ (799)	Not observed	Not observed	Not observed	Not observed	Not observed	Not observed
B6C3F1; M/F; 65−70/sex/dose; 2-year; 0, 19, 99, 292, 1,266 (M); 0, 24, 117, 354, 1,458 (F); Table_Apx B-2; (David et al., 2000a; David et al., 1999)	↑ (99)	↑ (354)	Not observed	Not observed	Not observed	Not observed	Not observed	Not observed

Study Details (Strain; Sexes Evaluated; N; Duration; Doses (mg/kg-day); Table with Tumor Incidence data; Reference[s])	Hepatocellular Adenomas and/or Carcinomas		Pancreatic Acinar Cell Tumors (PACTs)		Testicular Leydig Cell Adenomas [b]	Uterine Adenoma, Adenocarcinoma, Squamous Cell Carcinoma, Squamous Cell Papilloma	MNCL [c]	
	Male	Female	Male	Female	Male	Female	Male	Female

F = female; M = male; SD = Sprague Dawley

[a] Cells highlighted in blue indicate studies in which a statistically significant increase in incidence of the tumor was observed, while cells with yellow indicate an equivocal tumor response.

[b] As discussed further in Appendix C, F344/N rats have a high spontaneous background rate of testicular Leydig cell tumors (ranging from 86−87%), which reduces the ability of this strain of rat to detect treatment-related increases in this tumor type.

[c] MNCL has been observed only in F344 rats, which have a high background rate of MNCL in control rats. As discussed further in Appendix C, there are a number of scientific uncertainties associated with MNCL in F344 rats. Consistent with the recommendations of the SACC (U.S. EPA, 2024d), EPA is not further considering MNCL as a factor in the determination of the cancer classifications for phthalates.

[d] NTP reported a slight, statistically non-significant increase in pancreatic acinar adenomas and/or carcinomas in female rats. NTP considered this lesion to be treatment related; however, given the low, statistically non-significant effect, EPA considered the finding equivocal.

4.3.1.1 Liver, Pancreatic, and Testicular Tumors (Tumor Triad)

Many PPARα activators are known to induce hepatocellular adenomas and/or carcinomas in rats and mice, as well as PACTs and testicular Leydig cell tumors in rats, but not mice (Klaunig et al., 2003). Again, the induction of liver tumors, PACTs, and testicular Leydig cell tumors in rats by PPARα activators is often referred to as the "tumor triad."

DEHP is an established PPARα activator, and across available chronic dietary studies of rats and mice, there is evidence of the tumor triad in rats, while only liver tumors have been observed in mice. As shown in Table 4-5 and Table 4-6, chronic dietary exposure to DEHP has been shown to consistently induce hepatocellular adenomas and/or carcinomas in seven studies of male and/or female rats (NTP, 2021b; Voss et al., 2005; David et al., 2000b; David et al., 1999; Rao et al., 1990; Rao et al., 1987; NTP, 1982a), two studies of male and female B6C3F1 mice (David et al., 2000a; David et al., 1999; NTP, 1982a), and in male transgenic RasH2 mice (Toyosawa et al., 2001). Across studies (Table 4-6), statistically significant increases in hepatocellular adenomas and/or carcinomas have been observed at doses as low as 147 mg/kg-day (lowest-observable-adverse-effect level [LOAEL]) in male F344 rats (David et al., 2000b; David et al., 1999), 196 mg/kg-day (LOAEL) in female SD rats (NTP, 2021b), and 99 mg/kg-day (LOAEL) in male B6C3F1 mice (David et al., 2000a; David et al., 1999). Additionally, chronic dietary exposure to DEHP has been shown to induce PACTs in three studies of male rats (NTP, 2021b; David et al., 2000b; David et al., 1999) at doses as low as 170 to 189 mg/kg-day DEHP (NTP, 2021b), while statistically significant increases in Leydig cell adenomas have been observed in one lifetime dietary exposure study of SD rats at doses as low as 300 mg/kg-day (Voss et al., 2005).

Establishing MOA is an important consideration for determining the most appropriate method to use for cancer risk assessment (application of linear low-dose extrapolation vs. a threshold approach) (U.S. EPA, 2005). EPA further considers the MOA for liver tumors in Section 4.3.1.1.1, while the MOA(s) for PACTs and Leydig cell tumors are discussed further in Section 4.3.1.1.2 and 4.3.1.1.3, respectively. Inferences from hypolipidemic drugs known to activate PPARα and induce the tumor triad in rats, but not humans, are provided in Section 4.3.1.1.4. Finally, remaining uncertainties and limitations and conclusions regarding the tumor triad are provided in Sections 4.3.1.1.5 and 4.3.1.1.6, respectively.

4.3.1.1.1 Mode of Action for Liver Tumors in Rats and Mice

Studies have demonstrated that DEHP can activate PPARα in hepatocytes and cause hepatocellular adenomas and carcinomas in mice and rats. Existing assessments of DEHP by ECB (2008), ECHA (2017a, b), NICNAS (2010), Health Canada (2015), and U.S. CPSC (2010c) have postulated that DEHP causes liver tumors in rats and mice through a PPARα MOA. In contrast, ATSDR (2022) concluded that the "exact mechanism(s) by which DEHP induces hepatic cancer in rodents are not precisely known; however, the available data suggest that multiple molecular targets and pathways are affected in multiple liver cell types." In addition to a role for PPARα, ATSDR postulated that other molecular targets may include constitutive androstane receptor (CAR) activation or activation of nuclear factor kappa B (NF-κB) leading to chronic inflammation. PPARα is a nuclear receptor that controls transcription of genes involved in fatty acid β-oxidation and peroxisome proliferation.

PPARα activation in hepatocytes in rodent models can cause hepatocellular cancer through a non-genotoxic MOA that involves activation of Kupffer cells. Activated Kupffer cells secrete cytokines such as tumor necrosis factor alpha (TNFα), interleukin 1-alpha (IL-1α), and interleukin 1-beta (IL-1β) that influence hepatocyte growth and fate. As discussed by Corton et al. (2018; 2014), studies have demonstrated that Kupffer cell activation following PPARα activation plays a crucial role in several tumor precursor effects. These effects include increased DNA synthesis and cell proliferation in both

normal and preneoplastic hepatocytes, as well as suppression of apoptosis. Altered cell growth and survival can facilitate clonal expansion of initiated cells leading to the selective clonal expansion of preneoplastic foci cells and ultimately tumor formation.

The PPARα MOA for liver tumorigenesis considered by EPA is described further by Corton et al. (2018; 2014). The PPARα MOA includes the following sequence of key events (KEs):

- **KE1: Activation of PPARα in hepatocytes.** PPARα activation can be assessed using trans-activation assays or by measuring specific events associated with PPARα activation, such as increased expression of genes involved in fatty acid beta oxidation or peroxisome proliferation, increased activity of palmitoyl-CoA oxidase, increased peroxisomal beta oxidation (PBOX), and/or peroxisome proliferation in hepatocytes. Studies have demonstrated that sustained activation of PPARα can lead to alterations in cell growth pathways.
- **KE2: Alterations in cell growth pathways.** For example, PPARα activation can lead to activation of Kupffer cells, which produce and secreted cytokines such as TNFα, IL-1α, and IL-1β. Secreted cytokines can alter hepatocyte fate and perturb hepatocyte growth and survival.
- **KE3: Perturbation of cell growth and survival.** Cytokines secreted by Kupffer cells can increase hepatocyte cell proliferation and inhibit apoptosis. Increased cell proliferation may increase the frequency of spontaneous mutations from increased errors in DNA repair or replication. This can enhance the rate of fixation of DNA damage and/or mutations in tumor suppressor genes or activate oncogenes contributing to the formation of preneoplastic foci.
- **KE4: Selective clonal expansion of preneoplastic foci cells.** Fixation of DNA damage and/or mutations in tumor suppressor genes and/or oncogenes can lead to changes in gene expression (*i.e.*, decreased expression of tumor suppressor genes and increased expression of oncogenes) that facilitate clonal expansion of initiated cells, leading to the formation of hepatic foci and the apical outcome, as well as hepatocellular adenomas and carcinomas.

Several modulating factors associated with the PPARα MOA have also been proposed, including increases in reactive oxygen species (ROS) and activation of NF-κB (Corton et al., 2018). These modulating factors are not considered necessary to induce liver tumorigenesis but may modulate the dose-response behavior or the probability of inducing one or more KEs (Corton et al., 2014).

Evidence supporting a PPARα MOA for DEHP-induced liver tumors in rodents has previously been evaluated by Corton et al. (2018; 2014) in a manner consistent with EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005) and the IPCS *Mode of Action Framework* (IPCS, 2007). The Agency reviewed the PPARα MOA evaluation reported in the publications by Corton et al. (2018; 2014), both of which are publicly available. *Overall, EPA supports the conclusion reached by Corton et al. that the weight of evidence indicates that DEHP-induces liver tumors in rodents through a PPARα MOA*.

A brief summary of evidence supporting the PPARα MOA for DEHP-induced liver tumors from Corton et al. (2018; 2014)—including a summary of evidence for KEs in the PPARα MOA, dose-response concordance, temporal relationship, biological plausibility and coherence, and other carcinogenic MOAs—is provided.

Summary of Evidence for KEs in PPARα MOA in Rats and Mice

Table 4-7 provides a summary of the occurrence of KEs in the PPARα MOA in rats and mice. As can be seen from Table 4-7, DEHP has been shown to activate PPARα in hepatocytes (KE 1) and alter cell growth pathways (KE 2) in studies of both rats and mice. DEHP has also been shown to alter cell hepatocyte cell growth and survival in rats and mice (KE 3). In mice, both acute and chronic

hepatocellular proliferative responses have been observed; however, no studies have evaluated apoptosis in the liver following exposure to DEHP. In rats, DEHP has been shown to cause acute cell proliferation, with chronic cell proliferation being observed in some but not all studies. However, lack of a consistent chronic cell proliferative response is not inconsistent with the PPARα MOA. As discussed by Corton et al. (2018), PPARα activators tend to "produce transient increases in replicative DNA synthesis during the first few days or weeks of exposure followed by a return to baseline levels." Chronic or sustained proliferative responses for potent PPARα activators tend to be much lower compared to acute proliferative responses. Comparatively, DEHP is a relatively weak PPARα activator, and low levels of chronic hepatic cell proliferation may be difficult to detect over variable background levels, which may explain some of the inconsistencies in chronic cell proliferation. In rats, studies have also demonstrated that treatment with DEHP can result in a decrease in apoptosis (part of KE 3). For KE 4 (clonal expansion of preneoplastic foci), no data are available for DEHP in either rats or mice. Finally, as discussed earlier, a number of bioassays of rats and mice have consistently demonstrated the chronic oral exposure to DEHP results in hepatocellular adenomas and carcinomas.

Table 4-7. Occurrence of Key Events in PPARα MOA in Rats and Mice[a]

Species	KE1: PPARα Activation	KE2: Alteration of Cell Growth Pathways	KE3: Perturbations of Cell Growth and Survival			KE4: Clonal Expansion of Preneoplastic Foci	Apical Outcome: Liver Tumors
			Acute Cell Proliferation	Chronic Cell Proliferation	Apoptosis		
Rat	↑[b]	↑[c] or NC [d]	↑ [e]	↑ [f] or NC [g]	↓[h]		↑[c]
Mouse	↑[i]	↑[j]	↑[k]	↑[l]			↑[m]

[a] Table adapted from Figures 1 and 2 in (Corton et al., 2018) and Tables 5 and 6 in (Corton et al., 2014).
[b] (Corton and Lapinskas, 2005)
[c] (Seo et al., 2004; Isenberg et al., 2001; Thottassery et al., 1992; Conway et al., 1989; Cattley et al., 1987; Lake et al., 1987; Rao et al., 1987; Hinton et al., 1986; Kluwe et al., 1985; Kluwe et al., 1982)
[d] (Seo et al., 2004; Tomaszewski et al., 1990; Conway et al., 1989)
[e] (Hasmall and Roberts, 2000; Hasmall et al., 2000; Isenberg et al., 2000; Soames et al., 1999; Marsman et al., 1988; Busser and Lutz, 1987; Smith-Oliver and Butterworth, 1987)
[f] (Marsman et al., 1988)
[g] (Marsman et al., 1988; Cattley et al., 1987)
[h] (Hasmall et al., 2000)
[i] (Corton and Lapinskas, 2005; Bility et al., 2004; Isenberg et al., 2001; Issemann and Green, 1990)
[j] (Lee and Lim, 2011; Dwivedi et al., 1989)
[k] (Isenberg et al., 2000)
[l] (Ward et al., 1988)
[m] (David et al., 1999; Kluwe et al., 1985; Kluwe et al., 1982)

Dose-Response Concordance

Corton et al. (2014) investigated the dose-response relationships of several KEs in the PPARα MOA in the livers of male F344 rats in two studies. In the first study by David et al. (2000b; 1999) (summarized in Appendix B.1.2.2), F344 rats were fed diets containing 0, 100, 500, 2,500, and 12,500 ppm DEHP for up to 104 weeks (equivalent to 6, 29, 147, and 780 mg/kg-day for males). In this study, dose-response relationships of palmitoyl-CoA oxidase activity (PBOX) (a surrogate measure of PPARα activation), liver-to-body weights (as a surrogate measure for hepatocyte hyperplasia and hypertrophy), and incidence of combined hepatocellular adenomas and carcinomas were evaluated. In the second study by Isenberg et al. (2000), male F344 rats were fed diets containing 0, 1,000, 6,000, 12,000, and 20,000 ppm

(equivalent to ≈100, 600, 1,200, and 2,000 mg/kg-day) DEHP in the diet for 2 weeks, and hepatocyte DNA synthesis was evaluated.

In the study by David et al (2000b; 1999), PBOX was induced at 12,500 ppm (only dose evaluated; equivalent to ≈780−939 mg/kg-day) at study weeks 1, 2, and 13 weeks, with induction of PBOX being higher at weeks 2 and 13, compared to week 1. At 104 weeks, PBOX, was significantly induced at 2,500 ppm (equivalent to 147−182 mg/kg-day) and above. Similarly, relative liver weights were significantly increased at 500 ppm (equivalent to 29−36 mg/kg-day) and above after 1 week and at 2,500 ppm (equivalent to 147−182 mg/kg-day) and above after 2, 13, and 104 weeks of exposure. Combined hepatocellular adenomas and carcinomas were significantly increased at 2,500 ppm (equivalent to 147−182 mg/kg-day) and above. In the study by Isenberg et al. (2000), increases in periportal and centrilobular hepatic replicative DNA synthesis were observed after two weeks of exposure to doses of 6,000 ppm DEHP (equivalent to ≈600 mg/kg-day) and above. Further dose response modeling of these data sets by Corton et al. (2014) indicated that increases in PBOX, relative liver weight (EC50 [effect concentration at which 50% of test organisms exhibit an effect] = 2,994 ppm) and intercellular communication (EC50 = 2,591 ppm) occur at lower doses compared to combined hepatocellular adenomas and carcinomas (EC50 = 15,940 ppm), while induction of DNA synthesis occurred at doses coincident with liver tumors (EC50 = 21,140−25,640 ppm); see figure 5 of (Corton et al., 2014). Overall, these findings provide evidence of dose-response concordance, and evidence that the more proximal the KE is to the apical outcome (*i.e.*, hepatocellular adenoma and/or carcinoma), the greater the dose needed to induce the KE.

Temporal Relationship

Corton et al. (2014) also considered the temporal relationship of KEs in the PPARα MOA leading to liver tumors. Following oral exposure to DEHP, peroxisomal enzyme activity (a surrogate measure for PPARα activation [KE 1]) can be detected with days of treatment, and enzyme activity levels quickly reach a maximum that is maintained for the duration of treatment (Isenberg et al., 2001; Isenberg et al., 2000; David et al., 1999; Ganning et al., 1990; Barber et al., 1987; Mitchell et al., 1985). Temporal associations of cell proliferation and inhibition of apoptosis (KE 3) are not as well-established for DEHP. Acute proliferative responses in the liver have been reported as early as one to two weeks following administration of DEHP (Isenberg et al., 2001; David et al., 1999; James et al., 1998; Conway et al., 1989; Smith-Oliver and Butterworth, 1987; Mitchell et al., 1985). Low levels of chronic hepatocellular proliferation have been observed in F344 rats for up to one year (Marsman et al., 1988) and up to 40 weeks in B6C3F1 mice (Ward et al., 1988). In contrast, a significant increase in liver tumors were only observed after 2 years of exposure to DEHP (David et al., 2000b; David et al., 1999).

Providing further evidence of a temporal relationship, *in vivo* data on liver tumor incidence indicate that cessation of exposure may alter liver carcinogenesis. For example, in the study by David et al (2000b; 1999), there was a lower incidence of liver adenomas, carcinomas and combined adenomas and carcinomas in rats fed diets containing 12,500 ppm DEHP for 78 weeks followed by 26 weeks of control diet compared to rats maintained on diets containing 12,500 ppm DEHP for 104 weeks (Table_Apx B-4).

Overall, reasonably available data provide evidence of a temporal relationship between exposure to DEHP and tumorigenesis in the context of KEs in the PPARα MOA in rodents.

Strength, Consistency, and Specificity

Corton et al. (2014) also considered the strength, consistency, and specificity of the PPARα MOA. As discussed by Corton et al., activation of PPARα is the only KE that has high specificity for the PPARα

MOA. KE2, KE3, and KE4 have low specificity to the PPARα MOA, and are common to the neoplastic process in the rodent liver and may overlap in part with other MOAs in the liver, such as the CAR or aryl hydrocarbon receptor (AhR) MOAs. For DEHP, there is strong and consistent evidence from available *in vivo* studies of mice and rats that provide evidence that DEHP can activate PPARα (KE1), alter hepatocellular growth pathways (KE2), cause perturbations of cell growth and survival, including induce acute and chronic proliferative responses (KE3), and cause hepatocellular tumors (apical outcome).

Biological Plausibility and Coherence

Biological plausibility for the PPARα MOA is well-established and is discussed by Corton et al. (2018; 2014). Exposure to DEHP has been shown to result in sustained PPARα activation, increase hepatic cellular proliferation, decreased apoptosis in the liver, and cause hepatocellular adenomas and carcinomas in rats and mice. Furthermore, the PPARα MOA is consistent with the biology of carcinogenesis and tumor formation. Perturbations in cell growth and survival is an inherent characteristic of tumor formation and carcinogenesis. Alterations in cellular cell growth and survival can enhance the rate of fixation of DNA damage and/or mutations in tumor suppressor genes or activate oncogenes, leading to preferential proliferation of cells within preneoplastic foci, such as hepatocellular foci, leading to tumor formation and carcinogenesis.

Other Modes of Carcinogenic Action

Mutagenicity: As discussed in Section 3.1, the genotoxicity and mutagenicity of DEHP and its major metabolites MEHP and 2-EH have been evaluated extensively in various *in vitro* and *in vivo* test systems. Available genotoxicity studies have been reviewed by several authoritative and regulatory agencies. The U.S. CPSC (U.S. CPSC, 2010c), ECHA (ECHA, 2017a, b), EFSA (EFSA, 2019), and Australia NICNAS (NICNAS, 2010) have concluded that the overall evidence supports the conclusion that DEHP is non-genotoxic and non-mutagenic. Similarly, the ECB (ECJRC, 2008) and Environment Canada (1994) concluded that DEHP and its major metabolites (*i.e.*, MEHP and 2-EH) are not genotoxic or mutagenic. Similarly, NTP (2021b) has concluded "The consensus from published data is that DEHP shows limited evidence of genotoxic potential, and for the sporadic positive results that have been reported, the response is either weak, not reproducible, obtained in a nonstandard test system, or qualified to some degree by the authors." Most recently, ATSDR concluded that "The weight of evidence from these assays indicates that DEHP is not a potent genotoxin but may lead to genotoxic effects secondary to oxidative stress." Herein, EPA did not independently re-evaluate the extensive database of *in vitro* and *in vivo* genotoxicity studies of DEHP and its major metabolites. However, EPA agrees with the conclusions of ATSDR, NTP, and other authoritative and regulatory agencies that available evidence indicates that DEHP and its metabolites are not mutagenic, but that there is some limited evidence that DEHP may be weakly genotoxic inducing effects such as DNA damage and/or chromosomal aberrations. As noted by ATSDR, these effects may be secondary to oxidative stress.

Studies of PPARα-Null Mice: Several studies of DEHP have been conducted in *PPARα*-null mice (Ren et al., 2010; Eveillard et al., 2009; Ito et al., 2007a). Ito and colleagues. fed wild-type and *PPARα*-null male mice diets containing 0, 0.01, 0.05 percent DEHP (equivalent to ≈15 and 75 mg/kg-day) for 22 months (see Appendix B.1.4.4 for study summary). No significant increase in liver tumors was observed in wild-type mice, while a slight, yet statistically significant increase in combined hepatocellular adenomas and carcinomas, and cholangiocellular carcinomas was observed in 8 out of 31 high-dose *PPARα*-null mice. This result suggests MOAs other than PPARα may be operative in the liver and contribute to liver tumorigenesis. However, there are a number of limitations associated with the study by Ito et al. (2007a), which have been discussed extensively elsewhere (Corton et al., 2018; Corton et al., 2014). First, to achieve statistical significance, Ito and colleagues combined tumor types originating

from different cell types. It is inappropriate to combine hepatocellular adenomas and carcinomas with hepatoblastomas for purposes of determining statistical significance. However, a statistical re-analysis by Guyton et al. (2009) found that adenomas and combined adenomas and carcinomas were significantly increased in high-dose *PPARα*-null mice, addressing this limitation. A second source of uncertainty stems from the fact that no significant increase in liver tumors was observed in wild-type mice at either dose tested after 22 months, which complicates the interpretation of the small increase in liver tumors in *Ppara*-null mice. Furthermore, given the lack of liver tumors in wild-type mice, the small increase in liver tumors in *PPARα*-null mice may represent a chance finding. This is supported by the fact that aged *Ppara*-null mice are known to have increased incidence of spontaneous hepatocellular adenoma and carcinoma in the absence of chemical treatment compared to similarly aged wild-type mice (Howroyd et al., 2004). Spontaneous occurrence of liver tumors in *PPARα*-null mice appears to be related to increased hepatic lipid accumulation (steatosis) compared to wild-type mice due to decreased constitutive expression of lipid metabolizing enzymes (Kersten et al., 1999; Leone et al., 1999; Aoyama et al., 1998). The possibility remains that DEHP is contributing to the mechanism related to the increase in spontaneously occurring liver tumors. Another possibility is that DEHP is inducing liver tumors though another nuclear receptor, such as CAR in the absence of PPARα.

Gene expression changes in the liver have also been evaluated by microarrays in wild-type and *Ppara*-null mice gavaged with 0, 200, or 1,150 mg/kg-day DEHP for 4 days (Ren et al., 2010). A comparison of gene expression changes in the livers of wild-type and *PPARα*-null mice indicated that PPARα is required for approximately 94 percent of transcriptional changes. The remaining 6 percent of genes were predominantly involved in xenobiotic metabolism and are known to be targets of CAR or PXR. Additionally, CAR-regulated genes were more strongly induced by DEHP in *PPARα*-null mice compared to wild-type mice, which may indicate that in the absence of PPARα other nuclear receptors such as CAR become a dominant pathway for carcinogenesis (Ren et al., 2010). Similar results were obtained in an gene array study of 320 nuclear receptor target genes in the livers of male wild-type and male *PPARα*-null mice gavaged with 0, 20 or 200 mg/kg-day DEHP for 21 days (Eveillard et al., 2009). In this study, most DEHP-regulated genes in the liver were PPARα -dependent; however, several genes specifically regulated by CAR were identified.

Other Nuclear Receptors: Pregnane X receptor (PXR), CAR, and AhR are known to play a role in liver homeostasis and disease. Although their precise role, if any, in liver tumorigenesis in response to chronic exposure to DEHP is unknown. In addition to PPARα, DEHP has been shown to activate multiple nuclear receptors that may play a role in liver tumorigenesis. For example, DEHP has been shown to be a weak inducer of AhR activity *in vitro*. In an AhR-CALUX assay with transfected mouse hepatoma cells (Hepa1.12cR) exposed to concentrations of 1×10^{-10} to 1×10^{-4} M DEHP, AhR activity was induced only at the highest concentration of DEHP tested and was only induced 1.75-fold above the solvent control (Kruger et al., 2008). In another *in vitro* study, mouse 3T3-L1 fibroblasts were transfected with mouse or human PPARα, PPAR gamma (PPARγ) or PPAR beta (PPARβ) reporters and exposed to 3 to 200 µM concentrations of MEHP for 24 hours (Bility et al., 2004). MEHP was found to activate mouse and human PPARα (lowest activation concentration: 10 µM [mouse] and 30 µM [human]), mouse and human PPARγ (lowest activation concentration: 30 µM [mouse] and 10 µM [human]), as well as mouse (but not human) PPARβ (lowest activation concentration: 200 µM). DeKeyser et al. (2011) demonstrated that DEHP can activate human PXR as well as certain human CAR splice variants (*e.g.,* CAR2) in various *in vitro* cell models. Briefly, COS-1 cells were transfected with the 2B6-XREM-PBREM luciferase reporter and treated with 0 (0.1% DMSO vehicle control), 0.1, 1, or 10 µM DEHP for 48 hours. DEHP was found to be strong activator of human CAR2 (EC50 = 0.1 µM) and PXR (EC50 = 3.8 µM), but showed little to no activation of CAR1 or CAR3 splice variants (EC50 values could not be determined). Finally, Laurenzana et al. (2016) demonstrated that MEHP can activate

human CAR2 and PXR, as well as human PPARα, PPARβ, and PPARγ in several *in vitro* models. Briefly, COS-1 cells were transfected with the 2B6-XREM-PBREM luciferase reporter (for the CAR2, CAR3, and PXR assays) or the PPRE luciferase reporter (for the PPARα, PPARβ, and PPAR$_\gamma$ assays) and exposed to 0.1 to 100 µM MEHP for 24 hours. Treatment with MEHP activated the human CAR2 splice variant at 1 µM and above, PPAR$_\gamma$ at 10 µM and above, and human PXR, PPARα, and PPARβ at 100 µM, while no human CAR3 activity was detected at any concentration.

As discussed above, gene expression changes in the liver of mice gavaged with DEHP consistent with activation of CAR and PXR have also been noted in several *in vivo* studies (Ren et al., 2010; Eveillard et al., 2009). These *in vivo* studies of mice provide evidence that oral exposure to DEHP can activate CAR and PXR signaling pathways in the liver.

Cytotoxicity and Regenerative Proliferation: Cytotoxicity followed by regenerative proliferation is an established nongenotoxic MOA (Felter et al., 2018). However, available evidence of DEHP generally does not support this MOA for induction of liver tumors. The KEs for establishing a cytotoxic MOA are (1) the chemical is not DNA reactive; (2) evidence of cytotoxicity by histopathology (*e.g.,* the presence of necrosis and/or increased apoptosis); (3) evidence of toxicity by increased serum enzymes indicative of cellular damage that are relevant to humans; (4) presence of increased cell proliferation as evidenced by increased labeling index and/or increased number of hepatocytes; (5) demonstration of a parallel dose response for cytotoxicity and formation of tumors; and (6) reversibility upon cessation of exposure (Felter et al., 2018). As discussed in Section 3.1, EPA does not consider DEHP to be mutagenic or a direct-acting genotoxicant.

Evidence of increased cytotoxicity (as demonstrated by increased incidence of necrosis) has been observed inconsistently and infrequently across available studies of rats and mice, and only doses much higher than those that cause PPARα activation. For example, Berman et al. (1995) report increased incidence of hepatocellular necrosis in female F344 rats gavaged with 1,500 mg/kg-day DEHP for 1 and 14 days, but not at doses of 500 mg/kg-day or less. Zhang et al. (2017) report increased incidence of hepatocellular necrosis in male SD rats gavaged with 500 mg/kg-day DEHP for 15 weeks, but not at doses of 5 mg/kg-day or less. Finally, increased incidence of focal necrosis was observed in male and female B6C3F1 mice fed diets containing 1,209 mg/kg-day DEHP for 28-days, but not at doses of approximately 245 to 270 mg/kg-day (Hazleton, 1992). Given that hepatocellular necrosis has been observed inconsistently across studies of rodents and only at high doses ranging from 500 to 1,500 mg/kg-day, EPA does not consider available evidence of DEHP to support the cytotoxicity and regenerative proliferation MOA for liver tumorigenesis.

Uncertainties and Limitations

There are several limitations and uncertainties associated with the available data set for the PPARα MOA. First, no data are available for KE4 for rats or mice, which is a source of uncertainty. Another uncertainty is potential contribution to carcinogenesis by other nuclear receptors. DEHP and its metabolite MEHP have been shown to activate CAR, PXR, and to a lesser extent AhR *in vitro*, while transcriptomics studies have also demonstrated that DEHP can activate CAR and PXR signaling pathways *in vivo* in mice. However, the majority of transcriptional changes in these studies appear to attributable to PPARα, and to a lesser extent CAR and PXR (Ren et al., 2010; Eveillard et al., 2009). Despite remaining uncertainties, there is strong evidence to support the PPARα MOA. Available evidence indicates that DEHP is not mutagenic or a directly genotoxic (Section 3.1). Furthermore, other potential modes of carcinogenic action, such as activation of CAR, PXR, and AhR, are also non-genotoxic threshold MOAs.

4.3.1.1.2 Mode of Action for Pancreatic Acinar Cell Tumors (PACTs)

Some initial work has been done to establish the MOA for induction of PACTs through PPARα activation. Klaunig et al. (2003) proposed an initial MOA for induction of PACTs through PPARα activation in rat. In the proposed MOA, PACTs occur secondary to liver toxicity. However, little work has been done to refine the initially proposed MOA. The MOA for induction of PACTs proposed by Klaunig et al. involves four KEs. The proposed MOA and supporting evidence is discussed in detail in the publication by Klaunig et al. (2003), and is briefly summarized below.

- ***KE 1: Activation of PPARα in the liver.*** PPARα activation in the liver leads to a decrease in transcription of cholesterol 7α-hydroxylase (CYP7A1), which leads to a disruption of bile acid synthesis. Cholesterol 7α-hydroxylase is the first and rate-limiting enzyme in bile acid synthesis from cholesterol.
- ***KE 2a: Decreased bile acid flow.*** Treatment with certain PPARα activators such as WY 14,643 (WY) have been demonstrated to decrease bile acid flow in the liver, which in turn can increase cholecystokinin (CCK).
- ***KE2b: Altered bile acid composition.*** Treatment with several PPARα activators such as WY, clofibrate, and nafenopin have been shown to alter bile acid composition. Decreased bile acid flow (KE 2a) and/or altered bile acid composition (KE 2b) lead to increases in CCK release from mucosal cells in the intestine into the bloodstream.
- ***KE3: Cholestasis.*** Several PPARα activators such as WY, gemfibrozil, methylclofenopate, and tibric acid have been shown to produce clinical pathology indicative of cholestasis. Cholestasis is believed to occur as a consequence of KE 2a and KE 2b. Decreasing bile acid flow (KE 2a) and/or composition (KE 2b) have been shown to increase CCK levels. Bile acids are believed to enhance the effectiveness of trypsin, and thus decreased bile acid flow and altered bile acid composition are believed to reduce the effectiveness of trypsin, which in turn leads to an increase in monitor peptide binding to M(I) cells in the duodenal mucosa leading to increases in CCK release.
- ***KE4: Increased plasma CCK.*** Treatment with the PPARα activator WY has been shown to increase plasma CCK levels, which correlated with cholestasis (KE 3). Increase plasma CCK levels are thought to cause pancreatic acinar cell proliferation, which in turn leads to the apical outcome, PACTs.

Although an MOA has been proposed for PACTs, which involves an increase in CCK that drives proliferation of pancreatic acinar cells, little work has been done to refine this MOA. Furthermore, data for the KEs in the proposed MOA are generally not available for DEHP beyond evidence of PPARα activation in the liver (KE 1) and the apical outcome, PACTs, based on information provided in previous assessments of DEHP. EPA did not further evaluate evidence for DEHP supporting KEs in the MOA proposed by Klaunig et al. (2003).

Another possibility is that pancreatic tumors could arise through cytotoxicity and regenerative proliferation, which is another established nongenotoxic MOA (Felter et al., 2018). The KEs for establishing a cytotoxic MOA are (1) the chemical is not DNA reactive; (2) evidence of cytotoxicity by histopathology (*e.g.*, the presence of necrosis and/or increased apoptosis); (3) evidence of toxicity by increased serum enzymes indicative of cellular damage that are relevant to humans; (4) presence of increased cell proliferation as evidenced by increased labeling index and/or increased number of cells; (5) demonstration of a parallel dose response for cytotoxicity and formation of tumors; and (6) reversibility upon cessation of exposure (Felter et al., 2018). However, no necrosis or other evidence of cytotoxicity was observed in the pancreas of rats in any of the three available 2-year cancer bioassays

that reported increased incidence of PACTs (NTP, 2021b; David et al., 2000b; David et al., 1999), indicating that a cytotoxic MOA for pancreatic tumors is unlikely.

4.3.1.1.3 Mode of Action for Leydig Cell Tumors

Some initial work has been done to establish the MOA for induction of Leydig cell tumors for PPARα activators. Klaunig et al. (2003) proposed two potential pathways for induction of Leydig cell tumors by PPARα activators in the rat, both of which may contribute to Leydig cell tumor formation. As part of the first pathway, Leydig cell adenomas occur secondary to liver toxicity, and tumorigenesis is driven by increases in interstitial fluid estradiol and transforming growth factor alpha (TGFα) levels. In the second pathway, direct inhibition of testis testosterone biosynthesis leads to a disruption of the hypothalamic-pituitary-thyroid axis leading to an increase in Luteinizing hormone and Leydig cell tumors. However, little work been done to refine the two initially proposed pathways since 2003. The two proposed pathways for Leydig cell tumorigenesis and supporting evidence is discussed in detail in the publication by Klaunig et al. (2003), and is briefly summarized below.

Pathway 1 (Secondary to Liver Induction)

- ***KE 1: Activation of PPARα in the liver*.**
- ***KE 2a: Increased aromatase (CYP19A1).*** Aromatase is an enzyme that plays a role in converting androgens to estrogens. Several PPARα activators have been shown to increase hepatic aromatase, as well as estradiol levels, indicating induction of aromatase in Leydig cells.
- ***KE 2b: Decreased estradiol metabolism*.** Several PPARα activators such as clofibrate, gemfibrozil, and WY-14,643 have been shown to reduce estradiol metabolism, which leads to an increase in serum estradiol levels.
- ***KE 3: Increased serum estradiol levels*.** Increased serum estradiol levels may be due to increased expression of aromatase (KE 2a) and/or decreased estradiol metabolism (KE 2b).
- ***KE 4: Increased interstitial fluid estradiol.*** An increase in serum estradiol levels leads to an increase in interstitial fluid estradiol levels. Interstitial fluid bathes Leydig cells and seminiferous tubules leading to increased estradiol exposure for these cell types.
- ***KE 5: Increased transforming growth factor alpha (TGFα) levels in interstitial fluid.*** Increases in TGFα have been observed in the interstitial fluid for some PPARα activators.
- ***KE 6: Increased Leydig Cell Proliferation.*** TGFα has been shown to stimulate Leydig-cell proliferation, which can in turn lead to the apical outcome, Leydig cell tumors.

Pathway 2 (Direct Inhibition of Testosterone Biosynthesis at the Level of the Testis)

- ***KE 7: ↓ Testosterone biosynthesis*.**
- ***KE 8: Decreased testosterone levels.*** Several PPARα activators, including DEHP, have been shown to decrease testosterone levels due to decreases in testosterone biosynthesis.
- ***KE 9: Increased Luteinizing hormone levels.*** Inhibition of testosterone biosynthesis leads to a disruption of the hypothalamic-pituitary-thyroid axis, leading to increased Luteinizing hormone levels.
- ***KE 10: Leydig cell tumorigenesis*.** Increases in Luteinizing hormone is established to induce Leydig cell tumors.

Although an MOA has been proposed for Leydig cell tumors, little work has been done to refine this MOA, and EPA did not further evaluate evidence for DEHP supporting KEs in the MOA proposed by Klaunig et al. (2003).

Another possibility is that Leydig cell tumors could arise through cytotoxicity and regenerative proliferation, which is another established nongenotoxic MOA (Felter et al., 2018). The KEs for establishing a cytotoxic MOA are (1) the chemical is not DNA reactive; (2) evidence of cytotoxicity by histopathology (*e.g.*, the presence of necrosis and/or increased apoptosis); (3) evidence of toxicity by increased serum enzymes indicative of cellular damage that are relevant to humans; (4) presence of increased cell proliferation as evidenced by increased labeling index and/or increased number of cells; (5) demonstration of a parallel dose response for cytotoxicity and formation of tumors; and (6) reversibility upon cessation of exposure (Felter et al., 2018). However, no necrosis or other evidence of cytotoxicity was observed in the testis or Leydig cells of rats in any of the available 2-year cancer bioassays that reported increased incidence of Leydig cell tumors (NTP, 2021b; David et al., 2000b; David et al., 1999), indicating that a cytotoxic MOA for Leydig cell tumors is unlikely.

4.3.1.1.4 Inferences from Hypolipidemic Drugs and Other Prototypical PPARα Activators

Although there is uncertainty pertaining to the precise mechanisms underlying DEHP-induced PACTs and Leydig cell tumors, there is evidence to suggest that the tumor triad is a fingerprint of chronic PPARα activation in rats (Klaunig et al., 2003). For example, similar to DEHP, prototypical PPARα activators such as WY 14,643 (WY, also known as prinixic acid) and hypolipidemic drugs (*e.g.*, clofibrate, fenofibrate, gemfibrozil) that are commonly prescribed to humans to lower serum cholesterol and triglyceride levels have also been shown to induce the tumor triad in rats (Table 4-8), but not humans (discussed further below). Mechanistically, WY and these lipid-lowering agents operate through activation of PPARα. Notably, these drugs are commonly prescribed at doses several orders of magnitude higher than levels of exposure to DEHP for the general U.S. population based on NHANES urinary biomonitoring data (discussed further below).

Clofibrate (trade name Atromid-S), which was first approved for use as lipid-lowering agent in 1963, was discontinued in 2002 due to adverse effects unrelated to cancer (*i.e.*, gallstone formation). Methylclofenapate is a derivative of clofibrate that underwent clinical studies for use as a hypolipidemic agent but was never approved for use by the FDA. Fenofibrate (trade names Tricor, Antara, Lipofen, etc.) has been used as a lipid-lowering agent since 1975 and is one of the most commonly prescribed medications in the United States. In 2022, fenofibrate was prescribed over 7.8 million times and was the 88th most prescribed drug in the Unites States. (ClinCalc, 2024a). Maximum prescribed doses of fenofibrate are 200 mg/day, equivalent to a dose of 2.5 mg/kg-day for an 80 kg individual. Gemfibrozil (trade name Lopid) was approved for use as a lipid-lowering agent in 1982 and was the 231st most prescribed drug in the United States in 2022 with over 1.5 million prescriptions (ClinCalc, 2024b). Maximum prescribed doses of gemfibrozil are 1,200 mg/day, which equates to a dose of 15 mg/kg-day for an 80 kg individual. Notably, slightly higher doses of 30 mg/kg-day gemfibrozil have been shown to induce the tumor triad in rats (Table 4-8) but have no effect on cancer outcomes in humans (discussed further below). Comparatively, administered doses of fenofibrate and gemfibrozil are approximately three orders of magnitude higher than the 95th percentile DEHP daily intake estimate of 4.5 µg/kg-day for all NHANES participants surveyed in the most recent NHANES cycle between 2017 to 2018 (see EPA's *Environmental Media and General Population and Environmental Exposure for Diethylhexyl Phthalate (DEHP)* for further details (U.S. EPA, 2025c)). As can be seen from Table 4-8, clofibrate, methylclofenapate, fenofibrate, gemfibrozil and WY have all been demonstrated to induce the tumor triad in rats.

Several large retrospective epidemiological studies examined the relationships between chronic treatment with the hypolipidemic agents gemfibrozil and clofibrate, and liver cancer (reviewed in (Peters et al., 2005; Klaunig et al., 2003)). In two large studies, there was no reported elevated risk of mortality from liver cancer associated with over a decade of chronic use of these pharmaceuticals (Tenkanen et al., 2006; Huttunen et al., 1994; Frick et al., 1987). One possible exception is a cohort in which excess mortality due to a higher incidence of the malignant neoplasms of the "liver, gallbladder and intestines" was reported in clofibrate-treated subjects. However, death rates among the clofibrate-treated group for cancer were similar to the official mortality statistics for individuals from the same area; the number of observed cases of gastrointestinal cancers was very small; and importantly, there was no difference among groups in a follow-up analysis of the mortality trends in this cohort (WHO, 1978). A meta-analysis of 17 randomized placebo-controlled trials was carried out by Bonovas et al. (2012). The analysis included 44,929 participants with an average follow-up of 5.2 years from 4 trials for bezafibrate, 6 trials for clofibrate, 3 trials for fenofibrate, and 4 trials for gemfibrozil. Overall, the authors found that fibrates have no effect on cancer outcomes in humans. In summary, fibrate drugs have been on the market since 1977 without an apparent increase in cancer in people taking them chronically— even at doses approximately three orders of magnitude higher than phthalate exposure levels for the general U.S. civilian population based on NHANES biomonitoring data.

Collectively, studies of WY and hypolipidemic drugs, which are prototypical PPARα activators, provide evidence indicating that the tumor triad is a signature of PPARα activation and given that these hypolipidemic drugs have not been linked to cancer outcomes in humans, raise questions pertaining to the human relevancy of the tumor triad observed in rats following chronic exposure to DEHP.

Table 4-8. Summary of 2-Year Tumor Findings in Rats Administered Hypolipidemic Drugs

Drug	Exposure Route (Method); Duration; Species (Strain); Sexes Tested; Dose Levels (Reference[s])	Tumor Incidence (Number of Animals with Tumors/Number Examined by Dose Group)
Clofibrate	Oral (not specified); 2 years; Rat (Wistar); Males; 0, 200, or 400 mg/kg [(PDR, 1995) as reported in Table 35 of (Klaunig et al., 2003)]	Liver (Male): Positive liver tumor finding reported (incidence data not provided) Leydig cell tumor (Male): Positive liver tumor finding reported (incidence data not provided)
	Oral (dietary); 24−28 months; Rat (F344); Males; 0, 0.5% (v/w) (Reddy and Qureshi, 1979)	Liver (Male): 0/14, 10/11 (carcinoma) PACT (Male): 0/14, 2/11 (carcinoma)
	Oral (dietary); 72−97 weeks; Rat (F344); Males; 0, 0.5% (v/w) (Svoboda and Azarnoff, 1979)	Liver (Male): 0/25, 4/25 (carcinoma) PACT (Male): 0/25, 4/11 (combined adenoma and carcinoma)
Fenofibrate	Oral (not specified); 2 years; Rat (not specified); Male and Female; 0, 10, 45, or 200 mg/kg-day [(PDR, 2002) as reported in Table 35 of (Klaunig et al., 2003)]	Liver (Male): Positive tumor finding in high-dose group (incidence data not provided) Leydig cell tumor (Male): Positive tumor finding in high-dose group (incidence data not provided) PACT (Male): Positive tumor finding in high-dose group (incidence data not provided) Liver (Female): Positive tumor finding in high-dose group (incidence data not provided) PACT (Female): No tumors observed
Gemfibrozil	Oral (dietary); 2 years; Rat (SD); Males and Females; 0, 30, or 300 mg/kg (Fitzgerald et al., 1981)	Liver (Male): 1/50, 6/60, 23/50 (combined adenoma and carcinoma) Leydig cell tumor (Male): 1/50, 8/50, 17/50 PACT (Male): 0/50, 6/50, 2/50 Liver (Female): 9/50, 5/50, 3/50 (combined adenoma and carcinoma) PACT (Female): 0/50, 0/50, 0/50
Methylclofenapate	Oral (dietary); Rat (Wistar); 2 years; Males and Females; 0, 10, 50, or 250 ppm [(Tucker and Orton, 1995) as reported in Table 35 of (Klaunig et al., 2003)]	Liver (Male): 0/24, 0/24, 9/25, 22/23 (carcinoma) Leydig cell tumor (Male): 1/24, 3/24, 10/25, 9/23 PACT (Male): 2/24, 5/24, 6/25, 9/23 Liver (Female): 0/24, 1/24, 4/25, 20/24 (carcinoma) PACT (Female):0/24, 0/24, 1/25, 2/20

Drug	Exposure Route (Method); Duration; Species (Strain); Sexes Tested; Dose Levels (Reference[s])	Tumor Incidence (Number of Animals with Tumors/Number Examined by Dose Group)
WY-14,643	Oral (dietary); 2 years; Rat (CD); Males only; 0 or 50 ppm (reduced to 25 ppm on study day 301 due to increased mortality) (Biegel et al., 2001)	Liver (Male): 2/80, 17/67 (combined adenoma and carcinoma) Leydig cell tumor (Male): 0/80, 16/67 (adenoma) PACT (Male): 0/80, 25/67 (adenoma)

4.3.1.1.5 Uncertainties, Limitations, and Human Relevance

There are several limitations and uncertainties associated with the available data set for the occurrence of liver tumors in mice and rats, and PACTs and Leydig cell tumors in rats. First, there is uncertainty related to the precise mechanisms underlying PACTs and Leydig cell tumors in rats. Although initial MOAs that involve PPARα activation have been proposed for both tumor types (see Sections 4.3.1.1.2 and 4.3.1.1.3), little work has been done to refine the initially proposed MOAs. This uncertainty reduces EPA's confidence that DEHP causes PACTs and Leydig cell tumors through PPARα activation. However, inferences from hypolipidemic drugs help to address this uncertainty. For example, WY, a selective PPARα activator, and other hypolipemic drugs that reduce serum lipids by activating PPARα, also cause PACTs and Leydig cell tumors in rats, but, as discussed further below, not humans (see Section 4.3.1.1.4). Regardless, the possibility remains that mechanisms other than PPARα may play a role in the observed PACTs and Leydig cell tumors in rats, such as activation of other nuclear receptors.

Another source of uncertainty stems from the fact that not all phthalates induce the tumor triad in rats. As discussed further in subsequent sections of this document, chronic oral exposure to DINP induces liver tumors in mice and rats, but has not been shown to cause PACTs in F344 rats, SD rats, or B6C3F1 mice (see Section 4.3.4 and (U.S. EPA, 2025a)). Although, as discussed in (U.S. EPA, 2025a), one study of SD rats does provide some limited evidence of a carcinogenic response in the testis following chronic dietary exposure to DINP (Bio/dynamics, 1987), as demonstrated by a statistically significant increase in Leydig cell hyperplasia (incidence: 4/69 [5.8%] in control vs. 22/70 [31%] in high-dose (553 mg/kg-day) group); however, the incidence of Leydig cell tumors in this study was statistically non-significant (2/69 [2.9%] in controls vs. 7/70 [10%] in high-dose group). Chronic oral exposure to DIDP induces liver tumors in transgenic rasH2 male mice, but does not induce liver tumors, PACTs, or Leydig cell tumors in F344 rats (see Section 4.3.5 and (U.S. EPA, 2024a)). As will be discussed further in Section 4.3.2, chronic oral exposure to BBP induces PACTs in F344 rats but does not induce liver tumors or Leydig cell tumors in F344 rats. Finally, and as will be discussed further in Section 4.3.3, chronic dietary exposure to DBP induces PACTs in male SD rats, and there is some limited evidence of Leydig cell hyperplasia in male SD rats; however, statistically significant increases in Leydig cell tumors have not been observed, nor have liver tumors been observed following chronic exposure to DBP.

Some of the observed inconsistencies in induction of the tumor triad by phthalates may be explained by the strain of rat tested, doses tested, or differences in phthalate potencies to induce PPARα activation. For example, BBP and DIDP have only been evaluated for carcinogenicity in F344 rats (Section 4.3.3 and Section 4.3.5), which is a strain of rats that has a high (ranging from 86−87%) spontaneous background rate of Leydig cell tumors (Cook et al., 1999), making it difficult to detect treatment-related increases in this tumor type in this strain of rat (discussed further in Appendix C). In the one available study of DIDP with F344 rats (Cho et al., 2010; Cho et al., 2008), biomarkers of PPARα activation in the liver were increased after 12, but not 32 weeks of exposure, indicating that exposure to DIDP did not sustain PPARα activation, which may explain the lack of observed liver tumors and PACTs in this study (Section 4.3.5 and (U.S. EPA, 2024a)). Finally, compared to WY and other hypolipidemic drugs, phthalates are generally considered weak PPARα activators (Klaunig et al., 2003; Barber et al., 1987), though DEHP, DIDP, and DINP do appear to be more potent activators of PPARα *in vivo* in rats compared to BBP and DBP (Barber et al., 1987). Differences in potency for activating hepatic PPARα may account for differences in observed liver tumors, PACTs, and Leydig cell tumors across DEHP, DINP, DIDP, BBP, and DBP.

Another source of uncertainty is human relevance of tumors in the triad. Several panels have been convened to address the human relevancy of liver tumors in rodents occurring through a PPARα MOA

(Felter et al., 2018; Corton et al., 2014). These panels have generally concluded that the PPARα MOA is not relevant to humans or unlikely to be relevant to humans based on qualitative and quantitative differences between species. Consistent with the recommendations of previous panels, most SACC committee members during the July 2024 peer review meeting of DIDP and DINP supported the conclusion that liver tumors seen in rodents caused by a PPARα MOA are not likely to be or are not relevant to humans because "the preponderance of the evidence that PPARα activation in the human does not trigger, at any dose, the obligatory KEs that would lead to the liver tumors observed in rodents" (U.S. EPA, 2024d). Nevertheless, uncertainty and differing scientific opinions on the human relevance of the PPARα MOA for liver tumorigenesis remain, despite the related efforts of previous panels and workshops. Additionally, and as discussed above in Section 4.3.1.1.4, fibrate drugs have been on the market since 1977 without an apparent increase in cancer in people taking them chronically, even at doses approximately three orders of magnitude higher than phthalate exposure levels for the general U.S. civilian population based on NHANES biomonitoring data. These findings for fibrate drugs raise questions pertaining to the human relevance of observed liver tumors, PACTs, and Leydig cell tumors observed in rats chronically treated with DEHP.

4.3.1.1.6 Conclusions Regarding Tumor Triad

Despite some remaining uncertainties, the weight of scientific evidence indicates that the tumor triad is related to PPARα activation in rats following chronic exposure to DEHP and hypolipidemic drugs. Given that DEHP is not a direct acting mutagen or genotoxicant (Section 3.1), a non-linear threshold approach is supported for cancer risk assessment of the tumor triad for DEHP.

4.3.1.2 Uterine Tumors

There is some evidence for uterine tumors in female SD rats following chronic oral exposure to DEHP based on two studies by NTP (2021b).

In the first study, time-mated female SD rats were fed diets containing 0, 300, 1,000, 3,000, or 10,000 ppm DEHP throughout gestation and lactation starting on gestation day (GD) 6. At weaning on postnatal day (PND) 21, groups of 50 male and female F1 offspring were fed diets containing the same respective DEHP concentrations for 2 years. Received doses for female F1 offspring were 18, 62, 196, and 772 mg/kg-day during the 2-year phase of the study. At study termination, there was a significant trend in increased incidence of uterus endometrium adenocarcinoma and combined incidence of uterus adenoma, adenocarcinoma, squamous cell carcinoma, or squamous cell papilloma (Table 4-9). However, pairwise comparisons to the control were not statistically significant, and NTP characterized the uterine tumors as an equivocal finding. Although DEHP did not significantly affect female survival in any treatment group, and no DEHP-related clinical findings were observed, body weight gain was significantly lower in females of the 10,000 ppm group throughout the study, and terminal mean body weight for high-dose females was 32 percent lower than that of the concurrent control group, indicating exceedance of the maximum tolerable dose (MTD).

Table 4-9. Incidence of Uterine Tumors in SD Rats Chronically Exposed to DEHP (Perinatal and Postweaning Exposure Study) (NTP, 2021b) [a]

Tissue: Tumor Type	0 ppm	300 ppm	1,000 ppm	3,000 ppm	10,000 ppm
Adenoma [b f]	0/50	1/50	0/50	0/50	0/48
Adenocarcinoma (overall rate) [b g]	3/50 (6%)	0/50	1/50 (2%)	3/50 (6%)	6/48 (13%)
Adenocarcinoma (rate per litter) [c]	3/25 (12%)	0/25	1/25 (4%)	3/25 (12%)	6/25 (24%)
Adenocarcinoma (adjusted rate) [d]	7%	0%	2.4%	7%	16.4%
Rao-Scott-adjusted Poly-3 test [e]	p = 0.008	p = 0.147	p = 0.325	p = 0.653	p = 0.184
Squamous cell carcinoma (includes multiple) [h]	0/50	1/50	0/50	0/50	1/48
Squamous cell papilloma (includes multiple) [i]	0/50	0/50	0/50	1/50	0/48
Adenoma, adenocarcinoma, squamous cell carcinoma, squamous cell papilloma (combined) (overall rate) [j]	3/50 (6%)	1/50 (2%)	1/50 (2%)	3/50 (6%)	7/48 (15%)
Adenoma, adenocarcinoma, squamous cell carcinoma, squamous cell papilloma (combined) (rate per litter)	3/25 (12%)	1/25 (4%)	1/25 (4%)	3/25 (12%)	7/25 (28%)
Adenoma, adenocarcinoma, squamous cell carcinoma, squamous cell papilloma (combined) (adjusted rate)	7%	2.4%	2.4%	7%	19%
Rao-Scott-adjusted Poly-3 test [e]	p = 0.005	p = 0.325	p = 0.317	p = 0.651	p = 0.113

[a] Adapted from Table 17 in (NTP, 2021b).
[b] Number of animals with neoplasm or lesion per number of animals necropsied.
[c] Number of litters with neoplasm-bearing animals per number of litters examined at site.
[d] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality.
[e] Beneath the control incidence is the p-value associated with the trend test. Beneath the exposed group incidence are the p-values corresponding to pairwise comparisons between the control group and that exposed group. The Rao-Scott test adjusts the Poly-3 test (which accounts for differential mortality in animals that do not reach study termination) for within-litter correlation.
[f] Historical control incidence for all routes of 2-year studies (mean ± standard deviation): 1/350 (0.29% ± 0.76%); range: 0−2%.
[g] Historical control incidence: 20/350 (5.71% ± 3.35%); range: 2−10%.
[h] Historical control incidence: 2/350 (0.57% ± 1.51%); range: 0−4%.
[i] Historical control incidence: 0/350.
[j] Historical control incidence: 23/350 (6.57% ± 3.41%); range: 2−10%.

In the second study, male and female SD rats were fed diets containing 0, 300, 1,000, 3,000, or 10,000 ppm DEHP for 2 years (mean received doses: 17, 54, 170, and 602 mg/kg-day for males and 17, 60, 177, and 646 mg/kg-day for females) (see Appendix B.1.2.7 for full study summary). Survival of male and female rats to study termination in all treatment groups was commensurate with or greater than that of control rats, and no exposure-related clinical findings were observed in any treatment groups. Feed consumption by male and female rats was comparable to across treatment groups, with the exception of 21 percent lower feed consumption for high-dose males during study week 1. At study termination, high-dose male and female rat body weight was approximately 16 and 22 percent lower than respective controls, providing some indication of exceedance of the MTD for high-dose animals. As can be seen from Table 4-10, treatment with DEHP caused a significant increase in incidence of uterine endometrial adenocarcinomas and combined uterine adenoma, adenocarcinoma, squamous cell carcinoma, and squamous cell papilloma in high-dose female rats compared to concurrent controls. Furthermore, incidence of adenocarcinomas and combined adenoma, adenocarcinoma, squamous cell carcinoma, and

squamous cell papilloma in high-dose females was outside the range of NTP historical controls (see footnotes *e*–*i* in Table 4-10 below). A significant positive trend in incidence of uterine squamous cell papilloma was also observed; however, pairwise comparisons to the control were not significant. Additionally, chronic uterine inflammation was observed in the 300, 1,000, and 10,000 ppm groups compared to controls; however, the effect was not dose-related.

Table 4-10. Incidence of Uterine Tumors in SD Rats Chronically Exposed to DEHP in the Diet for 2 Years (NTP, 2021b) [a]

Tissue: Tumor Type	0 ppm	300 ppm	1,000 ppm	3,000 ppm	10,000 ppm
Inflammation, Chronic [b]	2/50	9/50*	6/50*	8/50	8/49*
Adenoma [b e]	0/50	1/50	0/50	0/50	0/49
Adenocarcinoma (overall rate) [b]	2/50 (4%)	2/50 (4%)	1/50 (2%)	4/50 (8%)	10/50 (20%)
Adenocarcinoma (adjusted rate) [c f]	4.7%	4.9%	2.4%	9%	23.8%
Poly-3 test [d]	p < 0.001	p = 0.678	p = 0.508N	p = 0.352	p = 0.011
Squamous cell carcinoma (includes multiple) [g]	0/50	1/50	0/50	2/50	1/49
Squamous cell papilloma (includes multiple) [h]	0/50	0/50	0/50	0/50	2/49
Adenoma, adenocarcinoma, squamous cell carcinoma, squamous cell papilloma (combined) (overall rate) [i]	2/50 (4%)	4/50 (8%)	1/50 (2%)	6/50 (12%)	13/50 (26%)
Adenoma, adenocarcinoma, squamous cell carcinoma, squamous cell papilloma (combined) (adjusted rate)	4.7%	9.7%	2.4%	13.4%	30.7%
Poly-3 test[d]	p < 0.001	p = 0.315	p = 0.508N	p = 0.145	p < 0.001

*Statistically significant at $p \leq 0.05$ by the Poly-3 test.
[a] Adapted from Table 28 in (NTP, 2021b).
[b] Number of animals with neoplasm or lesion per number of animals necropsied.
[c] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality.
[d] Beneath the control incidence is the p-value associated with the trend test. Beneath the exposed group incidence are the p-values corresponding to pairwise comparisons between the control group and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach study termination. A negative trend or a lower incidence in an exposure group is indicated by N.
[e] Historical control incidence for all routes of 2-year studies (mean ± standard deviation): 1/350 (0.29% ± 0.76%); range: 0–2%.
[f] Historical control incidence: 20/350 (5.71% ± 3.35%); range: 2–10%.
[g] Historical control incidence: 2/350 (0.57% ± 1.51%); range: 0–4%.
[h] Historical control incidence: 0/350.
[i] Historical control incidence: 23/350 (6.57% ± 3.41%); range: 2–10%.

In contrast to the findings of studies of SD rats, no significant increases in uterine tumors were observed in two chronic (2-year) dietary studies of female F344 rats at doses of up to 774 to 939 mg/kg-day (David et al., 2000b; David et al., 1999); two chronic (2-year) dietary studies of female B6C3F1 mice at doses of up to 1,325 to 1,458 mg/kg-day (David et al., 2000a; David et al., 1999; NTP, 1982a); one inhalation study and one intraperitoneal injection study of female Syrian golden hamsters (Schmezer et al., 1988); or in four studies of various strains of female transgenic mice (Mortensen et al., 2002; Eastin et al., 2001; Toyosawa et al., 2001) (see Table 4-5 and Table 4-6 for additional study details).

4.3.1.2.1 Conclusions for Uterine Tumors

EPA did not identify any human epidemiologic studies that evaluated the association between exposure to DEHP and uterine cancer (Section 4.1).

Across available carcinogenicity studies of DEHP, there is some limited evidence for uterine tumors in female SD rats. In the chronic perinatal and post-weaning exposure study by NTP (2021b), a significant trend in increased incidence of uterus endometrium adenocarcinoma and combined uterus adenoma, adenocarcinoma, squamous cell carcinoma, or squamous cell papilloma was observed; however, pairwise comparisons to the control were not statistically significant, and NTP characterized the uterine tumors as an equivocal finding. Furthermore, body weight gain was significantly lower in high-dose (772 mg/kg-day) females throughout the study, and terminal body weight was 32 percent lower than that of the concurrent control group, indicating exceedance of the MTD for high-dose females. In a second study by NTP (2021b), treatment with DEHP caused a significant increase in incidence of uterine endometrial adenocarcinomas and combined uterine adenoma, adenocarcinoma, squamous cell carcinoma, and squamous cell papilloma in high-dose (646 mg/kg-day) female rats compared to concurrent controls. Further incidence of these tumor types in high-dose females was outside the range of NTP historical controls. However, as with the first NTP study, high-dose female body weight gain and terminal body weight was significantly reduced by 22 percent compared to concurrent controls, providing some indication of exceedance of the MTD in the high dose group.

In contrast to the findings of studies of SD rats by NTP (2021b), no significant increases in uterine tumors were observed in two chronic (2-year) dietary studies of female F344 rats at doses of up to 774 to 939 mg/kg-day (David et al., 2000b; David et al., 1999); two chronic (2-year) dietary studies of female B6C3F1 mice at doses of up to 1,325 to 1,458 mg/kg-day (David et al., 2000a; David et al., 1999; NTP, 1982a); one inhalation study and one intraperitoneal injection study of female Syrian golden hamsters (Schmezer et al., 1988); or in four studies of various strains of female transgenic mice (Mortensen et al., 2002; Eastin et al., 2001; Toyosawa et al., 2001) (see Table 4-5 and Table 4-6 for additional study details).

At present, the precise mechanism(s) underlying the observed uterine neoplasms in female SD rats has not been established. However, the increase in uterine tumors may be linked to the observed decrease in female rat body weight in the high-dose group. As reviewed by Harleman et al. (2012), simple food restriction leading to reduced body weight gain is known to affect the incidence of pituitary tumors (decreasing tumor incidence), mammary gland tumors (decreasing tumor incidence), and uterine tumors (increasing tumor incidence) in female Wistar and SD rats. The decrease in incidence of pituitary and mammary tumors and increased incidence of uterine tumors is believed to be linked to lower sustained levels of prolactin in aging rats due to dietary restriction (Harleman et al., 2012). Consistent with a potential role for food restriction and reduced body weight, incidence of mammary gland adenocarcinoma and fibroadenoma and pituitary gland adenoma decreased in high-dose female rats, and incidence of uterine tumors increased in female high-dose rats fed diets containing DEHP for 2 years (2021b).[3] Similarly, in the chronic perinatal and post-weaning exposure study of DEHP (2021b), incidence of pituitary gland adenoma and carcinoma decreased and incidence of uterine tumors increased in high-dose females, while incidence of mammary gland tumors was low across control and all treatment groups. Although, the trends in incidence of pituitary, mammary gland, and uterine tumors are consistent with the mechanism (*i.e.*, dietary restriction leading to reduced prolactin levels) outlined by (Harleman et al., 2012), prolactin levels were not measured in either NTP (2021b) study of DEHP, so some uncertainty remains.

[3] See P05 – Incidence Rates of Non-Neoplastic Lesions by Anatomic Site (Systemic Lesions Abridged) at TR-601: Technical Report Pathology Tables and Curves (accessed December 3, 2025).

Overall, EPA considers there to be slight evidence for DEHP-induced uterine tumors. This is based on the fact that uterine tumors have only been observed in studies of female SD rats, but not in studies of female F344 rats, female B6C3F1 mice, or various transgenic strains of female mice. Furthermore, the uterine tumor response was equivocal in one of the two studies of SD rats, and in both studies of SD rats, uterine tumors were increased only at high-doses (646−772 mg/kg-day), which coincided with a 22 to 32 percent decrease in terminal body weight indicating exceedance of the MTD. Furthermore, there is some evidence that the increase in uterine tumors may be linked with reduced body weight and sustained low levels of prolactin (Harleman et al., 2012), and not due to direct DEHP exposure. Given the observed inconsistencies across species and strains of rats, unknown MOA, and the fact that uterine tumors only occurred at high doses that exceeded the MTD, EPA considers there to be too much scientific uncertainty to consider using data for uterine tumors to derive quantitative estimates of cancer risk for DEHP.

4.3.1.3 Mononuclear Cell Leukemia (MNCL)

There is some limited evidence for MNCL in F344 rats following chronic oral exposure to DEHP. David et al. (2000b; 1999) fed male and female F344 rats diets containing 0, 100, 500, 2,500, or 12,500 ppm DEHP for 2 years (equivalent to 6, 29, 147, and 780 mg/kg-day for males; 7, 36, 182, and 939 mg/kg-day for females). Increased incidence of MNCL was observed in male (but not female) rats in the 2,500 and 12,500 ppm dose groups compared to concurrent controls (Table 4-11). Furthermore, incidence of MNCL in 2,500 and 12,500 ppm males was outside the range of historical control data from the same laboratory conducting the study (historical control incidence: 128/420 [30%] for males and 82/424 [19%] for females over a 5-year period for rats of the same strain, age and from the same supplier).

Table 4-11. Incidence of MNCL in F344 Rats Administered DEHP Through the Diet for 2 Years (David et al., 2000b; David et al., 1999) [a]

Sex	0 ppm (M/F: 0/0 mg/kg-day)	100 ppm (M/F: 6/7 mg/kg-day)	500 ppm (M/F: 29/36 mg/kg-day)	2,500 ppm (M/F: 147/182 mg/kg-day)	12,500 ppm (M/F: 780/939 mg/kg-day)
Male	15/65 (23%)	13/50 (26%)	16/55 (27%)	32/65* (49%)	27/65* (42%)
Female	14/65 (22%)	17/50 (34%)	11/55 (20%)	16/65 (25%)	17/65 (26%)

[a] Asterisk (*) indicates statistically significant pairwise comparison to the control by Fisher exact test ($P \leq 0.05$) as determined by original study authors. Data from Table 5 of (David et al., 1999) and Tables 6 and 7 of (David et al., 2000b).

In contrast to the study by David et al. (2000b; 1999), increased incidence of MNCL was not observed in two other chronic (95−108 weeks) dietary studies of male F344 rats (Rao et al., 1990; Rao et al., 1987) or in one other chronic (2-year) dietary study of male and female F344 rats at doses as high at 674 to 774 mg/kg-day DEHP (NTP, 1982a). Although the two dietary studies by Rao et al. are limited by a small sample size of 8 to 14 rats per dose groups, which may have limited the sensitivity of the studies, the study by NTP (1982a) was well conducted and similar in design to the study by David et al. (*i.e.*, male and female F344 rats [50/sex/dose group] were fed diets containing 0, 6,000, or 12,000 ppm DEHP for 103 weeks). Therefore, even across studies of F344 rats, the evidence for increased incidence of MNCL following chronic dietary exposure to DEHP is inconsistent and limited to a single study of male (but not female) F344 rats.

In addition to the noted inconsistencies for MNCL across studies of F344 rats, MNCL was not observed in three chronic (95 to 159 weeks) dietary studies of male and female SD rats exposed to up to 678 to

772 mg/kg-day DEHP (NTP, 2021b; Voss et al., 2005); two chronic (2-year) dietary studies of male and female B6C3F1 mice exposed to up to 1,325 to 1,821 mg/kg-day DEHP (David et al., 2000a; David et al., 1999; NTP, 1982a); one inhalation study and one intraperitoneal injection study of Syrian golden hamsters (Schmezer et al., 1988); or in five studies of various strains of transgenic mice (Ito et al., 2007a; Mortensen et al., 2002; Eastin et al., 2001; Toyosawa et al., 2001) (see Table 4-5 and Table 4-6 for additional study details).

4.3.1.3.1 Conclusions for MNCL

There is some limited evidence for MNCL in F344 rats following chronic oral exposure to DEHP. In one study of male (but not female) F344 rats, the incidence of MNCL was significantly increased at doses of 147 and 780 mg/kg-day DEHP compared to concurrent controls and was outside the range of historical control incidence (David et al., 2000b; David et al., 1999). In contrast, MNCL was not observed in two other chronic (95−108 weeks) dietary studies of male F344 rats that were limited by small sample sizes (*i.e.*, included 8−14 rats/group) (Rao et al., 1990; Rao et al., 1987) or in one other well-conducted chronic (2-year) dietary study of male and female F344 rats at doses as high at 674 to 774 mg/kg-day DEHP (NTP, 1982a). Additionally, MNCL was not observed in three chronic (104−159 weeks) dietary studies of male and female SD rats exposed to up to 678 to 772 mg/kg-day DEHP (NTP, 2021b; Voss et al., 2005); two chronic (2-year) dietary studies of male and female B6C3F1 mice exposed to up to 1,325 to 1,821 mg/kg-day DEHP (David et al., 2000a; David et al., 1999; NTP, 1982a); one inhalation study and one intraperitoneal injection study of Syrian golden hamsters (Schmezer et al., 1988); or in five studies of various strains of transgenic mice (Ito et al., 2007a; Mortensen et al., 2002; Eastin et al., 2001; Toyosawa et al., 2001). Furthermore, there are significant scientific uncertainties related to the human relevance of MNCL in F344 rats (see Appendix C for a discussion of uncertainties).

In addition to the observed inconsistencies in MNCL across studies of DEHP, there is scientific uncertainty related to MNCL in F344 rats. As discussed further in Appendix C, MNCL is a spontaneously occurring neoplasm of the hematopoietic system that reduces the lifespan and is one of the most common tumor types occurring at a high background rate in the F344 strain of rat (also referred to as Fisher rat leukemia because it is so common) (Thomas et al., 2007). Historical control data from NTP have demonstrated an increase in the spontaneous background incidence of MNCL in untreated male and female F344 rats from 7.9 and 2.1 percent in males and females, respectively, in 1971 to 52.5 and 24.2 percent in males and females, respectively, from 1995 through 1998 (Thomas et al., 2007). Spontaneous incidence of MNCL in other strains of rat appear to be rare, and MNCL does not appear to occur naturally in mice (Thomas et al., 2007). The F344/N strain of rat was used in NTP 2-year chronic and carcinogenicity bioassays for nearly 30 years (King-Herbert et al., 2010; King-Herbert and Thayer, 2006). However, in the early 2000s, NTP stopped using the F344/N strain of rat, in large part because of high background incidence of MNCL and testicular Leydig cell tumors that confounded bioassay interpretation. NTP subsequently replaced the F344 strain of rats with the Harlan SD strain (King-Herbert et al., 2010; King-Herbert and Thayer, 2006).

Additional sources of uncertainty include lack of MOA information for induction of MNCL in F344 rats and uncertainty related to the human correlate to MNCL in F344 rats. Some researchers have suggested that based on the biological and functional features in the F344 rat, MNCL is analogous to large granular lymphocyte (LGL) in humans (Caldwell et al., 1999; Caldwell, 1999; Reynolds and Foon, 1984). There are two major human LGL leukemias, including CD3+ LGL leukemia and CD3− LGL leukemia with natural killer cell activity (reviewed in (Maronpot et al., 2016; Thomas et al., 2007)). Thomas et al. (2007) contend that MNCL in F344 rats shares some characteristics in common with aggressive natural killer cell leukemia (ANKCL) in humans, and that ANKCL may be a human correlate. However,

Maronpot et al. (2016) point out that ANKCL is extremely rare with less than 98 cases reported worldwide, and its etiology is related to infection with Epstein-Barr virus, not chemical exposure. This is in contrast to MNCL in F344 rats, which is a more common form of leukemia and is not associated with a viral etiology.

Given the limitations and uncertainties regarding MNCL in F344 rats discussed above, during the July 2024 peer review meeting of the DIDP and DINP human health hazard assessments, the SACC recommended that "the observation of an increased incidence of MNCL in a chronic bioassay employing the Fisher 344 rat should not be considered a factor in the determination of the cancer classification…" and "Most Committee members agreed that given the material presented in a retrospective review, MNCL and Leydig Cell Tumors, among other tumor responses in F344 rat carcinogenicity studies lack relevance in predicting human carcinogenicity (Maronpot et al., 2016)" (U.S. EPA, 2024d). Consistent with the recommendations of the SACC, EPA is not further considering MNCL as a factor in the determination of the cancer classification for DEHP.

4.3.1.4 Cancer Classification for DEHP

Under the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), EPA reviewed the weight of scientific evidence and in the draft DEHP cancer assessment concluded that DEHP is *not likely to be carcinogenic to humans* at doses below levels that do not result in PPARα activation. However, based on feedback from the SACC (U.S. EPA, 2025v), EPA has revised its cancer classification for DEHP to *not likely to be carcinogenic to humans*. Briefly, SACC reported the following:

> The SACC agreed with the sentiment of the classification (that is, humans were not likely to develop any of these tumors from exposure to DEHP), but not with the wording. The SACC preferred a wording of Not likely to be carcinogenic in humans for several reasons.
>
> The Agency has already acknowledged that exposure concentrations that result in any of the triad tumors are high (>100 mg/kg/day in a rodent), higher than humans might be exposed to under environmentally relevant conditions. However, the wording used suggests that cancer could occur if exposures were sufficiently high. This creates an uncertainty for exposed populations without defining the exposure levels.
>
> The Agency has reached the conclusion that DEHP is Not likely to be carcinogenic to humans based on exposure levels that "do not result in PPARα activation." This seems unrealistic since experimental data show that activation of the receptor can occur in the absence of tumors, and human tissue does possess PPARα. It would seem that the "Not likely to be carcinogenic to humans" based on experimental evidence showing that the carcinogenic effects observed in animals are not relevant to humans classification is most appropriate because (1) the Agency's perspective on the likelihood of exposures that are sufficiently high to trigger a carcinogenic event, and (2) the data suggesting a lack of or diminished response in humans (or human tissue) exposed to DEHP.

EPA's classification of *not likely to be carcinogenic to humans* is based on the following weight of scientific evidence considerations:

- Evidence indicates that DEHP is not a direct acting mutagen or genotoxicant (Section 3.1).
- The epidemiologic evidence is insufficient to identify an association between DEHP exposure and subsequent cancer outcomes in humans (Section 4.1.3).
- DEHP exposure resulted in treatment related liver tumors (adenomas and/or carcinomas combined) in male and female rats at doses greater than or equal to 147 mg/kg-day DEHP

(David et al., 2000b; David et al., 1999) and male and female mice at doses greater than or equal to 99 mg/kg-day DEHP (David et al., 2000a; David et al., 1999).

- DEHP exposure resulted in treatment related PACTs in male rats at doses greater than or equal to 170 mg/kg-day (NTP, 2021b).
- DEHP exposure resulted in treatment related Leydig cell tumors in male rats at doses greater than or equal to 300 mg/kg-day (Voss et al., 2005).
- Available MOA data for liver tumors in mice and rats support a non-genotoxic, threshold PPARα MOA (Section 4.3.1.1.1).
- Limited data are available that potentially indicate a role for other non-genotoxic, threshold MOAs, in the liver, including activation of other nuclear receptors (*e.g.,* CAR, PXR, AhR).
- Inferences from hypolipidemic drugs and other prototypical PPARα activators (*e.g.,* WY-14,643) provide evidence indicating that the tumor triad (*i.e.*, hepatocellular tumors, PACTs, and Leydig cell tumors) is a fingerprint of chronic PPARα activation in rats (Section 4.3.1.1.4). However, there is some scientific uncertainty, as not all PPARα activators induce the triad, which may be related to differences in potency for activating PAPRα. Regardless, some uncertainty remains that mechanisms other than PPARα activation may be involved in development of PACTs and Leydig cell tumors.
- Despite some remaining uncertainties, the weight of scientific evidence indicates that the tumor triad is related to PPARα activation in rats following chronic exposure to DEHP and hypolipidemic drugs.
- The non-cancer POD (NOAEL [no-observed-adverse-effect level]/LOAEL of 4.8/14 mg/kg-day) based on effects on the developing male reproductive system consistent with a disruption of androgen action and phthalate syndrome (see *Non-Cancer Human Health Hazard Assessment for Diethylhexyl Phthalate (DEHP)* (U.S. EPA, 2025h)) that was selected to characterize risk for acute, intermediate, and chronic exposures scenarios is expected to adequately account for all chronic toxicity, including carcinogenicity, which could potentially result from exposure to DEHP (discussed further in Appendix E).
- As discussed in Section 4.3.1.2.1, there is slight evidence for DEHP-induced uterine tumors in female SD rats, but not in studies of F344 female rats, B6C3F1 mice, or various transgenic strains of female mice. Furthermore, the uterine tumor response was equivocal in one of the two studies of SD rats, and in both studies of SD rats, uterine tumors were increased only at high-doses (646−772 mg/kg-day), which coincided with a 22 to 32 percent decrease in terminal body weight indicating exceedance of the MTD. Additionally, there is some evidence that the increase in uterine tumors may be linked with reduced body weight and reduced levels of prolactin (Harleman et al., 2012), and not due to direct DEHP exposure. Given the observed inconsistencies across species and strains of rats, unknown MOA, and fact that uterine tumors only occurred at high-doses that exceeded the MTD, EPA considers there to be too much scientific uncertainty to consider using data for uterine tumors to derive quantitative estimates of cancer risk for DEHP.
- As discussed in Section 4.3.1.3.1, given the limitations and uncertainties regarding MNCL in F344 rats, EPA is not considering MNCL as a factor in the determination of the cancer classification for DEHP. This is consistent with the recommendations of the SACC (U.S. EPA, 2024d).

4.3.2 Butyl Benzyl Phthalate (BBP)

BBP has been evaluated for carcinogenicity by a number of authoritative and regulatory agencies. As summarized in Table 4-12, BBP has been classified by the EPA's Integrated Risk Information System (IRIS) program as Group C (possible human carcinogen) (U.S. EPA, 1988a); as *Likely to be carcinogenic to humans* by the U.S. EPA PPRTV (Provisional Peer-reviewed Toxicity Value) program (U.S. EPA, 2002); by the International Agency for Research on Cancer (IARC) as Group 3 (not classifiable as to its carcinogenicity to humans) (IARC, 1999); and was considered, but not listed by the Office of Environmental Health Hazard Assessment under California's Proposition 65 for carcinogenicity because it "has not been clearly shown to cause cancer" (OEHHA, 2013b). Furthermore, BBP was not evaluated quantitatively for cancer risk in assessments by ECB (2007), ECHA (2017a, b), Australia NICNAS (2015a), Health Canada (ECCC/HC, 2020), and U.S. CPSC (2014).

The PPRTV program evaluated BBP for carcinogenicity under EPA's 1999 draft *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1999). Consistent with the guidelines available at the time of the assessment (U.S. EPA, 1999), BBP was assessed under an assumption of low-dose linearity. However, since the 2002 PPRTV assessment of BBP, the science has evolved, and EPA's current *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005) emphasize a data-first approach, rather than use of default options, stating:

> Rather than viewing default options as the starting point from which departures may be justified by new scientific information, these cancer *guidelines view a critical analysis of all of the available information that is relevant to assessing the carcinogenic risk as the starting point from which a default option may be invoked if needed to address uncertainty or the absence of critical information* [emphasis added].

Moreover, TSCA requires EPA to use the '"best available science"; therefore, the cancer classification and risk assessment approach for BBP has been re-evaluated.

Table 4-12. Summary of Cancer Classifications and Listings for BBP

Agency	Cancer Classification/ Listing
EPA (IRIS) (1988a)	Group C (possible human carcinogen)
IARC (1999)	Group 3 (not classifiable as to its carcinogenicity to humans)
EPA (PPRTV) (2002)	Likely to be carcinogenic to humans
California OEHHA (2013b)	Not listed as a carcinogen under Proposition 65 (has not been clearly shown to cause cancer)
IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; OEHHA = Office of Environmental Health Hazard Assessment; PPRTV = Provisional Peer-Reviewed Toxicity Values	

BBP has been evaluated for carcinogenicity by NTP in six chronic oral exposure studies, including five studies of F344/N rats and one of B6C3F1 mice (NTP, 1997a, b, 1982b). Available studies of BBP are summarized in Table 4-13 and Appendix B.2. Across available studies, statistically significant increases in MNCL and PACTs have been observed in F344/N rats. Additionally, slight, but statistically non-significant, increases in urinary bladder papilloma and/or carcinoma have been observed in female F344/N rats. No tumors were observed in one study of male and female B6C3F1 mice (NTP, 1997a). Evidence for MNCL, PACTs, and urinary bladder tumors is discussed further in Sections 4.3.2.1, 4.3.2.2, and 4.3.2.3, respectively, whereas EPA's cancer classification for BBP is provided in Section 4.3.2.4.

Table 4-13. Summary of Available Carcinogenicity Studies of BBP in Rodents

Brief Study Description	Tumor Type(s) Observed (Table Summarizing Tumor Incidence Data)
Studies of rats	
Male and female F344/N rats (50/sex/dose) fed 0, 6,000, or 12,000 ppm BBP for 103 weeks (equivalent to ≈300 and 600 mg/kg-day) (NTP, 1982b) (see Appendix B.2.2.1 for further study details).	- MNCL (females only) [a] (Table_Apx B-18)
Male F344/N rats (60/dose) fed 0, 3,000, 6,000, or 12,000 ppm BBP and female F344/N rats (60/dose) fed 0, 6,000, 12,000, or 24,000 ppm BBP for 2 years (equivalent to 120, 240, and 500 mg/kg-day [males]; 300, 600, and 1,200 mg/kg-day [females]) (NTP, 1997b) (see Appendix B.2.2.2 for further study details).	- PACTs (males only) (Table 4-14, Table_Apx B-19) - Transitional epithelium papilloma in urinary bladder (females only; not statistically significant) (Table 4-16, Table_Apx B-19)
Study 1 (*Ad Libitum* and Weight-Matched Control Protocol): Male F344/N rats (60/sex/dose) fed 0 or 12,000 ppm BBP, while female F344/N rats fed 0 or 24,000 ppm BBP in feed that was available *ad libitum* for 104 weeks. Two control groups were included: rats fed *ad libitum* and weight-matched controls (diet restricted such that mean body weight matched the dose group) (NTP, 1997a) (see Appendix B.2.2.3 for further study details). Study 2 (2-Year Restricted Feed Protocol): Male and female F344/N rats (60/sex/dose) were diet restricted to limit the mean body weight of the control group to ≈85% of controls fed *ad libitum* in study 1. BBP was administered at the same concentrations as in study 1 for 104 weeks (NTP, 1997a) (see Appendix B.2.2.4 for further study details). Study 3 (Lifetime Restricted Feed Protocol): Male and female F344/N rats (60/sex/dose) were diet restricted and administered BBP as described for studies 1 and 2 until survival fell to 20% (*i.e.*, 30 months for males, 32 months for females) (NTP, 1997a) (see Appendix B.2.2.5 for further study details).	- PACTs (males only) (Table 4-15, Table_Apx B-20, Table_Apx B-21) - Urinary bladder carcinomas/papilloma (females only; not statistically significant) (Table 4-17, Table 4-18, Table_Apx B-20, Table_Apx B-21)
Studies of mice	
Male and female B6C3F1 mice (50/sex/dose) fed 0, 6,000, 12,000 ppm BBP for 103 weeks (equivalent to 900 and 1,800 mg/kg-day) (NTP, 1982b) (see Appendix B.2.1.1 for further study details).	- None

[a] As described in Appendix B.2, male rats from this study were not evaluated for carcinogenicity because of high mortality rates that led study authors to terminate the study of male rats between study weeks 29 and 30.

4.3.2.1 Mononuclear Cell Leukemia (MNCL)

Statistically significant increases in the incidence of MNCL have been observed in one out of five studies of F344/N rats chronically exposed to BBP in the diet for 2 years. MNCL was not observed in one study of male or female B6C3F1 mice treated with up to 1,800 mg/kg-day BBP for 2 years (NTP, 1982b).

NTP (1982b) report a statistically significant increase in the incidence of MNCL in female F344/N rats treated with 600 mg/kg-day BBP in the diet for 2 years (Table_Apx B-18). In this study, MNCL was observed in 18/50 (36%) high-dose (600 mg/kg-day) female rats, compared to 7/49 (14%) of controls. Incidence of MNCL in high-dose females was outside the range of historical control data for female F344/N rats with "all leukemias" from the laboratory conducting the study (observed in 77/399 [19%]; range 12−24%). As described further in Appendix B.2, male rats from this study were not evaluated for carcinogenicity because of high mortality rates that led study authors to terminate the study of male rats between study weeks 29 and 30.

In contrast to the study by NTP (1982b), no increase in incidence of MNCL was observed in male F344/N rats treated with up to 500 mg/kg-day BBP or female F344/N rats treated with up to 1,200 mg/kg-day BBP for 2 years in a subsequent dietary study by NTP (1997b) (Table_Apx B-19). Notably, this study was similar in design and tested doses of BBP twice as high as those used in the first NTP study (*i.e.*, 1,200 vs. 600 mg/kg-day for female F344/N rats).

Clear treatment-related increases in MNCL were not observed in a series of three dietary restriction studies of F344/N rats reported by NTP (1997a). In the first study (*Ad Libitum* and Weight-Matched Control Protocol; Appendix B.2.2.3), incidence of MNCL was comparable between *ad libitum* fed control rats and BBP treated male (500 mg/kg-day) and female (1200 mg/kg-day) F344/N rats following 2 years of dietary exposure (MNCL reported in 60−62% of control and BBP-treated males and 38−42% for females). In contrast, lower incidence of MNCL was observed in weight-matched controls of both sexes (15/50 [30%] for males; 13/50 [26%] for females) (Table_Apx B-20). Furthermore, incidence of MNCL in BBP-treated rats of both sexes was reported by NTP to be within the historical control ranges for leukemia (all types) in untreated F344/N rats. In the second dietary restriction study of BBP with F344/N rats (2-year restricted feed protocol; Appendix B.2.2.4), no statistically significant increase in MNCL was observed in male or female rats treated with 500 and 1,200 mg/kg-day BBP, respectively, compared to controls (incidence: 21/50 [42%] in control vs. 27/50 [54%] in BBP-treated males; 16/50 [32%] in control vs. 18/50 [36%] in BBP-treated females) (Table_Apx B-21) (NTP, 1997a). Similarly, in the lifetime restricted feed study of BBP with F344/N rats (Appendix B.2.2.5), no statistically significant increase in MNCL was observed in male or female rats treated with 500 and 1,200 mg/kg-day BBP, respectively, compared to controls (incidence: 39/50 [78%] controls vs. 36/50 [72%] BBP-treated males; 29/50 [58%] controls vs. 39/50 [78%] BBP-treated females) (Table_Apx B-21) (NTP, 1997a).

4.3.2.1.1 Conclusions for MNCL

Increased incidence of MNCL was observed in one dietary study of female F344/N rats treated with 600 mg/kg-day BBP for 2 years (incidence in control and 600 mg/kg-day group: 7/49 [14%], 18/50 [36%]) (NTP, 1982b). In this study, incidence of MNCL in females at 600 mg/kg-day was outside of the range of NTP historical control data (observed in 77/399 female F344/N rats [19%]; range 12−24%). In contrast, treatment-related increases in MNCL were not observed in four other chronic dietary studies in which female F344/N rats dosed with up to 1,200 mg/kg-day BBP (a dose twice as high as the study in which MNCL was observed), four chronic dietary studies of male F344/N rats dosed with up to 500 mg/kg-day BBP, or in male or female B6C3F1 mice treated with up to 1,800 mg/kg-day BBP for 2 years (NTP, 1997a, b, 1982b).

In addition to the observed inconsistencies in MNCL across studies of BBP, there is scientific uncertainty related to MNCL in F344 rats. As discussed further in Appendix C, MNCL is a spontaneously occurring neoplasm of the hematopoietic system that reduces the lifespan and is one of the most common tumor types occurring at a high background rate in the F344 strain of rat (also referred

to as Fisher rat leukemia because it is so common) (Thomas et al., 2007). Historical control data from NTP have demonstrated an increase in the spontaneous background incidence of MNCL in untreated male and female F344 rats from 7.9 and 2.1 percent in males and females, respectively, in 1971 to 52.5 and 24.2 percent in males and females, respectively, from 1995 through 1998 (Thomas et al., 2007). Spontaneous incidence of MNCL in other strains of rat appear to be rare and MNCL does not appear to occur naturally in mice (Thomas et al., 2007). The F344/N strain of rat was used in NTP 2-year chronic and carcinogenicity bioassays for nearly 30 years (King-Herbert et al., 2010; King-Herbert and Thayer, 2006). However, in the early 2000s, NTP stopped using the F344/N strain of rat in large part because of high background incidence of MNCL and testicular Leydig cell tumors that confounded bioassay interpretation. NTP subsequently replaced the F344 strain of rats with the Harlan SD strain (King-Herbert et al., 2010; King-Herbert and Thayer, 2006).

Additional sources of uncertainty include lack of MOA information for induction of MNCL in F344 rats and uncertainty related to the human correlate to MNCL in F344 rats. Some researchers have suggested that based on the biological and functional features in the F344 rat, MNCL is analogous to LGL in humans (Caldwell et al., 1999; Caldwell, 1999; Reynolds and Foon, 1984). There are two major human LGL leukemias, including CD3+ LGL leukemia and CD3- LGL leukemia with natural killer cell activity (reviewed in (Maronpot et al., 2016; Thomas et al., 2007)). Thomas et al. (2007) contend that MNCL in F344 rats shares some characteristics in common with ANKCL in humans, and that ANKCL may be a human correlate. However, Maronpot et al. (2016) point out that ANKCL is extremely rare with less than 98 cases reported worldwide, and its etiology is related to infection with Epstein-Barr virus, not chemical exposure. This contrasts with MNCL in F344 rats, which is a more common form of leukemia and is not associated with a viral etiology.

Given the limitations and uncertainties regarding MNCL in F344 rats discussed above, during the July 2024 peer review meeting of the DIDP and DINP human health hazard assessments, the SACC recommended that "the observation of an increased incidence of MNCL in a chronic bioassay employing the Fisher 344 rat should not be considered a factor in the determination of the cancer classification…" and "Most Committee members agreed that given the material presented in a retrospective review, MNCL and Leydig Cell Tumors, among other tumor responses in F344 rat carcinogenicity studies lack relevance in predicting human carcinogenicity (Maronpot et al., 2016)" (U.S. EPA, 2024d). Consistent with the recommendations of the SACC, EPA is not further considering MNCL as a factor in the determination of the cancer classification for BBP.

4.3.2.2 Pancreatic Acinar Cell Tumors (PACTs)

Statistically significant increases in the incidence of pancreatic acinar cell hyperplasia, adenomas, and combined adenomas and carcinomas have been observed in two out of five studies of F344/N rats chronically exposed to BBP in the diet. Adenomas and carcinomas represent a progression from pre-neoplastic pancreatic acinar cell hyperplasia, and these pre-neoplastic and neoplastic findings are discussed further below. In contrast to studies of F344/N rats, pancreatic acinar cell hyperplasia, adenomas, and carcinomas were not observed in the one study of male or female B6C3F1 mice treated with up to 1,800 mg/kg-day BBP for 2 years (NTP, 1982b).

NTP (1997b) reports a statistically significant increase in the incidence of pancreatic acinar cell hyperplasia, adenomas, and combined adenomas and carcinomas in high-dose (500 mg/kg-day) male F344/N rats (Table 4-14). Notably, the increase in adenomas and carcinomas was outside the range of laboratory historical control data (see footnotes b to e in Table 4-14) and occurred at a dose that did not cause overt toxicity. That is, no effect on survival, clinical observations, or food consumption was observed in male rats treated with 500 mg/kg-day, though body weight was reduced 4 to 10 percent

throughout most of the study. In contrast, treatment-related increases in pancreatic acinar cell hyperplasia were not observed in high-dose female rats exposed to up to 1,200 mg/kg-day BBP, while a marginal, statistically non-significant increase in pancreatic acinar cell adenomas was observed in 2 out of 50 high-dose (1,200 mg/kg-day) females (Table 4-14).

Table 4-14. Incidence of Non-Neoplastic and Neoplastic Findings in the Pancreas of F344/N Rats Fed Diets Containing BBP for 2 Years (NTP, 1997b) [a]

Study Details	0 ppm	3,000 ppm (M/F: 120/NA mg/kg-d)	6,000 ppm (M/F: 240/300 mg/kg-d)	12,000 ppm (M/F: 500/600 mg/kg-d)	24,000 ppm (M/F: NA/1,200 mg/kg-d)
Male rats					
Number examined	50	49	50	50	NA
Pancreas, acinus, focal hyperplasia	4/50	7/49	9/50	12/50*	NA
Pancreas, acinus, adenoma [b]	3/50 (6%)	2/49 (4%)	3/50 (6%)	10/50* (20%)	NA
Pancreas, acinus, carcinoma [c]	0/50	0/49	0/50	1/50 (2%)	NA
Pancreas, acinus, adenoma or carcinoma [d]	3/50 (6%)	2/49 (4%)	3/50 (6%)	11/50* (22%)	NA
Female rats					
Number examined	50	NA	50	50	50
Pancreas, acinus, focal hyperplasia	1/50	NA	4/50	2/50	0/50
Pancreas, acinus, adenoma [e]	0/50	NA	0/50	0/50	2/50 (4%)

NA = Not applicable (dose not tested for this sex)
Asterisk (*) indicates significant difference ($P \leq 0.05$) from the control by the logistic regression test, as calculated by NTP.
[a] Incidence data from Tables 9 and 10 in (NTP, 1997b).
[b] Historical incidence for 2-year NTP feed studies with untreated controls (acinus, adenoma, males): 19/1,191 (1.6% ± 2.4%); range 0−10%.
[c] Historical incidence (acinus, carcinoma, males): 0/1,919 (0.0%).
[d] Historical incidence (acinus, adenoma or carcinoma, males): 19/1,191 (1.6% ± 2.4%); range 0−10%.
[e] Historical incidence (acinus, adenoma, females): 2/1,194 (0.2% ± 0.8%); range 0−4%.

Similar to the results of NTP (1997b), statistically significant increases in incidence of pancreatic acinar cell hyperplasia, adenomas, and combined adenomas and carcinomas have been observed in one of three dietary restriction studies of F344/N rats (NTP, 1997a). In the first study (*ad libitum* and weight-matched controls protocol) of BBP, statistically significant increases in the incidences of pancreatic acinar cell hyperplasia, adenomas, and combined adenomas and carcinomas were observed in high-dose (500 mg/kg-day) male F344/N rats compared to *ad libitum* and weight-matched controls (Table 4-15). Notably, the increase in pancreatic tumors occurred at a dose that did not cause overt toxicity. Treatment of male rats with BBP had no effect on survival, clinical observations, or food consumption compared to the *ad libitum* controls, though body weight was reduced approximately 8 percent in BBP-treated males throughout most of the study. Pancreatic acinar cell hyperplasia was not observed in high-dose female rats exposed to up to 1,200 mg/kg-day BBP, while a marginal, statistically non-significant increase in pancreatic acinar cell adenomas was observed in 2 out of 50 high-dose (1,200 mg/kg-day) females

(Table 4-15). In contrast, no significant increase in pancreatic acinar cell hyperplasia, adenomas, or carcinomas were observed in male or female rats treated with up to 500 and 1,200 mg/kg-day BBP, respectively, in the 2-year and lifetime restricted feed studies of BBP with F344/N rats (Table_Apx B-21).

Finally, no pancreatic acinar cell hyperplasia, adenomas, and carcinomas were observed in another 2-year dietary study of female F344/N rats dosed with up to 600 mg/kg-day BBP (Table_Apx B-18) (NTP, 1982b). However, the carcinogenicity of BBP was not assessed in male rats in this study due to high rates of mortality, which resulted in all male rats being sacrificed between study weeks 29 and 30.

Table 4-15. Incidence of Neoplasms and Non-Neoplastic Lesions in the Pancreas in F344/N Rats (*Ad Libitum* and Weight-Matched Controls Protocols) (NTP, 1997a) [a]

Lesion/ Tumor Type	*Ad Libitum*-Fed Control	Weight-Matched Control	12,000 ppm (Males) or 24,000 ppm (Females)
Male rats			
Number examined	50	50	50
Pancreas, Acinus, Focal Hyperplasia	4/50	2/50	12/50
Pancreas, Acinus, Adenoma	3/50 (6%)	0/50	10/50* (20%)
Pancreas, Acinus, Carcinoma	0/50	1/50 (2%)	1/50 (2%)
Pancreas, Adenoma or Carcinoma	3/50 (6%)	1/50 (2%)	11/50* (22%)
Female rats			
Number Examined	50	49	50
Pancreas, Acinus, Focal Hyperplasia	1/50 (2%)	0/49	0/50
Pancreas, Acinus, Adenoma	0/50	0/49	2/50 (4%)

Asterisk (*) indicates significant difference (P≤0.05) from the control by the logistic regression test, as calculated by NTP.
[a] Incidence data from Tables 3, 4, B1a, and B3a of (NTP, 1997a).
[b] Incidence of MNCL significantly increased compared to weight-matched, but not *ad libitum* fed controls.

4.3.2.2.1 Conclusions for Pancreatic Acinar Cell Tumors

Pancreatic adenomas and carcinomas (PACTs) represent a progression from pre-neoplastic pancreatic acinar cell hyperplasia. EPA did not identify any human epidemiologic studies that evaluated the association between exposure to BBP and pancreatic cancer (Section 4.1). As discussed in Section 4.3.2.1.1, clear treatment-related increases in pancreatic acinar cell hyperplasia and PACTs have been observed in two out of four studies of male F344/N rats treated with 500 mg/kg-day BBP (NTP, 1997a, b). Marginal (statistically non-significant) increases in PACTs were also observed in high-dose (*i.e.*, 1,200 mg/kg-day BBP) female F344/N rats in two studies (NTP, 1997a, b). Studies in which significant increases in hyperplasia and PACTs were observed utilized *ad libitum* feeding protocols and reported no evidence of overt toxicity in male F344/N rats. In contrast, no statistically significant treatment-related increases in acinar cell hyperplasia or PACTs were noted in male or female F344/N rats treated with 500 and 1,200 mg/kg-day BBP, respectively, in 2-year and lifetime restricted feed studies (NTP, 1997a). However, as discussed by NTP (1997a), feed and/or caloric restriction is known to suppress tumorigenesis in the pancreas (Roebuck et al., 1993; Roebuck et al., 1981); thus, dietary restriction may have prevented BBP-induced PACTs in the 2-year and lifetime dietary restriction studies.

As discussed previously in Section 4.3.1.1.2, a MOA for induction of PACTs has been proposed, which involves activation of PPARα in the liver (KE 1), leading to decreased bile acid flow (KE2a) and/or bile acid composition (KE 2b) in the liver leading to increased release of CCK into the bloodstream, which can lead to cholestasis (KE 3), and increased plasma CCK levels (KE 4), which in turn are believed to cause increased pancreatic acinar cell proliferation and PACT formation (apical outcome). Evidence supporting this MOA for BBP is limited, though BBP has been shown to activate PPARα in the liver. For example, Barber et al. (1987) demonstrate that BBP and other phthalates (*i.e.*, DEHP, DINP, DIDP, DBP) can all activate PPARα in the livers of male F344 rats exposed to each phthalate in the diet for 21 days based on induction of hepatic palmitoyl CoA oxidase activity. Although BBP (and DBP) was found to be a much weaker PPARα activator than DEHP, DINP, and DIDP. Similarly, Bility et al. (2004) demonstrated that monoester metabolites of BBP and other phthalates (*i.e.*, DEHP, DINP, DIDP, and DBP) can activate both mouse and human PPARα *in vitro*; however, for all five phthalates, human PPARα was less sensitive to activation compared to mouse PPARα. Notably, similar trends in potency for PPARα activation were observed *in vitro* with mouse PPARα as were observed *in vivo* with studies of rats, with BBP (and DBP) being a considerably weaker PPARα activator than DIDP, DINP, and DEHP.

As discussed previously in Section 4.3.1.1, PPARα activators have been shown to cause the tumor triad in rats (*i.e.*, liver tumors, PACTs, and Leydig cell tumors); however, no evidence of liver tumors or Leydig cell tumors were observed following chronic exposure to BBP in any study. The lack of liver tumors following chronic exposure to BBP may be related to the fact that BBP is a relatively weak PPARα activator compared to other phthalates such as DEHP (Section 4.3.1.1), DINP (Section 4.3.4), and DIDP (Section 4.3.5) that have been shown to cause liver tumors. Additionally, BBP has only been evaluated for carcinogenicity in F344/N rats, which have a high spontaneous background rate of testicular Leydig cell tumors (ranging from 86−87%), which reduces the ability of this strain of rat to detect treatment-related increases in this tumor type (see Appendix C for further discussion).

Another possibility is that pancreatic tumors could arise through cytotoxicity and regenerative proliferation, which is another established nongenotoxic MOA (Felter et al., 2018). The KEs for establishing a cytotoxic MOA are (1) the chemical is not DNA reactive; (2) evidence of cytotoxicity by histopathology (*e.g.*, the presence of necrosis and/or increased apoptosis); (3) evidence of toxicity by increased serum enzymes indicative of cellular damage that are relevant to humans; (4) presence of increased cell proliferation as evidenced by increased labeling index and/or increased number of cells; (5) demonstration of a parallel dose response for cytotoxicity and formation of tumors; and (6) reversibility upon cessation of exposure (Felter et al., 2018). However, no necrosis or other evidence of cytotoxicity was observed in the pancreas of rats in three available 2-year cancer bioassays (NTP, 1997a, b, 1982b), indicating that a cytotoxic MOA for pancreatic tumors is unlikely.

Overall, EPA considers there to be evidence to support the conclusion that chronic oral exposure to BBP induces PACTs in F344/N rats.

4.3.2.3 Urinary Bladder Papillomas and/or Carcinomas

Statistically significant increases in the incidence of transitional epithelium hyperplasia and statistically non-significant increases in papilloma and/or carcinoma in the urinary bladder have been observed in four out of five studies of female F344/N rats chronically exposed to BBP in the diet. Papillomas and carcinomas represent a progression from pre-neoplastic transitional epithelium hyperplasia, and these pre-neoplastic and neoplastic findings are discussed further below. In contrast to studies of F344/N rats, transitional epithelium hyperplasia, papilloma, and carcinoma were not observed in the one study of male or female B6C3F1 mice treated with up to 1,800 mg/kg-day BBP for 2 years (NTP, 1982b).

NTP (1997b) report a statistically significant increase in the incidence of transitional epithelium hyperplasia in high-dose (1,200 mg/kg-day) female (but not male) F344/N rats exposed to BBP for 2 years (Table 4-16). Transitional epithelium papillomas were observed in two high-dose females and one control female. Although the increase in papilloma was not statistically significant, the incidence in high-dose females was outside the range of NTP historical control data (historical incidence of transitional epithelium papilloma: 4/1,182 [0.3% ± 0.8%]; range 0−2%). No transitional epithelium papillomas were observed in male F344/N rats at any dose, nor were any transitional epithelium carcinomas observed at any dose for either sex. Although there was no evidence of overt toxicity or exceedance of the MTD for male rats at any dose, there was evidence of exceedance of the MTD for high-dose (1,200 mg/kg-day) female rats, as demonstrated by a 7 to 27 percent reduction in body weight throughout the duration of the study and a 27 percent reduction in body weight compared to controls at study termination.

Table 4-16. Incidence of Non-Neoplastic and Neoplastic Findings in the Urinary Bladder in F344/N Rats Fed Diets Containing BBP for 2 Years (*Ad Libitum* and Weight-Matched Controls Protocol) (NTP, 1997b) [a]

	0 ppm	3,000 ppm	6,000 ppm	12,000 ppm	24,000 ppm
Male rats					
Number examined microscopically	50	49	50	50	NA
Hyperplasia, transitional epithelium	0/50	0/49	0/50	2/50	NA
Papilloma, transitional epithelium	0/50	0/49	0/50	0/50	NA
Female rats					
Number examined microscopically	50	NA	50	50	50
Hyperplasia, transitional epithelium	4/50	NA	0/50	1/50	10/50*
Papilloma, transitional epithelium [b]	1/50 (2%)	NA	0/50	0/50	2/50 (4%)

NA = not applicable (dose not tested for this sex)
Asterisk (*) indicates significant difference ($p \leq 0.05$) from the control by the logistic regression test, as calculated by NTP.
[a] Incidence data from Tables 10 and A5 in (NTP, 1997b).
[b] Historical incidence (transitional epithelium papilloma): 4/1,182 (0.3% ± 0.8%); range 0−2%.

Similar to the results of NTP (1997b), statistically significant increases in incidence of transitional epithelium hyperplasia have been observed in three dietary restriction studies of female (but not male) F344/N rats dosed with 1,200 mg/kg-day for 24- to 32-months (Table 4-17 and Table 4-18) (NTP, 1997a). Increases in transitional epithelium hyperplasia were accompanied by slight, statistically non-significant increases in transitional epithelium papilloma and/or carcinoma (Table 4-17 and Table 4-18). In the first study (*ad libitum* and weight-matched controls protocol) of BBP, transitional epithelium papilloma was observed in two high-dose (1,200 mg/kg-day) females and one control female. No papilloma was observed in male rats treated with 500 mg/kg-day BBP (Table 4-17). In the second study (2-year restricted feed protocol), transitional epithelium papilloma was observed in two high-dose (1,200 mg/kg-day) female rats and one high-dose (500 mg/kg-day) male rat (Table 4-18). Finally, in the third study (lifetime restricted feed protocol), transitional epithelium papilloma and carcinoma were each observed in 1 male rat dosed with 500 mg/kg-day BBP, while transitional epithelium papilloma and carcinoma were observed in 2 and 4 high-dose (1,200 mg/kg-day) female rats, respectively, with papilloma noted in 1 of 49 control females (Table 4-18). However, across the three dietary restriction studies, the slight increases in incidence of transitional epithelium papilloma and/or carcinoma were not

statistically significant in any case. Across all three studies, there was no evidence of overt toxicity to suggest the MTD was exceeded for males, while terminal body weight for females dosed with 1,200 mg/kg-day BBP was reduced by 23 to 29 percent, indicating exceedance of the MTD.

Finally, no transitional epithelium hyperplasia or papilloma or carcinoma of the urinary bladder were observed in a 2-year dietary study of female F344/N rats dosed with up to 600 mg/kg-day BBP (NTP, 1982b). However, the highest achieved dose in this study was lower than the dose (*i.e.*, 1,200 mg/kg-day) shown to cause transitional epithelium hyperplasia or papilloma and carcinoma in other chronic dietary studies of female F344/N rats.

Table 4-17. Incidence of Non-Neoplastic and Neoplastic Findings in the Urinary Bladder in F344/N Rats Fed Diets Containing BBP for 2 Years (NTP, 1997a) [a]

	Lesion/Tumor Type	*Ad Libitum*-Fed Control	Weight-Matched Control	12,000 ppm (Males) or 24,000 ppm (Females)
Male rats				
Number examined		50	50	50
Urinary bladder	Hyperplasia, transitional epithelium	0/50	0/50	2/50
	Papilloma, transitional epithelium	0/50	0/50	0/50
Female rats				
Urinary bladder	Hyperplasia, transitional epithelium	4/50 (8%)	0/50	10/50 (20%)
	Papilloma, transitional epithelium	1/50 (2%)	0/50	2/50 (4%)

Asterisk (*) indicates significant difference ($p \leq 0.05$) from the control by the logistic regression test, as calculated by NTP.
[a] Incidence data from Tables 3, 4, B1a, and B3a of (NTP, 1997a).

Table 4-18. Incidence of Non-Neoplastic and Neoplastic Findings in the Urinary Bladder in F344/N Rats Treated with BBP (2-Year Restricted Feed and Lifetime Restricted Feed Protocols) (NTP, 1997a) [a]

	2-Year Restricted Feed Protocol		Lifetime Restricted Feed Protocol	
	0 ppm	12,000 ppm (Males) or 24,000 ppm (Females)	0 ppm	12,000 ppm (Males) or 24,000 ppm (Females)
Male rats				
Number examined	50	50	50	50
Hyperplasia	1/50	2/50	0/50	1/50
Papilloma	0/50	1/50 (2%)	0/50	1/50 (2%)
Carcinomas	0/50	0/50	0/50	1/50 (2%)
Female rats				
Number examined	50	50	49	50

	2-Year Restricted Feed Protocol		Lifetime Restricted Feed Protocol	
	0 ppm	12,000 ppm (Males) or 24,000 ppm (Females)	0 ppm	12,000 ppm (Males) or 24,000 ppm (Females)
Hyperplasia	0/50	14/50*	0/49	16/50*
Papilloma	0/50	2/50 (4%)	1/49 (2%)	2/50 (4%)
Carcinomas	0/50	0/50	0/49	4/50 (8%)
Papilloma or carcinoma (combined)	0/50	2/50 (4%)	1/49 (2%)	6/50 (12%)
Asterisk (*) indicates significant difference ($p \leq 0.05$) from the control by the logistic regression test, as calculated by NTP. [a] Incidence date from Table 7 of (NTP, 1997a).				

4.3.2.3.1 Conclusions for Urinary Bladder Tumors

Transitional epithelium papilloma and carcinoma in the urinary bladder represent a progression of pre-neoplastic transitional epithelium hyperplasia. As discussed in Section 4.3.2.3, consistent increases in pre-neoplastic transitional epithelium hyperplasia of the urinary bladder have been observed in four out of five studies of female F344/N rats chronically exposed to 1,200 mg/kg-day BBP (NTP, 1997a, b). In a 5th study, no transitional epithelium hyperplasia was observed in female F344/N rats; however, the highest achieved dose (*i.e.*, 600 mg/kg-day) in this study was lower than in the studies where hyperplasia was observed (NTP, 1982b). In contrast to studies of female F344/N rats, no significant increases in transitional epithelium hyperplasia have been observed in male F344/N rats treated with up to 500 mg/kg-day BBP in four studies (NTP, 1997a, b) or in male or female B6C3F1 mice treated with up to 1,800 mg/kg-day BBP for 2 years (NTP, 1982b).

Coinciding with increased incidence of transitional epithelium hyperplasia, marginal, statistically non-significant increases in urinary bladder papilloma and/or carcinoma were also observed in female F344/N rats treated with high doses of 1,200 mg/kg-day BBP in four studies (NTP, 1997a, b). It is plausible that the significantly increased incidences of hyperplasia noted in the urinary bladder at 1,200 mg/kg-day are proliferative responses that can lead to the marginal (not significant) increases in urinary bladder tumors. However, there are several sources of uncertainty associated with this tumor type. First, the marginal increase in urinary bladder tumors did not reach statistical significance in any study. Second, the MOA for induction of urinary bladder tumors in F344/N female rats is unknown. Lack of MOA information makes it difficult to determine human relevancy, and EPA did not identify any human epidemiologic studies that examined the link between BBP (or any other phthalate) exposure and incidence of bladder cancer. Third, this tumor type has only been observed in one sex of one species (*i.e.*, female F344/N rats). Significant increases in this tumor type were not observed in male or female B6C3F1 mice treated with up to 1,800 mg/kg-day BBP or male F344/N rats in four studies. However, the highest achieved dose in studies of male rats was 500 mg/kg-day, which is considerably lower than the dose (*i.e.*, 1,200 mg/kg-day) linked with marginal increases in urinary bladder tumors in female F344/N rats, which may explain the sex difference in tumor response. Finally, the marginal (not significant) increase in urinary bladder tumors in female rats only occurred at a very high-dose (*i.e.*, 1,200 mg/kg-day). In all four studies in which marginal increases in urinary bladder tumors were observed, there was evidence that the MTD was exceeded, as demonstrated by a 23 to 29 percent reduction in mean terminal body weight for female rats. Overall, EPA considers there to be too much scientific uncertainty to consider using data for urinary bladder tumors to derive quantitative estimates of cancer risk.

4.3.2.4 Cancer Classification for BBP

Under the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), EPA reviewed the weight of evidence for the carcinogenicity of BBP and in the draft BBP cancer assessment concluded that there is *Suggestive evidence of carcinogenic potential* of BBP in rodents based on evidence of pancreatic acinar cell adenomas in male and female F344 rats. However, based on the majority opinion of the SACC (U.S. EPA, 2025v), EPA has revised its cancer classification for BBP to *not likely to be carcinogenic to humans.* In briefly, the SACC stated

> As the PACTs were reported as significantly increased for male F344 rats in only two out of four studies (NTP 1997a; NTP 1997b), the Committee deems a dose-response assessment to be unnecessary and is supported by the lack of response for female rats and both male/female mice, especially since dose response is not apparent for male rats developing pancreas, acinus, adenoma, or carcinoma (Table 4-15; and NTP 1997a Table 4-16). NTP (1997b) characterized the results in the same way. Furthermore, the lack of dose response obviates the determination of a POD for PACTs; especially when reviewing the PACT incidence for BBP, DBP, and DEHP (NTP 1978; David et al. 2000a).
>
> The PACT arises secondary to PPARα agonism and appears to occur only at excessively high doses. Any uncertainties or scientific deficiencies in the data to support the complicated MOA are not needed to be filled since the PACT response would not occur without PPARα agonism. The constellation of tumors, regardless of tissue of origin, would be adequately prevented using the non-cancer POD as presented for individual, as well as cumulative, risk evaluations. Pancreatic acinar cell tumors are related to PPARα agonism secondary to the liver and would not be expected to be present at doses below which there is PPARα agonism (Klaunig et al. 2003).
>
> Considering EPA's proposed MOA for PACT, the Committee deemed it reasonable to attribute the lack of PACT response for BBP and DBP to the decreased PPARα activation for these phthalates. As stated in the Draft Cancer Human Health Hazard Assessment for DEHP, DBP, BBP, DIBP, DCHP: "Differences in potency for activating hepatic PPARα may explain differences in observed liver tumors, PACTs, and Leydig cell tumors across DEHP, DINP, DIDP, BBP, and DBP" (pg 62, line 1836). Thus, the majority of the Committee agrees that the carcinogenic classification of "Not Likely Carcinogenic" is applicable. Based on the data available, a minority of the Committee agrees that the EPA is correct in its characterization of the carcinogenic potential of BBP. Rationale includes inconsistent (at best) evidence of tumors across models and across the five epidemiological studies (exposure to multiple phthalates).

Further weight of scientific evidence considerations supporting EPA's determination of *not likely to be carcinogenic to humans* are listed below.

- BBP is not likely to be genotoxic or mutagenic (Section 3.2).
- The epidemiologic evidence is insufficient to identify an association between BBP exposure and subsequent cancer outcomes in humans (Section 4.1.3).

- Significant treatment-related increases in incidence of pancreatic acinar cell hyperplasia, adenomas, and combined adenomas and carcinomas have been observed in two chronic dietary studies of male F344/N rats treated with 500 mg/kg-day BBP for 2 years (NTP, 1997a, b). The MTD was not exceeded for high-dose males in either study (*i.e.*, no treatment-related effects on survival, food consumption, or clinical findings; mean body weight was within 10% that of concurrent controls both studies).
- Marginal (statistically non-significant) increases in incidence of pancreatic acinar cell adenomas were observed in two chronic dietary studies of female F344/N rats treated with 1,200 mg/kg-day BBP for 2 years (NTP, 1997a, b).
- In 2-year and lifetime dietary restriction studies of BBP, no significant increase in acinar cell hyperplasia or pancreatic tumors was observed in male or female F344/N rats exposed to 500 and 1,200 mg/kg-day BBP, respectively (NTP, 1997b). However, as discussed in Section 4.3.2.2, dietary restriction can suppress tumorigenesis in the pancreas (Roebuck et al., 1993; Roebuck et al., 1981) and therefore dietary restriction may have suppressed BBP-induced tumorigenesis in the pancreas in these studies.
- PACTs have also been observed in male rats following chronic oral exposure to toxicologically similar phthalates, including DEHP (Section 4.3.1.1) and DBP (Section 4.3.3.1). Occurrence of PACTs following chronic exposure to these phthalates increases EPA's confidence in the conclusion that chronic oral exposure to BBP causes PACTs in rats.
- Available mechanistic evidence indicates PACTs arise secondary to PPARα activation in the liver (Section 4.3.2.2).
- The non-cancer point of departure (POD) (NOAEL/LOAEL of 50/100 mg/kg-day) based on effects on the developing male reproductive system consistent with a disruption of androgen action and phthalate syndrome (see *Non-Cancer Human Health Hazard Assessment for BBP)* (U.S. EPA, 2025e)) that was selected to characterize risk for acute, intermediate, and chronic exposures scenarios is expected to adequately account for all chronic toxicity, including carcinogenicity, which could potentially result from exposure to BBP.
- No carcinogenic activity of BBP was observed in the one study of male and female B6C3F1 mice treated with up to 1,800 mg/kg-day BBP for 2 years (NTP, 1982b).

4.3.3 Dibutyl Phthalate (DBP)

DBP has previously been classified as Group D (not classifiable as to human carcinogenicity) by U.S. EPA (1987). Similarly, assessments of DBP by other regulatory and authoritative bodies have concluded that there is insufficient information to evaluate DBP for carcinogenicity—primarily due to the lack of 2-year rodent cancer bioassays at the time of the assessments (NICNAS, 2013; U.S. CPSC, 2010b; ECB, 2004). However, EPA identified two new cancer bioassays of DBP (NTP, 2021a) that have not been considered in previous assessments of DBP but are considered by EPA herein.

DBP has been evaluated for carcinogenicity in two chronic oral exposure studies (1 in rats, 1 in mice) published in an NTP Technical Report (NTP, 2021a), and an additional three studies of rats have evaluated DBP for carcinogenicity in the male reproductive system following gestational only exposure to DBP (Barlow et al., 2004; Mylchreest et al., 2000; Mylchreest et al., 1999). Available studies of DBP are summarized in Table 4-19. Across studies, there is some limited evidence for the carcinogenicity of DBP, which is based on marginal increases in the incidence of pancreatic acinar cell adenomas and statistically non-significant incidence of Leydig cell adenomas following chronic and/or gestational exposure to DBP. Evidence for acinar cell adenomas and Leydig cell adenomas following exposure to

DBP is discussed further in Sections 4.3.3.1 and 4.3.3.2, respectively, whereas EPA's cancer classification for DBP is provided in Section 4.3.3.3.

Table 4-19. Summary of Available Rodent Carcinogenicity Studies of DBP

Brief Study Description	Tumor Type(s) Observed
Studies of rats	
Time-mated female SD rats (50/sex/dose) fed 0, 300, 1,000, 3,000, or 10,000 ppm DBP during gestation and lactation. Postweaning F1 offspring fed diets with same concentrations of DBP for 2 years (equivalent to 16, 54, 152, and 510 mg/kg-day [males]; 17, 57, 169, and 600 mg/kg-day [females]) (NTP, 2021a).	- Pancreatic acinus adenomas (males only; equivocal response) - Leydig cell adenoma (not statistically significant)
Timed pregnant SD rats (9−10 per dose) gavaged with 0, 100, 250, or 500 mg/kg-day DBP from GD 12−21 and allowed to deliver litters naturally. Testes of male F1 offspring examined microscopically on PND 100 or PND 105 (Mylchreest et al., 1999).	- Leydig cell adenoma (not statistically significant)
Timed pregnant SD rats (19−20 per dose, 11 in high-dose group) gavaged with 0, 0.5, 5, 50, 100, or 500 mg/kg-day DBP from GD 12−21 and allowed to deliver litters naturally. Testes of male F1 offspring examined microscopically on PND 110 (Mylchreest et al., 2000).	- Leydig cell adenoma (not statistically significant)
Time-mated pregnant CRL:CD(SD)BR rats gavaged with 0, 100, or500 mg/kg-day DBP from GD 12−21 and allowed to deliver litters naturally. Male F1 offspring were necropsied at PND 180, PND 370, or PND 540 (Barlow et al., 2004).	- Leydig cell adenoma (not statistically significant)
Studies of mice	
Adult male and female B6C3F1/N mice (50/sex/dose) fed 0, 1,000, 3,000, or 10,000 ppm DBP for 2 years (equivalent to 112, 347, and 1,306 mg/kg-day [males]; 105, 329, and 1,393 mg/kg-day [females]) (NTP, 2021a).	- None

4.3.3.1 Pancreatic Acinar Cell Adenomas

Pancreatic acinar cell adenomas have been observed in one chronic dietary study of SD rats (NTP, 2021a). Time-mated (F_0) SD rats were fed diets containing 0, 300, 1,000, 3,000, or 10,000 ppm DBP starting on GD 6 (45−47 dams/dose) continuously throughout gestation and lactation. Dams were allowed to deliver litters naturally, and on PND4, litters were culled to eight pups per litter (4 per sex). At weaning on PND 21, 25 litters per dose group were selected, and 2 males and 2 females were selected and fed diets containing the same respective DBP concentrations for 2 years. Treatment with DBP had no effect on pregnancy status, maternal survival, gestation length, number of dams that littered, or maternal body weight and weight gain during gestation. During lactation, mean body weights were reduced less than six percent in dams of the high-dose group. Mean received doses of DBP in units of mg/kg-day during gestation, lactation, and the main 2-year study are shown in Table 4-20. In the 2-year rat study, no exposure-related effects on survival or clinical observations were reported; however, terminal body weight was reduced by 3.5 and 10.6 percent for high-dose males and females, respectively.

Table 4-20. Mean Received Doses (mg/kg-day) for Male and Female SD Rats Exposed to DBP Through the Diet (NTP, 2021a)

Study Phase	0 ppm	300 ppm	1,000 ppm	3,000 ppm	10,000 ppm
F_0 Dams on GD 6−21	0	22	72	214	740
F_0 Dams on PND 1−14	0	47	155	466	1,514
F_1 Males (2-year study)	0	16	54	152	510
F_1 Females (2-year study)	0	17	57	169	600

No treatment-related neoplastic lesions were observed in female rats at any dose. In males, there was a statistically significant dose-related trend in increased pancreatic acinus adenomas (Table 4-21). The incidence of acinus adenomas was slightly higher in the 10,000 ppm group compared to concurrent controls (overall incidence: 4/49 (8%) in control vs. 10/49 (20%) in 10,000 ppm group); however, the pairwise comparison to the concurrent control was not statistically significant. Two acinus carcinomas were observed in control males (2/49) but were not observed in any males treated with DBP. The incidence of acinus adenomas in the 10,000 ppm group was within NTP historical control range (0−28%) for studies of SD rats on the same diet. Time to first occurrence of acinus adenomas was unaffected by treatment with DBP (first observed in control and 10,000 ppm males on study days 676 and 684, respectively). The incidence of acinus hyperplasia was unaffected by treatment with DBP (Table 4-21). Under the conditions of the study, NTP concluded there was "equivocal evidence of carcinogenic activity of di-n-butyl phthalate (DBP) in male [SD] rats based on marginal increases in the incidence of pancreatic acinus adenomas" and "no evidence of carcinogenic activity of DBP in female [SD] rats at exposure concentrations of 300, 1,000, 3,000, or 10,000 ppm."

In contrast to the study of SD rats (NTP, 2021a), exposure to DBP did not induce pancreatic tumors (or any other neoplastic findings) in male and female B6C3F1/N mice administered up to 1,306 to 1,393 mg/kg-day DBP through the diet for 2 years (NTP, 2021a). Under the conditions of the study, NTP concluded that there was "no evidence of carcinogenic activity of DBP in male or female B6C3F1/N mice…"

Table 4-21. Incidence of Neoplastic and Non-Neoplastic Lesions of the Pancreas in Male Rats in the Perinatal and 2-Year Feed Study of DBP (NTP, 2021a) [a]

	0 ppm	300 ppm	1,000 ppm	3,000 ppm	10,000 ppm
N (# animals with tissue examined microscopically)	49	50	50	50	49
Acinus, hyperplasia	19 [b] (2.3)[c]	21 (2.1)	18 (2.1)	23 (2.0)	18 (2.1)
Acinus, Adenoma, Multiple	2	1	0	0	2
Acinus, adenoma (includes multiple) [d]					
Overall rate [e]	4/49 (8%)	4/50 (8%)	3/50 (6%)	1/50 (2%)	10/49 (20%)
Rate per litters [f]	4/25 (16%)	4/25 (16%)	3/25 (12%)	1/25 (4%)	9/25 (36%)
Adjusted rate [g]	9.7%	8.9%	6.8%	2.3%	24.1%
Terminal rate [h]	2/27 (7%)	3/38 (8%)	3/31 (10%)	1/34 (3%)	8/33 (24%)
First incidence (days)	676	565	729 (T)	729 (T)	684
Rao-Scott-adjusted Poly-3 test [i]	p = 0.010	p = 0.595N	p = 0.472N	p = 0.192N	p = 0.094

	0 ppm	300 ppm	1,000 ppm	3,000 ppm	10,000 ppm
Acinus, carcinoma [i]	2	0	0	0	0
Acinus, Adenoma or Carcinoma (Combined) [j]					
Overall rate	6/49 (12%)	4/50 (8%)	3/50 (6%)	1/50 (2%)	10/49 (20%)
Rate per litters	6/25 (24%)	4/25 (16%)	3/25 (12%)	1/25 (4%)	9/25 (36%)
Adjusted rate	14.3%	8.9%	6.8%	2.3%	24.1%
Terminal rate	2/27 (7%)	3/38 (8%)	3/31 (10%)	1/34 (3%)	8/33 (24%)
First incidence (days)	611	565	729 (T)	729 (T)	684
Rao-Scott-adjusted Poly-3 test	p = 0.024	p = 0.349N	p = 0.243N	p = 0.072N	p = 0.217

(T) = terminal euthanasia
[a] Adapted from Table 13 in (NTP, 2021a)
[b] Number of animals with lesion
[c] Average severity grade of lesions in affected animals in parentheses: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked.
[d] Historical control incidence for all routes of 2-year studies (mean ± standard deviation): 60/488 (11.58% ± 9.25%); range: 0%–28%.
[e] Number of animals with neoplasm per number of animals necropsied.
[f] Number of litters with tumor-bearing animals per number of litters examined at anatomical site.
[g] Poly-3-estimated neoplasm incidence after adjustment for intercurrent mortality.
[h] Observed incidence at study termination.
[i] Beneath the control incidence is the p-value associated with the trend test. Beneath the exposed group incidences are the p-values corresponding to pairwise comparisons between the control group and that exposed group. The Rao-Scott test adjusts the Poly-3 test, which accounts for differential mortality in animals that do not reach study termination, for within-litter correlation. A negative trend or a lower incidence in an exposure group is indicated by N.
[j] Historical control incidence: 4/488 (0.8% ± 1.42%); range: 0–4%.
[k] Historical control incidence: 62/488 (12.03% ± 9.16%); range: 0–28%.

4.3.3.1.1 Conclusions on Pancreatic Acinar Cell Tumors

PACTs represent a progression from pre-neoplastic pancreatic acinar cell hyperplasia. EPA did not identify any human epidemiologic studies that evaluated the association between exposure to DBP and pancreatic cancer (Section 4.1). Pancreatic acinar cell adenomas have been observed in one chronic dietary study of DBP with a male SD rats at doses that did not result in overt toxicity (NTP, 2021a). Treatment with DBP caused a significant trend in increased incidence of pancreatic acinar cell adenomas in male SD rats fed diets containing DBP for 2 years; however, pairwise comparisons to concurrent controls were not statistically significant (incidence of adenomas in control and 10,000 ppm (equivalent to 510 mg/kg-day) groups: 4/49 [8%], 10/49 [20%]). Incidence of pancreatic acinar cell adenoma in high-dose males was within NTP historical control range (0−28%), and treatment with DBP did not reduce the time to onset of pancreatic tumors in high-dose male rats (days to first incidence: 676 vs. 684). Furthermore, treatment with DBP did not increase the incidence of pancreatic acinar cell hyperplasia, which is a preneoplastic lesion that precedes tumorigenesis in the pancreas. Overall, NTP concluded there was “equivocal evidence” of carcinogenic activity of DBP in male rats based on the observed pancreatic acinar cell tumors.

As discussed previously in Section 4.3.1.1.2, a MOA for induction of PACTs has been proposed, which involves activation of PPARα in the liver (KE 1), leading to decreased bile acid bile acid flow (KE2a) and/or bile acid composition (KE 2b) in the liver leading to increased release of CCK into the bloodstream, which can lead to cholestasis (KE 3) and increased plasma CCK levels (KE 4), which in turn are believed to cause increased pancreatic acinar cell proliferation and PACT formation (apical

outcome). Evidence supporting this MOA for DBP is limited, though DBP has been shown to activate PPARα in the liver. For example, Barber et al. (1987) demonstrate that DBP and other phthalates (*i.e.*, DEHP, DINP, DIDP, BBP) can all activate PPARα in the livers of male F344 rats exposed to each phthalate in the diet for 21 days based on induction of hepatic palmitoyl CoA oxidase activity. Although DBP (and BBP) was found to be a much weaker PPARα activator than DEHP, DINP, and DIDP. Similarly, Bility et al. (2004) demonstrated that monoester metabolites of DBP and other phthalates (*i.e.*, DEHP, DINP, DIDP, BBP) can activate both mouse and human PPARα *in vitro*; however, for all five phthalates, human PPARα was less sensitive to activation compared to mouse PPARα. Notably, similar trends in potency for PPARα activation were observed *in vitro* with mouse PPARα as were observed *in vivo* with studies of rats, with DBP (and BBP) being a considerable weaker PPARα activator than DIDP, DINP and DEHP. As discussed previously in Section 4.3.1.1, PPARα activators have been shown to cause the tumor triad in rats (*i.e.*, liver tumors, PACTs, and Leydig cell tumors); however, no evidence of liver tumors were observed following chronic exposure to DBP in mice or rats. The lack of liver tumors following chronic exposure to DBP may be related to the fact that DBP is a relatively weak PPARα activator compared to other phthalates such as DEHP (Section 4.3.1.1), DINP (Section 4.3.4), and DIDP (Section 4.3.5) that have been shown to cause liver tumors. As will be discussed further in Section 4.3.3.2, there is some limited evidence for a carcinogenic response in the testis.

Another possibility is that pancreatic tumors could arise through cytotoxicity and regenerative proliferation, which is another established nongenotoxic MOA (Felter et al., 2018). The KEs for establishing a cytotoxic MOA are (1) the chemical is not DNA reactive; (2) evidence of cytotoxicity by histopathology (*e.g.*, the presence of necrosis and/or increased apoptosis); (3) evidence of toxicity by increased serum enzymes indicative of cellular damage that are relevant to humans; (4) presence of increased cell proliferation as evidenced by increased labeling index and/or increased number of cells; (5) demonstration of a parallel dose response for cytotoxicity and formation of tumors; and (6) reversibility upon cessation of exposure (Felter et al., 2018). However, no necrosis or other evidence of cytotoxicity was observed in the pancreas of rats in the available 2-year cancer bioassay (NTP, 2021a), indicating that a cytotoxic MOA for pancreatic tumors is unlikely.

In contrast to the study of male SD rats, no PACTs (or any other neoplastic findings) were observed in the one study of male and female B6C3F1 mice exposed to up to 1,306 to 1,393 mg/kg-day DBP through the diet for 2 years or in female SD rats exposed to up to 600 mg/kg-day DBP through the diet for 2 years (NTP, 2021a).

Overall, EPA considers there to be limited evidence to support the conclusion that chronic oral exposure to DBP causes pancreatic tumors in rats. However, read-across from other toxicologically similar phthalates (*i.e.*, DEHP [Section 4.3.1.1] and BBP [Section 4.3.2.1.1]) that induce pancreatic acinar cell tumors in rats provides additional evidence to support the conclusion that phthalates, including DBP, can cause pancreatic acinar cell adenomas in rats.

4.3.3.2 Leydig Cell Adenomas

Leydig cell hyperplasia and/or adenomas have been reported in four studies of SD rats (NTP, 2021a; Barlow et al., 2004; Mylchreest et al., 2000; Mylchreest et al., 1999), but not in male B6C3F1 mice dosed with up to 1,306 mg/kg-day DBP for 2 years (NTP, 2021a). In the first study of SD rats by NTP (2021a), which was described previously in Section 4.3.3.1, a statistically significant increase in diffuse and focal interstitial cell hyperplasia was observed in high-dose males (10,000 ppm in the diet, equivalent to 510 mg/kg-day) compared to concurrent control males (incidence of focal hyperplasia: 11/50 [22%] for high-dose males vs. 1/49 [2%] for controls; Table 4-22). A slight, statistically non-

significant, increase in interstitial cell tumors was also observed, but without clear relationship to dose (Table 4-22).

Table 4-22. Incidence of Interstitial Cell Hyperplasia and Adenomas of the Testis in Male Rats in the Perinatal and 2-Year Feed Study of DBP (NTP, 2021a) [a]

	0 ppm	300 ppm	1,000 ppm	3,000 ppm	10,000 ppm
N (# animals with tissue examined microscopically)	49	50	50	47	50
Interstitial cell, hyperplasia, diffuse, bilateral [d]	0**	0	1[b] (2.0) [c]	0	9** (2.2)
Interstitial cell, hyperplasia, focal (includes bilateral) [d]	1* (3.0)	7* (1.6)	5 (1.2)	3 (1.7)	11** (1.5)
Testis, adenoma					
Overall rate [e]	2/49 (4%)	5/50 (10%)	1/50 (2%)	4/47 (9%)	5/50 (10%)
Rate per litters [f]	2/25 (8%)	5/25 (20%)	1/25 (4%)	4/25 (16%)	4/25 (16%)
Adjusted rate [g]	4.9%	11.2%	2.2%	9.8%	12%
Terminal rate [h]	2/27 (7%)	4/38 (11%)	0/31 (0%)	4/32 (13%)	4/33 (12%)
First incidence (days)	729 (T)	685	621	729 (T)	595
Rao-Scott-adjusted Poly-3 test [i]	P = 0.214	P = 0.287	P = 0.492N	P = 0.362	P = 0.255

(T) = terminal euthanasia.
[a] Adapted from Table 15 in (NTP, 2021a) and P08: Statistical Analysis of Primary Tumors
[b] Number of animals with lesion,
[c] Average severity grade of lesions in affected animals in parentheses: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked.
[d] Statistical significance for the vehicle control group indicates a significant trend test, while statistical significance for an exposure group indicates a significant pairwise test compared to the vehicle control group. * indicates statistical significance ($p \leq 0.05$) from the vehicle control group by the Rao-Scott adjusted Poly-3 test; **$p \leq 0.01$.
[e] Number of animals with neoplasm per number of animals necropsied.
[f] Number of litters with tumor-bearing animals per number of litters examined at anatomical site.
[g] Poly-3-estimated neoplasm incidence after adjustment for intercurrent mortality.
[h] Observed incidence at study termination.
[i] Beneath the control incidence is the p-value associated with the trend test. Beneath the exposed group incidences are the p-values corresponding to pairwise comparisons between the control group and that exposed group. The Rao-Scott test adjusts the Poly-3 test, which accounts for differential mortality in animals that do not reach study termination, for within-litter correlation. A negative trend or a lower incidence in an exposure group is indicated by N.

Three studies, all of similar design and conducted by the same laboratory (*i.e.*, the Chemical Industry Institute of Toxicology, CIIT), have reported slight, statistically non-significant increases in Leydig cell adenomas following gestation only exposure to DBP in SD rats. In the first study, Mylchreest et al. (1999) gavaged timed pregnant SD rats (9−10/dose) from GD 12 to 21 with 0, 100, 250, and 500 mg/kg-day DBP and allowed to deliver litters naturally. Testes of F1 males were then examined microscopically at sexual maturity on PND 100 to PND 105. Low, statistically non-significant increases in Leydig cell hyperplasia and adenomas were observed in high-dose F1 males (Table 4-23).

Table 4-23. Incidence of Interstitial Cell Hyperplasia and Adenomas in Rats Exposed Gestationally to DBP (Mylchreest et al., 1999) [a]

Lesion	0 mg/kg-day	100 mg/kg-day	250 mg/kg-day	500 mg/kg-day
No. of animals (litters)	51 (10)	51 (9)	55 (10)	45 (9)
Leydig cell hyperplasia	0 (0)	0 (0)	1 (1)	5 (2)
Leydig cell adenomas	0 (0)	0 (0)	0 (0)	2 (1)

[a] Adapted from Table 3 in (Mylchreest et al., 1999).

In a second study, Mylchreest et al. (2000) gavaged timed pregnant SD rats (19−20/dose, 11 in the high-dose group) from GD 12 through 21 with 0, 0.5, 5, 50, 100, or 500 mg/kg-day DBP and allowed to deliver litters naturally. Testes of F1 males were then examined microscopically at sexual maturity on PND 110. Similar to the first study, low, statistically non-significant increases in Leydig cell hyperplasia and adenomas were observed in F1 males at 500 mg/kg-day (Table 4-24).

Table 4-24. Incidence of Interstitial Cell Hyperplasia and Adenomas in Rats Exposed Gestationally to DBP (Mylchreest et al., 2000) [a]

Lesion	0 (mg/kg-day)	0.5 (mg/kg-day)	5 (mg/kg-day)	50 (mg/kg-day)	100 (mg/kg-day)	500 (mg/kg-day)
No. of animals (litters)	134 (19)	118 (20)	103 (19)	120 (20)	140 (20)	58 (11)
Interstitial cell hyperplasia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	14 (5)
Interstitial cell adenomas	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)

[a] Adapted from Table 3 in (Mylchreest et al., 2000).

In a third study, Barlow et al. (2004) gavaged time-mated pregnant CRL:CD(SD)BR rats with 0, 100, and 500 mg/kg-day DBP on GDs 12 through 21 and then allowed dams to deliver litters naturally. Male F1 offspring were weaned on PND 21 and necropsied at PND 180, PND 370, or PND 540. Low, statistically non-significant incidence of Leydig cell hyperplasia was observed in F1 males, including unilateral hyperplasia in three control males on PND 540, one to two low-dose males on PND 370 or PND 540, and one to three high-dose males on PND 180, PND 370, or PND 540. Additionally, bilateral hyperplasia was observed in three low-dose males on PND 540 (Table 4-25). Similarly, low, statistically non-significant increases in Leydig cell adenomas (unilateral) were observed, including in one control male on PND 370 and PND 540, and one low-dose F1 male on PND 540. No adenomas were observed in high-dose F1 males at any timepoint.

Table 4-25. Incidence of Interstitial Cell Hyperplasia and Adenomas in Rats Exposed Gestationally to DBP (Barlow et al., 2004) [a] [b]

	PND 180			PND 370			PND 540		
	0	100	500	0	100	500	0	100	500
No. of animals (litters)	60 (10)	65 (10)	45 (11)	61 (10)	61 (9)	74 (11)	45 (9)	49 (10)	35 (8)
LC hyperplasia (unilateral)	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)	3 (3)	3 (1)	2 (1)	1 (1)
LC hyperplasia (bilateral)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (2)	0 (0)
LC adenoma (unilateral)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)	1 (1)	0 (0)
LC adenoma (bilateral)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)

[a] Adapted from Table 2 in (Barlow et al., 2004).
[b] All DBP units in mg/kg-day

4.3.3.2.1 Conclusions on Leydig Cell Tumors

EPA did not identify any human epidemiologic studies that evaluated the association between exposure to DBP and testicular cancer (Section 4.1). As discussed above in Section 4.3.3.2, significant treatment-related increases in Leydig cell hyperplasia has been observed in one study of SD rats dosed with 510 mg/kg-day DBP for 2 years (NTP, 2021a), while three studies of SD rats reported slight but statistically non-significant increases in Leydig cell hyperplasia (Barlow et al., 2004; Mylchreest et al., 2000; Mylchreest et al., 1999). As discussed by NTP (2021a), Leydig cell hyperplasia is suggestive of systemic hormonal disturbance, including disturbance of the hypothalamus-pituitary-gonad axis. More specifically, decreased systemic testosterone levels may cause a decrease in negative feedback of testosterone on the hypothalamus-pituitary-gonad axis, which in turn can lead to increased luteinizing hormone that might have resulted in a stimulatory response of the Leydig cells (NTP, 2021a). This response would be consistent with pathway two of the MOA for Leydig cell tumors previously discussed in Section 4.3.1.1.3.

Leydig cell adenomas represent a progression from pre-neoplastic Leydig cell hyperplasia. Leydig cell adenomas have been observed in F1 male offspring in three studies of similar design and from the same laboratory (*i.e.*, CIIT) of SD rats exposed gestationally to up to 500 mg/kg-day DBP on GD 12 through GD 21 (Barlow et al., 2004; Mylchreest et al., 2000; Mylchreest et al., 1999). However, incidence of Leydig cell adenomas observed across all three studies was low (limited to 1−2 males per study) and did not reach statistical significance. Given that all three studies were designed to investigate the effects of gestation-only exposure to DBP on GD 12 through GD 21, the trend in Leydig cell adenomas is notable. However, in a subsequent study of SD rats by NTP, which included gestational and chronic (2-year) postnatal exposure, no significant increase in Leydig cell adenomas were observed in male SD rats exposed to up to 740 mg/kg-day DBP during gestation (GDs 6−21) and up to 510 mg/kg-day DBP for a further 2 years (NTP, 2021a). Additionally, Leydig cell tumors were not observed in male B6C3F1 mice treated with up to 1,306 mg/kg-day DBP for 2 years; however, this study did not include gestational exposure to DBP (NTP, 2021a).

EPA considers the low, statistically non-significant increase in Leydig cell adenomas reported by Mylchreest et al. (2000; 1999), Barlow et al. (2004), and NTP (2021a), which were not observed in chronic studies of male mice that achieved higher doses of DBP, to be of uncertain toxicological significance. Overall, *EPA considers there to be indeterminant scientific evidence to conclude that gestational and/or chronic oral exposure to DBP induce Leydig cell adenomas in rats.*

4.3.3.3 Cancer Classification for DBP

Under the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), EPA reviewed the weight of evidence for the carcinogenicity of DBP and in the draft DBP cancer assessment concluded that there is *Suggestive evidence of carcinogenic potential* of DBP in rodents based on evidence of pancreatic acinar cell adenomas in male SD rats. However, based on the majority opinion of the SACC (U.S. EPA, 2025v), EPA has revised its cancer classification for DBP to *not likely to be carcinogenic to humans.* Briefly, SACC stated the following:

> As discussed in the Committee response to CQ 7.a for BBP and also noted here in the Committee response to this charge question for DBP, the PACT arises secondary to PPARα agonism and appears to occur only at excessively high doses. Any uncertainties or scientific deficiencies in the data to support the complicated MOA are not needed to be filled since the PACT response would not occur without PPARα agonism. The constellation of tumors, regardless of tissue of origin, would be adequately prevented using the non-cancer POD as presented for individual and cumulative risk evaluation. Pancreatic acinar cell tumors are related to the PPARα agonism secondary to the liver and would not be expected to be present at doses below which there is no PPARα agonism (Klaunig et al. 2003) so a designation of "Not Likely Carcinogenic" would also be applicable for those with pancreatic tumors.

Further weight of scientific evidence considerations supporting EPA's determination of *Not Likely to be Carcinogenic to Humans* are listed below.

- DBP is not likely to be genotoxic or mutagenic (Section 3.3).
- The epidemiologic evidence is insufficient to identify an association between BBP exposure and subsequent cancer outcomes in humans (Section 4.1.3).
- DBP showed no carcinogenic activity in one study of male and female B6C3F1 mice exposed to up to 1,306 to 1,393 mg/kg-day DBP through the diet for 2 years (NTP, 2021a).
- DBP showed no carcinogenic activity in one study of female SD rats exposed to up to 600 mg/kg-day DBP through the diet for 2 years (NTP, 2021a).
- Treatment with DBP caused a significant increase in incidence of pancreatic acinar cell adenomas in male SD rats fed diets containing DBP for 2 years at doses that did not result in overt toxicity (NTP, 2021a).
- Read-across from other toxicologically similar phthalates (*i.e.*, DEHP [Section 4.3.1.1] and BBP [Section 4.3.2.1.1]), which have also been shown to induce pancreatic acinar cell tumors in rats, provides additional evidence to support the conclusion that phthalates, including DBP, may cause pancreatic acinar cell adenomas in rats.
- Available mechanistic evidence indicates PACTs arise secondary to PPARα activation in the liver (Section 4.3.3.1).
- The non-cancer point of departure (POD) ($BMDL_5$ [lower-bound of the confidence limit for the benchmark dose of 5%] of 9 mg/kg-day) based on effects on the developing male reproductive system consistent with a disruption of androgen action and phthalate syndrome (see *Non-Cancer Human Health Hazard Assessment for DBP)* (U.S. EPA, 2025f)) that was selected to characterize risk for acute, intermediate, and chronic exposures scenarios is expected to adequately account for all chronic toxicity, including carcinogenicity, which could potentially result from exposure to DBP.

4.3.4 Diisononyl Phthalate (DINP)

EPA has previously evaluated DINP for carcinogenicity in its *Cancer Human Health Hazard Assessment for Diisononyl Phthalate (DINP)* (U.S. EPA, 2025a). EPA's cancer assessment for DINP was peer-reviewed by the SACC during its July 2024 meeting (U.S. EPA, 2024d). A brief summary of carcinogenic findings and weight of evidence conclusions for DINP, which reflect recommendations from the SACC (U.S. EPA, 2024d) and public comments, are provided below.

DINP has been evaluated for carcinogenicity in two studies of male and female F344 (Covance Labs, 1998c; Lington et al., 1997), one study of SD rats (Bio/dynamics, 1987), and one study of male and female B6C3F1 mice (Covance Labs, 1998b). Across available studies, statistically significant increases in liver tumors, MNCL, and kidney tumors have been reported. EPA's conclusions regarding each of these tumor types and EPA's cancer classification for DINP are provided below.

- ***MNCL.*** Following chronic dietary exposure to DINP, MNCL has been observed in two studies of male and female F344 rats (Covance Labs, 1998c; Lington et al., 1997), but not in SD rats (Bio/dynamics, 1987) or B6C3F1 mice of either sex (Covance Labs, 1998b). As discussed in the *Cancer Human Health Hazard Assessment for Diisononyl Phthalate (DINP)* (U.S. EPA, 2025a) there are several sources of uncertainty associated with MNCL in F344 rats. First, MNCL has a high background rate of spontaneous occurrence in F344 rats. Historical control data from NTP (1995–1998) show a background rate of MNCL of 52.5 percent in males and 24.2 percent in females (Thomas et al., 2007). F344 strain of rat was used in NTP 2-year chronic and carcinogenicity bioassays for nearly 30 years (King-Herbert et al., 2010; King-Herbert and Thayer, 2006). However, in the early 2000s NTP stopped using the F344 strain of rat, in part because of high background incidence of MNCL and testicular Leydig cell tumors, and replaced the F344 strain of rats with the Harlan SD strain (King-Herbert et al., 2010; King-Herbert and Thayer, 2006). Additional sources of uncertainty include lack of MOA information and uncertainty related to the human correlate to MNCL in F344 rats. Given these uncertainties, SACC recommended that "the observation of an increased incidence of MNCL in a chronic bioassay employing the Fisher 344 rat should not be considered a factor in the determination of the cancer classification..." and "Most Committee members agreed that given the material presented in a retrospective review, MNCL and Leydig Cell Tumors, among other tumor responses in F344 rat carcinogenicity studies lack relevance in predicting human carcinogenicity (Maronpot et al., 2016)" (U.S. EPA, 2024d). Consistent with the recommendations of the SACC, and based on the above discussion, EPA did not consider MNCL as a factor in its determination of the cancer classification for DINP.
- ***Kidney Tumors.*** Following chronic dietary exposure to DINP, renal tubule cell carcinomas have been reported in two studies of male (but not female) F344 rats (Covance Labs, 1998c; Lington et al., 1997). Kidney tumors were not observed in male or female SD rats or B6C3F1 mice fed diets containing DINP for 2 years (Covance Labs, 1998b; Bio/dynamics, 1987). Overall, EPA concluded that much of the available literature supports an α_{2u}-globulin MOA to explain the incidences of renal tubule cell carcinomas observed in male rats exposed to DINP. EPA does not consider kidney tumors arising through a α_{2u}-globulin MOA to be human relevant (U.S. EPA, 1991). Therefore, *EPA did not consider it appropriate to derive quantitative estimates of cancer hazard for data on kidney tumors observed in these studies and did not further consider kidney tumors as a factor in the determination of the cancer classification for DINP*. This conclusion was supported by the SACC. In its final report to EPA, the SACC stated "The Agency has provided substantial evidence that the kidney tumors produced by DINP are due to a 2u-globulin MOA and correctly classified them as not relevant to humans" (U.S. EPA, 2024d). See Section 3.2.3 of (U.S. EPA, 2025a) for further details.

- ***Liver Tumors.*** Following chronic dietary exposure to DINP, hepatocellular adenomas (or neoplastic nodules) and/or carcinomas were consistently observed in male and female F344 rats (Covance Labs, 1998c; Lington et al., 1997), female SD rats (Bio/dynamics, 1987), and B6C3F1 mice of both sexes (Covance Labs, 1998b). Overall, EPA concluded that there is strong evidence to support the conclusion that DINP causes liver tumors in rodents through a non-genotoxic, threshold, peroxisome proliferator-activated receptor alpha (PPARα) MOA (see Section 4 of (U.S. EPA, 2025a) for further discussion). This conclusion was supported by the SACC during their July 2024 peer review meeting (U.S. EPA, 2024d).
- ***Cancer Classification for DINP.*** Under the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), *EPA reviewed the weight of evidence and determined that DINP is not likely to be carcinogenic to humans at doses below levels that do not result in PPARα activation* (KE 1 in the PPARα MOA) (see Section 4.8 of (U.S. EPA, 2025a) for further details). Furthermore, the non-cancer chronic POD (NOAEL/LOAEL of 15/152 mg/kg-day based on non-cancer liver effects (see *Non-Cancer Human Health Hazard Assessment for Diisononyl Phthalate (DINP)* (U.S. EPA, 2025j)) will adequately account for all chronic toxicity, including carcinogenicity, which could potentially result from exposure to DINP. In one study of male mice (Kaufmann et al., 2002), biomarkers of PPARα activation were significantly increased at 117 mg/kg-day, which is less than the chronic LOAEL of 152 mg/kg-day based on non-cancer liver effects. Although the study by Kaufman et al. did not test sufficiently low doses to establish a NOAEL for PPARα activation, other studies of mice have established a NOAEL of 75 mg/kg-day for PPARα activation (Smith et al., 2000). Therefore, the non-cancer chronic POD of 15 mg/kg-day is considered protective of PPARα activation.

  EPA acknowledges that during the July 2024 SACC peer review of DIDP and DINP, the committee provided significant feedback that liver tumors associated with PPARα activation are not human relevant (U.S. EPA, 2024d). Although EPA acknowledges this feedback from the SACC, this issue did not impact the Agency's overall approach to cancer risk assessment for DINP. As discussed above, the non-cancer POD for DINP is expected to adequately account for all chronic toxicity, including carcinogenicity, and no quantitative cancer risk assessment was conducted for DINP.

4.3.5 Diisodecyl Phthalate (DIDP)

EPA has previously evaluated DIDP for carcinogenicity in its *Human Health Hazard Assessment for Diisodecyl Phthalate (DIDP)* (U.S. EPA, 2024a). EPA's cancer assessment for DIDP was peer reviewed by the SACC during its July 2024 meeting (U.S. EPA, 2024d). A brief summary of carcinogenic findings and weight of evidence conclusions for DIDP, which reflect recommendations from the SACC (U.S. EPA, 2024d) and public comments, is provided below.

DIDP has been evaluated for carcinogenicity in one 2-year dietary study of male and female F344 rats (Cho et al., 2010; Cho et al., 2008) and in one 26-week dietary study of male and female wild-type and transgenic CB6F1-RasH2 mice (Cho et al., 2011). Across available studies, statistically significant increases in MNCL were observed in high-dose (479−620 mg/kg-day) male and female F344 rats, while hepatocellular adenomas were observed in high-dose (1,500 mg/kg-day) male transgenic CB6F1-RasH2 mice (Cho et al., 2011).

Under the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), *EPA reviewed the weight of evidence for the carcinogenicity of DIDP and concluded that DIDP is not likely to be carcinogenic to humans*. This conclusion is based on the following:

Weight of scientific evidence considerations supporting EPA's determination are listed below. Consistent with this cancer classification, EPA is not conducting a dose-response assessment for DIDP or evaluating DIDP for carcinogenic risk to humans.

- Hepatocellular adenomas were observed only in high-dose male CB6F1-rasH2 transgenic mice at 1,500 mg/kg-day but not in female transgenic mice or in wild-type male or female mice, which are more appropriate for use in human health risk assessment (Cho et al., 2011). However, in the studies of wild-type and transgenic mice, the highest dose tested, 1,500 mg/kg-day, was above the limit dose. This is demonstrated by the fact that terminal body weight was reduced 27 and 12 percent in male and female wild-type mice, respectively, and 31 and 15 percent in male and female transgenic mice, respectively, at 1,500 mg/kg-day. Per the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005) "signs of treatment-related toxicity associated with an excessive high dose may include (a) significant reduction of body weight gain (*e.g.*, greater than 10%)." Furthermore, EPA's Guidelines for Carcinogen Risk Assessment state that "overt toxicity or qualitatively altered toxicokinetics due to excessively high doses may result in tumor effects that are secondary to the toxicity rather than directly attributable to the agent."
- No evidence of carcinogenic activity was observed in male or female CB6F1-rasH2 transgenic mice dosed with 150 or 495 mg/kg-day DIDP (Cho et al., 2011). Evidence of overt treatment-related toxicity associated with exceedance of the limit dose was not apparent at these dose levels.
- EPA acknowledges that increased MNCL was observed in male and female F344 rats treated with DIDP for 2 years (Cho et al., 2010; Cho et al., 2008). However, MNCL was only observed at in the high-dose group and coincided with high mortality. No other preneoplastic or neoplastic findings were observed in any tissue for either sex at any dose.
- MNCL has a high rate of spontaneous occurrence in F344 rats. Although the historical control data are not available for the laboratory that conducted this study, historical control data from NTP (1995–1998) show 52.5 percent in males and 24.2 percent in females (Thomas et al., 2007). The F344 strain of rat was used in NTP 2-year chronic and carcinogenicity bioassays for nearly 30 years (King-Herbert et al., 2010; King-Herbert and Thayer, 2006). However, in the early 2000s, NTP stopped using the F344 strain of rat, in part because of high background incidence of MNCL and testicular Leydig cell tumors, and replaced the F344 strain of rats with the Harlan Sprague Dawley strain (King-Herbert et al., 2010; King-Herbert and Thayer, 2006). Consistent with recommendations of the SACC (U.S. EPA, 2024d), EPA is not further considering MNCL as a factor in the determination of the cancer classification for DIDP because this is likely a strain-specific effect.
- EPA's weight of scientific evidence conclusion is consistent with Health Canada (EC/HC, 2015c), U.S. CPSC (2014, 2010d), NICNAS (2015b), and ECHA (2013). None of these regulatory agencies have evaluated DIDP for carcinogenic risk to human health.

5 EVALUATING THE CARCINOGENICITY OF DIBP AND DCHP USING ReCAAP WEIGHT OF SCIENTIFIC EVIDENCE FRAMEWORK

No chronic toxicity or cancer bioassays are available for DIBP or DCHP in the published literature. EPA therefore evaluated the relevance of read-across approaches to assess potential cancer hazards of DIBP and DCHP based on cancer bioassays and MOA information available for other phthalates being evaluated under TSCA (*i.e.,* DEHP, BBP, DBP, DINP, and DIDP).

Hilton et al. (2022) published a weight of evidence-based framework for determining the need for rodent cancer bioassays for agrochemicals lacking chronic and/or carcinogenicity studies—known as the Rethinking Chronic Toxicity and Carcinogenicity Assessment for Agrochemicals Project (also referred to as "the ReCAAP Framework"). Although developed specific for agrochemicals, EPA believes many of the same scientific principles in the ReCAAP Framework apply to TSCA risk evaluations. As such, elements of the ReCAAP Framework is used as an organizational tool to evaluate the extent to which the lack of carcinogenicity studies imparts significant uncertainty on the human health risk assessments for DIBP and DCHP. EPA selected the ReCAAP Framework to evaluate DIBP and DCHP over other read-across frameworks (*e.g.,* framework by Lizarraga et al. (2023; 2019)). The ReCAAP Frameworks purpose is to determine the need for rodent cancer bioassays for chemicals, such as DIBP and DCHP, lacking the rodent cancer bioassays.

The ReCAAP framework takes into consideration multiple lines of evidence including information pertaining to nomenclature, physical and chemical properties; exposure and use patterns; absorption, distribution, metabolism, and excretion (ADME) properties; and toxicological data (*e.g.,* genetic toxicity, acute toxicity, subchronic toxicity, hormone perturbation, immunotoxicity, MOA). The framework was developed by a workgroup comprised of scientists from academia, government (including EPA), non-governmental organizations, and industry stakeholders. Recently, the Organisation for Economic Co-operation and Development (OECD) has published several Integrated Approach to Testing and Assessment (IATA) case studies demonstrating applicability of the weight of evidence ReCAAP framework (OECD, 2024). Further demonstrating the applicability of the ReCAAP framework, Goetz et al. (2024) published three retrospective case studies demonstrating application of the ReCAAP Framework for three agrochemical active substances.

Herein, EPA used most elements of the ReCAAP framework and OECD case studies. Elements of the ReCAAP framework considered herein include nomenclature and physical and chemical properties (Section 5.1), ADME properties (Section 5.2), acute toxicity (Section 5.3), evidence of hormone perturbation, developmental and reproductive toxicity (Section 5.4), subchronic toxicity (Section 5.5), immune systemic perturbation (Section 5.6), genotoxicity (Section 5.7), MOA (Section 5.8), and evidence of chronic toxicity and carcinogenicity from DEHP, BBP, DBP, DINP, and DIDP (Section 5.9). The one element of the ReCAAP Framework that was not included in the current evaluation was use patterns and exposure scenarios. However, use patterns and exposure information is discussed extensively in the individual risk evaluations for DEHP, BBP, DBP, DIBP, DCHP, DINP, DIDP. Read-across to other structurally and toxicologically similar phthalate diesters currently being evaluated under TSCA (*i.e.,* DEHP, BBP, DBP, DIBP, DCHP, DINP, DIDP) were considered as part of the current weight of evidence and read-across approach. The weight of evidence narrative provided in this section represents a brief synthesis of available information for DIBP, DCHP, and the five phthalates used to support read-across (DEHP, BBP, DBP, DINP, DIDP). Complete human health hazard and physical and chemical property information for the seven phthalates being evaluated under TSCA is provided in individual phthalate TSDs, including the following:

- *Non-Cancer Human Health Hazard Assessment for Diethylhexyl Phthalate (DEHP)* (U.S. EPA, 2025h);
- *Non-Cancer Human Health Hazard Assessment for Butyl benzyl phthalate (BBP)* (U.S. EPA, 2025e);
- *Non-Cancer Human Health Hazard Assessment for Dibutyl Phthalate (DBP*) (U.S. EPA, 2025f);
- *Non-Cancer Human Health Hazard Assessment for Diisobutyl phthalate (DIBP)* (U.S. EPA, 2025i);
- *Non-Cancer Human Health Hazard Assessment for Dicyclohexyl Phthalate (DCHP)* (U.S. EPA, 2025g);
- *Non-Cancer Human Health Hazard Assessment for Diisononyl Phthalate (DINP)* (U.S. EPA, 2025j);
- *Cancer Human Health Hazard Assessment for Diisononyl Phthalate (DINP)* (U.S. EPA, 2025a);
- *Human Health Hazard Assessment for Diisodecyl Phthalate (DIDP)* (U.S. EPA, 2024a);
- *Physical and Chemical Property Assessment and Fate and Transport Assessment for Di-ethylhexyl Phthalate (DEHP)* (U.S. EPA, 2025k);
- *Physical Chemistry and Fate and Transport Assessment for Butyl Benzyl Phthalate (BBP)* (U.S. EPA, 2025l);
- *Physical Chemistry and Fate and Transport Assessment for Dibutyl Phthalate (DBP)* (U.S. EPA, 2025b);
- *Physical Chemistry and Fate and Transport Assessment for Diisobutyl phthalate (DIBP)* (U.S. EPA, 2025n);
- *Physical Chemistry and Fate and Transport Assessment for Dicyclohexyl Phthalate (DCHP)* (U.S. EPA, 2025m);
- *Physical Chemistry Assessment for Diisononyl Phthalate (DINP)* (U.S. EPA, 2025o); and
- *Physical Chemistry Assessment for Diisodecyl Phthalate (DIDP)* (U.S. EPA, 2024b).

5.1 Nomenclature and Physical and Chemical Properties

Table 5-1 summarizes the CASRNs, Tanimoto coefficients, and physical and chemical properties of DIBP and DCHP, as well as DEHP, BBP, DBP, DINP, and DIDP. As a measure of structural similarity, Tanimoto coefficients were generated using EPA's Cheminformatics Search Module. DEHP, BBP, DBP, DINP, DIDP, and DCHP were indicated as structurally similar to DIBP based on Tanimoto coefficients of 0.8 to 0.9, while DEHP, BBP, DBP, DINP, DIDP, and DIBP were indicated as structurally similar to DCHP based on Tanimoto coefficients of 0.8 to 0.88. Based on the physical and chemical properties of DIBP and DCHP, and DEHP, BBP, DBP, DINP, and DIDP, the following conclusions can be drawn:

- DEHP, BBP, DBP, DIBP, DINP, and DIDP are liquid, whereas DCHP is a solid at room temperature.
- DEHP, BBP, DBP, DIBP, DCHP, DINP, and DIDP have very low to slight solubility in water. DEHP, DINP and DIDP have very low water solubility (0.003 mg/L for DEHP; 0.00061 mg/L for DINP; 0.00017 mg/L for DIDP), while BBP, DBP, DIBP, and DCHP are slightly soluble in water (2.3 mg/L for BBP; 11.2 mg/L for DBP; 6.2 mg/L for DIBP; 1.48 mg/L for DCHP).

- Sorption to organics present in sediment and suspended and dissolved solids present in water is expected to be a dominant process given the range of identified log K_{oc} values (2.09–5.78) across DEHP, BBP, DBP, DIBP, DCHP, DINP, and DIDP.
- Given the range of water solubility values and range of log K_{oc} values for DEHP, BBP, DBP, DIBP, DCHP, DINP, and DIDP, these phthalates are unlikely to exhibit mobility in soils.
- Phthalates generally have low volatility. Based on physical and chemical properties (*i.e.*, melting point, boiling point, Henry's Law coefficient/constant), DCHP is classified as a non-volatile organic compound, while DEHP, BBP, DBP, DIBP, DINP, and DIDP are marginally classified as semi-volatile organic compounds. However, volatilization of DEHP, BBP, DBP, DIBP, DINP, and DIDP from water-to-air or soil-to-air is expected to be negligible.

Table 5-1. Summary of Physical and Chemical Properties of DCHP, DBP, DIBP, BBP, DEHP, DIDP, and DINP

Property	DEHP (U.S. EPA, 2025k)	BBP (U.S. EPA, 2025l)	DBP (U.S. EPA, 2025b)	DIBP (U.S. EPA, 2025n)	DCHP (U.S. EPA, 2025m)	DINP (U.S. EPA, 2025o)	DIDP (U.S. EPA, 2024b)
CASRN(s)	117-81-7	85-68-7	84-74-2	84-69-5	84-61-7	28553-12-0 68515-48-0	26761-40-0 68515-49-1
Molecular formula	C_{24} H_{38} O_4	$C_{19}H_{20}O_4$	$C_{16}H_{22}O_4$	$C_{16}H_{22}O_4$	$C_{20}H_{26}O_4$	$C_{26}H_{42}O_4$	$C_{28}H_{46}O_4$
Molecular weight (g/mol)	390.56	312.37	278.35	278.35	330.43	418.62	446.7
Tanimoto coefficient (DIBP target) [a]	0.9	0.9	0.9	1.0	0.8	0.84	0.84
Tanimoto coefficient (DCHP target) [a]	0.85	0.88	0.88	0.8	1.0	0.87	0.87
Physical state of the chemical	Colorless, oily liquid	Clear oil, liquid	Colorless to faint yellow, oily liquid	Colorless, clear, viscous liquid	White, granular solid	Clear liquid	Clear liquid
Melting point (°C)	−55	−35	−35	−64	66	−48	−50
Boiling point (°C)	384	370	340	296.5	225	>400	>400
Density (g/cm^3)	0.981	1.119	1.0459 to 1.0465	1.049	1.383	0.97578	0.967
Vapor Pressure (mmHg)	1.42E−07	8.25E−06	2.01E−05	4.76E−05	8.69E−07	5.40E−07	5.28E−07
Water solubility (ng/L)	3,000	2,690,000	11,200,000	6,200,000	30,000 to 1,480,000	610	170
Log K_{OW}	7.6	4.73	4.5	4.34	4.82	8.8	10.21 (estimated)
Log K_{OA} (estimated using EPI Suite™)	10.76	9.2	8.63	9.47	10.23	11.9	13.0
Log K_{OC}	3.75–5.48	2.09–2.91	3.16–4.19	2.5–3.14	3.46–4.12	5.5–5.7	5.04–5.78
Henry's Law constant (atm-m^3/mol)	1.71E−05	7.61E−07	1.81E−06	1.83E−07	9.446E−08	9.14−05	21.3E−05
Flash point (°C)	206	199	157.22	185	207	213	>200
Autoflammability (°C)	390	–	402.778	432	No data	400	402
Viscosity (cP)	57.94	55	20.3	41	Not applicable (solid)	77.6	87.797

Property	DEHP (U.S. EPA, 2025k)	BBP (U.S. EPA, 2025l)	DBP (U.S. EPA, 2025b)	DIBP (U.S. EPA, 2025n)	DCHP (U.S. EPA, 2025m)	DINP (U.S. EPA, 2025o)	DIDP (U.S. EPA, 2024b)
Overall environmental persistence	Low	Low	Low	Low	Low	Low	Low
Bioaccumulation factor (Log BAF A-G)	3.02	1.60	2.20	1.41	2.14	1.14	2.06
Bioconcentration factor (Log BCF A-G)	2.09	2.88	2.20	1.41	2.13	0.39	1.04

[a] Structural similarity (Tanimoto coefficients) of DEHP, BBP, DBP, DINP, and DIDP to DIBP and DCHP was evaluated in EPA's Cheminformatics Search Module (https://www.epa.gov/comptox-tools/cheminformatics; accessed December 4, 2025).

5.2 Absorption, Distribution, Metabolism, and Excretion

The ADME properties of DIBP and DCHP, as well as the five phthalates used to support read-across (DEHP, BBP, DBP, DINP, and DIDP) following oral exposure, are discussed briefly below. Readers are directed to the human health hazard assessments for DEHP (U.S. EPA, 2025h), BBP (U.S. EPA, 2025e), DBP (U.S. EPA, 2025f), DIBP (U.S. EPA, 2025i), DCHP (U.S. EPA, 2025g), DINP (U.S. EPA, 2025j), and DIDP (U.S. EPA, 2024a) for more detailed summaries of their ADME properties.

Limited information is available pertaining to the ADME properties of DIBP and DCHP. No *in vivo* studies of experimental animal models or controlled human exposure studies are available that have evaluated the ADME properties of DCHP. However, *in vitro* studies have demonstrated that DCHP is rapidly hydrolyzed to its corresponding monoester, monocyclohexyl phthalate (MCHP). Furthermore, human biomonitoring studies have measured MCHP in urine, demonstrating that DCHP can be metabolized to MCHP and excreted in urine in humans (U.S. EPA, 2025g). Similarly, no *in vivo* studies of experimental animal models are available that have evaluated the ADME properties of DIBP. However, in a controlled human oral exposure study of DIBP, approximately 90 percent of administered DIBP was recovered in urine within 24 hours. DIBP was excreted primarily as the monoester metabolite, monoisobutyl phthalate (MIBP, accounted for ≈70% of excreted DIBP), while several other oxidated derivatives of MIBP (*i.e.*, 2OH-MIBP and 3OH-MIBP) were found to be minor urinary metabolites accounting for around 20 percent of excreted DIBP. Overall, this study indicates rapid and near complete oral absorption of DIBP, which is metabolized to MIBP and can then undergo further oxidative metabolism before being rapidly eliminated in urine (U.S. EPA, 2025i).

For the five phthalates (*i.e.*, DEHP, BBP, DBP, DINP, and DIDP) used to support read-across, more extensive databases of studies evaluating ADME properties are available, including controlled human oral exposure studies, studies of rats and mice, as well as *in vitro* metabolism studies. Available data indicate that following oral exposure, DEHP, BBP, DBP, DINP, and DIDP are rapidly absorbed and systemically distributed. For input into the risk evaluations for DEHP, BBP, DBP, DINP, and DIDP (as well as for DIBP and DCHP), EPA assumed 100 percent oral absorption. Furthermore, available studies indicate that DEHP, BBP, DBP, DINP, and DIDP are all rapidly metabolized into monoester metabolites by esterases in the gut or other tissues following absorption. Monoester metabolites then undergo further oxidative metabolism and/or can also be conjugated with glucuronic acid before being excreted in urine, or to a lesser extent, in feces. Many unique but also some common metabolites across phthalates have been identified. For example, phthalic acid is a potential metabolite of DEHP, BBP, DBP, DINP, and DIDP (as well as of DIBP and DCHP). Available studies of rats and mice have shown that these five phthalates are nearly completely excreted within 72 to 96 hours. Given the rapid elimination kinetics, DEHP, BBP, DBP, DINP, and DIDP are not considered bioaccumulative.

5.3 Acute Toxicity

The acute toxicity of DIBP and DCHP, and DEHP, BBP, DBP, DINP, and DIDP have been evaluated extensively by various authoritative and regulatory agencies, including U.S. CPSC (2014, 2011, 2010a, b, c, d, e, f), ECB (2008; 2007, 2004, 2003a, c), ECHA (2017a, 2013), Australia NICNAS (2016, 2015a, b, 2013, 2012, 2010, 2008a, b, c), and ATSDR (2022, 2001). Table 5-2 summarizes some of the available acute oral LD_{50}, dermal LD_{50}, and inhalation LC_{50} values, as well as results from skin irritation, eye irritation, and skin sensitization testing for the seven phthalate diesters being evaluated under TSCA. Across existing assessments of phthalates, there is consensus that DEHP, BBP, DBP, DIBP, DCHP, DINP, and DIDP are not acutely toxic in terms of lethality via the oral, dermal, or inhalation exposure routes. However, as will be discussed further in Sections 5.4 and 5.9, DEHP, BBP, DBP, DIBP, DCHP, DINP, and DIDP are all developmental toxicants, and EPA considers

developmental effects such as reduced offspring survival in the case of DIDP and effects on the developing male reproductive system consistent with phthalate syndrome in the cases of DEHP, BBP, DBP, DIBP, DCHP, and DINP relevant for assessing risk from acute duration exposures.

Furthermore, DEHP, BBP, DBP, DIBP, DCHP, DINP, and DIDP are not considered corrosive and cause no or minimal irritant effects to the eye or skin. Finally, phthalates are considered to have low skin sensitizing potential, with the one possible exception being DCHP. As discussed in EPA's *Non-Cancer Human Health Hazard Assessment for Dicyclohexyl Phthalate (DCHP)* (U.S. EPA, 2025g), DCHP tested positive as a dermal sensitizer in one local lymph node assay and is classified (harmonised) as a sensitizer in the European Union (ECHA, 2014). However, only the ECHA robust study summary was available to EPA for review, and the original study report was not available to EPA for independent review. Therefore, EPA considers there to be indeterminant evidence to draw a conclusion on the skin sensitizing potential of DCHP.

Table 5-2. Summary of Acute Toxicity Data for DEHP, BBP, DBP, DIBP, DCHP, DINP, and DIDP[a]

	DEHP	BBP	DBP	DIBP	DCHP	DINP	DIDP
Oral LD_{50} (mg/kg)	30,600–40,000 (rat)	2,330–20,400 (rat)	6,300–8,000 (rat)	16,000–60,320 (rat)	>3,200 (rat)	>10,000 (rat) [b]	>29,100
Dermal LD_{50} (mg/kg)	24,750 (rabbit)	6,700 (rat)	>20,000 (rabbit)	No study	>300 (rabbit)	>3,160 (rabbit) [b]	>2910 (rat)
Inhalation LC_{50} (mg/L)	>10.62 (rat)	No study	≥15.68 (rat)	No study	>3.2 (rat)	>4.4 (rat) [b]	>12.54 (rat)
Skin irritation	Minimal effect	Minimal effect	Minimal effect	Minimal effect	Minimal effect	Minimal effect [b]	Minimal effect
Eye irritation	Minimal effect	Minimal effect	Minimal effect	Not a eye irritant	Minimal effect	Minimal effect [b]	Minimal effect
Skin sensitization	Not a sensitizer	Not a sensitizer	Not a sensitizer	Not a sensitizer	Insufficient data[c]	Not a sensitize r[b]	Not a sensitizer

[a] Data from Table 4 of (NICNAS, 2008c) unless otherwise noted.
[b] Data from (U.S. EPA, 2025j; ECHA, 2013; NICNAS, 2012; ECB, 2003c).
[c] Only the ECHA robust study summary was available to EPA for review (ECHA, 2014), and the original study report was not available to EPA for independent review. Therefore, EPA considers there to be indeterminant evidence to draw a conclusion on the skin sensitizing potential of DCHP.

5.4 Evidence of Hormone Perturbation, and Developmental and Reproductive Toxicity

Hormone perturbation, as well as subsequent developmental and reproductive toxicity, are hallmarks of exposure to certain phthalate diesters, including DIBP and DCHP, and DEHP, BBP, DBP, and DINP (but not DIDP; see more below). As discussed in EPA's *Draft Proposed Approach for Cumulative Risk Assessment of High-Priority Phthalates and a Manufacturer-Requested Phthalate under the Toxic Substances Control Act* (U.S. EPA, 2023)—and in the human health hazard assessments for DEHP (U.S. EPA, 2025h), BBP (U.S. EPA, 2025e), DBP (U.S. EPA, 2025f), DIBP (U.S. EPA, 2025i), DCHP (U.S. EPA, 2025g), and DINP (U.S. EPA, 2025j)—these phthalates are antiandrogenic. Studies in rats have demonstrated that exposure to DIBP and DCHP, and DEHP, BBP, DBP, and DINP, during the critical window of development can disrupt testosterone biosynthesis in the fetal testis, leading to decreased male anogenital distance, increased male nipple retention, and seminiferous tubule atrophy (Table 5-4).

Severe reproductive tract malformations such as hypospadias and cryptorchidism, sperm effects, and decreases in male fertility have also been observed for some of these phthalates (Table 5-4). Although qualitatively these phthalates are toxicologically similar, important differences in potency are apparent based on reductions in fetal testicular testosterone, with DCHP being the most potent, followed by DBP, DEHP, DIBP, BBP, and DINP being the least potent (Table 5-3) (see (U.S. EPA, 2025d) for further details).

Table 5-3. Summary of Phthalate Potency for Reducing Fetal Testicular Testosterone

Phthalate	BMD_{40} (mg/kg-day) for Reduced Fetal Testicular Testosterone[a]
DCHP	90
DBP	149
DEHP	178
DIBP	279
BBP	284
DINP	699

[a] BMD_{40} = benchmark dose (BMD) associated with a 40% reduction in fetal testicular testosterone.

In contrast to DEHP, BBP, DBP, DIBP, DCHP, and DINP, DIDP is not antiandrogenic and does not disrupt fetal testis testosterone biosynthesis in studies of rats (U.S. EPA, 2024a, 2023). However, as discussed in EPA's *Human Health Hazard Assessment for Diisodecyl Phthalate (DIDP)* (U.S. EPA, 2024a), DIDP is a developmental toxicant and has been shown to induce skeletal and visceral variations in fetal rats in prenatal developmental studies, as well as reduce F1 and F2 offspring survival, body weight, and body weight gain in several two-generation studies of reproduction. Similar developmental effects as observed for DIDP have also been observed for DEHP, BBP, DBP, DIBP, DCHP, and DINP, albeit at higher doses than those that cause antiandrogenic effects on the developing male reproductive system.

Table 5-4. Summary of Phthalate Syndrome-Related Effects Observed in Studies of Rat[a]

Phthalate Syndrome-Related Effect	DEHP	BBP	DBP	DIBP	DCHP	DINP	DIDP
↓ Steroidogenic gene and *Insl3* expression in the fetal testis	✓	✓	✓	✓	✓	✓	*x*
↓ Fetal testis testosterone	✓	✓	✓	✓	✓	✓	*x*
↓ Anogenital distance	✓	✓	✓	✓	✓	*i*	*x*
Nipple retention	✓	✓	✓	✓	✓	*i*	*x*
Hypospadias	✓	✓	✓	✓	✓	*x*	*x*
Seminiferous tubule atrophy	✓	✓	✓	✓	✓	*i*	*x*
Multinucleated gonocytes (MNGs)	✓	✓	✓	✓	✓	✓	–
↓ Reproductive organ weight [b]	✓	✓	✓	✓	✓	*i*	*x*
Testicular pathology [c]	✓	✓	✓	✓	✓	✓	*x*

Phthalate Syndrome-Related Effect	DEHP	BBP	DBP	DIBP	DCHP	DINP	DIDP
Epididymal agenesis	✓	✓	✓	✓	–	✓	*x*
Gubernaculum agenesis	✓	–	✓	–	–	–	*x*
Undescended testes	✓	✓	✓	✓	*x*	*x*	*x*
Sperm effects [d]	✓	✓	✓	–	✓	✓	*x*
↓ Male fertility [e]	✓	✓	✓	–	*x*	*x*	*x*

✓ = Studies available, effects observed.
x = Studies available, no effects observed.
i = Studies available, inconsistent effects observed.
– = No study available.
[a] Adapted from Table 3-22 in EPA's *Draft Proposed Approach for Cumulative Risk Assessment of High-Priority Phthalates and a Manufacturer-Requested Phthalate under the Toxic Substances Control Act* (U.S. EPA, 2023).
[b] May include decreased absolute testis, epididymis, seminal vesicle, and/or prostate weight.
[c] May include, but is not limited to, Leydig cell aggregation, interstitial cell hyperplasia or adenoma, Sertoli cell only. tubules, and/or epididymal oligospermia or azoospermia.
[d] May include, but is not limited to, decreased sperm motility and/or concentration.
[e] May include, but is not limited to decreased mating, pregnancy, and/or fertility indices.

5.5 Subchronic Toxicity

Although hormone perturbation (*i.e.,* disruption of testis testosterone biosynthesis) and effects on the developing male reproductive system have been identified as the most sensitive non-cancer effects for DEHP, BBP, DBP, DIBP, and DCHP, the liver has also been consistently identified as a target organ for DIBP, DCHP, as well as DEHP, BBP, DBP, DINP and DIDP.

As discussed in Section 3.3 of the *Non-Cancer Human Health Hazard Assessment for Dicyclohexyl Phthalate (DCHP)* (U.S. EPA, 2025g), intermediate and subchronic duration exposure studies have consistently demonstrated that oral exposure to DCHP can cause dose-related increases in relative liver weight in rats, as well as cause increases in hepatocellular hypertrophy and serum chemistry markers of liver toxicity (*i.e.,* ALT, AST) (Ahbab et al., 2017; Saillenfait et al., 2009; Yamasaki et al., 2009; Hoshino et al., 2005; Lake et al., 1982). As discussed further in Section 5.8, there is some mechanistic evidence that DCHP can activate PPARα in the liver, and it is possible that PPARα activation underlies the observed liver effects of DCHP. For DIBP, there is less evidence for liver toxicity in rodents following oral exposure. As discussed by Yost et al. (2019), there is robust evidence that oral exposure to DIBP can increase relative liver weight in multiple studies of rats and mice (Wang et al., 2017; Oishi and Hiraga, 1980a, b, c, d; University of Rochester, 1954, 1953). However, available studies have generally not evaluated serum chemistry markers of liver toxicity or conducted histopathologic evaluations of the liver following oral exposure to DIBP.

For DEHP, BBP, DBP, DINP, and DIDP, there is consistent evidence of dose-related liver toxicity following subchronic oral exposure. Observed effects include, increases in relative liver weights, increases in serum markers of liver toxicity (*e.g.,* ALT, AST, ALP, GGT), and non-cancer histopathologic findings such as hepatocellular hypertrophy, focal necrosis, and spongiosis hepatis (limited to studies of F344 rats). Furthermore, and as discussed in Section 5.8, there is evidence that all of these phthalates can activate PPARα, which is mechanistically linked to many of the observed non-cancer liver effects. One exception to this is the observed increase in spongiosis hepatis in male F344 rats, which is not believed to be mechanistically linked to PPARα activation. Non-cancer liver effects

are discussed further in the human health hazard assessments for DEHP (U.S. EPA, 2025h), BBP (U.S. EPA, 2025e), DBP (U.S. EPA, 2025f), DINP (U.S. EPA, 2025j), and DIDP (U.S. EPA, 2024a).

5.6 Evidence of Immune System Perturbation

As discussed by Hilton et al. (2022), immune system suppression can increase the likelihood of cancer in humans. DIBP and DCHP, as well as DEHP, BBP, DBP, DINP, and DIDP have been evaluated extensively by various authoritative and regulatory agencies, including U.S. CPSC (2014, 2011, 2010a, b, c, d, e, f), NTP's Center for the Evaluation of Risks to Human Reproduction (NTP-CERHR) (2006, 2003a, b, c, d), ECB (2008; 2007, 2004, 2003a, c), ECHA (2017a, 2013), Australia NICNAS (2016, 2015a, b, 2013, 2012, 2010, 2008a, b, c), ATSDR (2022, 2001), EFSA (2019, 2005a, b, c, d, e), the National Research Council (NRC) (2008), and the National Academies of Science, Engineering, and Medicine (NASEM) (2017). Immune system suppression has not been identified as a hazard of concern for DIBP or DCHP or any of the other phthalates included in the current assessment by any authoritative or regulatory agencies. However, immune adjuvant effects (*i.e.*, enhanced immune response) have been identified for several phthalates, including DEHP (U.S. EPA, 2025h), DBP (U.S. EPA, 2025f), DINP (U.S. EPA, 2025j), and DIDP (U.S. EPA, 2024a).

5.7 Genotoxicity

Genotoxicity data for DIBP and DCHP, as well as DEHP, BBP, and DBP is discussed in Sections 3.1 through 3.8 of this document, while genotoxicity data for DINP and DIDP is summarized in EPA's *Cancer Human Health Hazard Assessment for Diisononyl Phthalate (DINP)* (U.S. EPA, 2025a) and *Human Health Hazard Assessment for Diisodecyl Phthalate (DIDP)* (U.S. EPA, 2024a). Table 5-5 provides a summary of EPA's conclusions regarding the genotoxicity and mutagenicity of DIBP and DCHP, as well as DEHP, BBP, DBP, DINP, and DIDP.

As discussed in Sections 3.4 and 3.5 of this document, limited genotoxicity testing of DIBP and DCHP has been conducted. DIBP showed no mutagenic activity in four bacterial reverse mutation assays with or without metabolic activation (Section 3.4), while DCHP showed no mutagenic activity in one bacterial reverse mutation assay with or without metabolic activation (Sections 3.5). Other phthalates have been evaluated more extensively for genotoxicity in a broader array of i*n vitro* and *in vivo* assays. Available data for BBP, DBP, DINP, and DIDP support the conclusion that these phthalates are not genotoxic or mutagenic. For DEHP, available data indicate that DEHP and its metabolites are not direct acting mutagens; however, there is some limited evidence that DEHP may be weakly genotoxic inducing effects such as DNA damage and/or chromosomal aberrations. As noted by ATSDR (2022), these effects may be secondary to oxidative stress.

Overall, based on the available genotoxicity data for DIBP and DCHP, and on the genotoxicity data for DEHP, BBP, DBP, DINP, and DIDP, EPA does not consider DIBP or DCHP likely to be genotoxic or mutagenic. This conclusion is consistent with other assessments, which have also concluded that phthalate esters as a class are not genotoxic or mutagenic (ECHA, 2017a, b; NICNAS, 2016; U.S. CPSC, 2014).

Table 5-5. Summary of EPA Conclusions Regarding Genotoxicity and Mutagenicity of Phthalates

Phthalate	EPA Conclusion (Section or Reference for Additional Information)
DEHP	Evidence indicates that DEHP and its metabolites are not mutagenic. There is some limited evidence that DEHP may be weakly genotoxic inducing effects such as DNA damage and/or chromosomal aberrations. These effects may be secondary to oxidative stress (Section 3.1).
BBP	Not likely to be genotoxic or mutagenic (Section 3.2)
DBP	Not likely to be genotoxic or mutagenic (Section 3.3)
DIBP	Not likely to be genotoxic or mutagenic (based on read-across) (Sections 3.4 and 3.8)
DCHP	Not likely to be genotoxic or mutagenic (based on read-across) (Sections 3.5 and 3.8)
DINP	Not likely to be genotoxic or mutagenic (U.S. EPA, 2025a) (Section 3.6).
DIDP	Not likely to be genotoxic or mutagenic (U.S. EPA, 2024a) (Section 3.7).

5.8 Mechanistic Studies to Support a Proposed Mode of Action

For DEHP and DINP, EPA has concluded that liver tumors observed in rodents occur through a PPARα MOA (see Section 4.3.1.1.1 for DEHP and Section 4.3.4 and (U.S. EPA, 2025a) for DINP). Furthermore, for DEHP, EPA has concluded the tumor triad (liver tumors, PACTs, Leydig cell tumors) in rats is related to PPARα activation following chronic exposure to DEHP and some hypolipidemic drugs (discussed in Sections 4.3.1.1.4 through 4.3.1.1.6).

In addition to DEHP and DINP, comparative *in vivo* and *in vitro* studies have also consistently demonstrated that BBP, DBP, and DIDP, can also activate PPARα. For example, Barber et al. (1987) demonstrate that DEHP, BBP, DBP, DINP, and DIDP, can all activate PPARα in the livers of male F344 rats exposed to each phthalate in the diet for 21 days. Compared to hypolipidemic drugs, all five phthalates were found to be relatively weak PPARα activators based on induction of hepatic palmitoyl CoA oxidase activity, though DEHP, DINP, and DIDP were found to be stronger PPARα activators than BBP and DBP (Table 5-6). Similarly, Bility et al. (2004) demonstrated that monoester metabolites of DEHP, BBP, DBP, DINP, and DIDP, can activate both mouse and human PPARα *in vitro*; however, for all five monoester metabolites, human PPARα was less sensitive to activation than mouse PPARα (Table 5-6). Notably, similar trends in potency for PPARα activation were observed *in vitro* with mouse PPARα as were observed *in vivo* with studies of rats (*i.e.,* DIDP ≈ DINP > DEHP >> BBP ≈ DBP) (Table 5-6). Furthermore, the two weakest PPARα activators (*i.e.,* BBP and DBP) *in vivo* and *in vitro* did not induce liver tumors in chronic studies of rats or mice.

As discussed in Section 3.3 of the *Non-Cancer Human Health Hazard Assessment for Dicyclohexyl Phthalate (DCHP)* (U.S. EPA, 2025g), only one study of DCHP was identified by EPA that evaluated PPARα activation. Briefly, Saillenfait et al. (2009) gavaged pregnant SD rats with 0, 250, 500, and 750 mg/kg-day DCHP on GDs 6 through 20 and sacrificed dams on GD 21. Maternal hepatic palmitoyl CoA oxidase activity (a biomarker for PPARα activation) increased 75 to 108 percent at 250 mg/kg-day and above, indicative of a weak induction of PPARα activation, while relative liver weight increased 23 to 35 percent at 500 mg/kg-day and above. Several additional repeat-dose oral exposure studies of DCHP with rats provide additional indirect evidence consistent with PPARα activation in the liver, including increases in relative liver weight and hepatocellular hypertrophy (Ahbab et al., 2017; Saillenfait et al., 2009; Yamasaki et al., 2009; Hoshino et al., 2005; Lake et al., 1982).

EPA did not identify any *in vivo* or *in vitro* studies that directly evaluated PPARα activation following exposure to DIBP. However, as discussed by Yost et al. (2019), there is robust evidence that oral exposure to DIBP can increase relative liver weight in repeat-dose oral exposure studies of rats and mice. Although not direct evidence, increased relative liver weight is consistent with PPARα activation.

Table 5-6. Comparative Analysis of PPARα Activation by DIDP, DINP, DEHP, BBP, and DBP

Parent Phthalate (Metabolite)	*In vivo* Induction of Hepatic Palmitoyl CoA Oxidase Activity[a] [b] (Barber et al., 1987)	Lowest *In Vitro* Activation Concentration for Mouse PPARα (Maximal fold-induction) [c] (Bility et al., 2004)	Lowest *In Vitro* Activation Concentration for Human PPARα (Maximal Fold-Induction) [c] (Bility et al., 2004)
DEHP (mono(2-ethylhexyl) phthalate)	15	10 µM (11.1)	30 µM (4.8)
BBP (monobenzyl phthalate)	2	100 µM (12.3)	200 µM (2.5)
DBP (monobutyl phthalate)	3	100 µM (3.7)	200 µM (2.4)
DINP (monoisononyl phthalate)	11	3 µM (27.1)	10 µM (5.8)
DIDP (monoisodecyl phthalate)	17	3 µM (26.9)	30 µM (3.9)

[a] Units: [(nmoles/min/mg)/µmoles/kg/day)] × 10E−03
[b] Based on dosing with parent phthalate.
[c] Based on exposure to metabolite of parent phthalate.

5.9 Evidence of Chronic Toxicity and Carcinogenicity from Read-Across to Related Chemicals

No chronic toxicity or carcinogenicity studies of DIBP or DCHP are available. Chronic toxicity and carcinogenicity studies are available for DEHP, BBP, DBP, DINP, and DIDP. For these phthalates, EPA has consistently identified developmental toxicity as a more sensitive and robust outcome for characterizing risk to human health from acute, intermediate, and chronic exposures. This is demonstrated by the PODs selected by EPA to characterize risk to human health for these durations (Table 5-7). The only exception to this is for DINP, in which non-cancer liver effects observed in a 2-year dietary study of F344 rats were identified as a more sensitive and relevant effect for setting the chronic POD compared to developmental toxicity (Table 5-7).

Furthermore, though available carcinogenicity data support differing cancer classifications for DEHP, BBP, DBP, DINP, and DIDP (summarized in Table 5-8), EPA has determined that quantitative cancer risk assessment is not needed for any of these phthalates. For DIDP, DEHP, BBP, and DBP, the Agency has concluded that these phthalates are *not likely to be carcinogenic to humans* and cancer risk was not quantitatively evaluated (Sections 4.3.1.4, 4.3.2.4, 4.3.3.3, and 4.3.5; (U.S. EPA, 2024a)). Finally, for DINP (Section 4.3.4), treatment-related increases in hepatocellular adenomas and/or carcinomas have been consistently observed in rats and mice of both sexes. EPA has previously concluded that DINP causes liver tumors in rodents through a PPARα MOA (U.S. EPA, 2025a). Notably, this conclusion was supported by the SACC during their July 2024 peer review meeting (U.S. EPA, 2024d). EPA further concluded that DINP is *not likely to be carcinogenic to humans* at doses below levels that do not result

in PPARα activation (U.S. EPA, 2025a). Furthermore, for DINP, the non-cancer POD based on non-cancer liver toxicity (DINP) is lower than the hazard value for PPARα activation identified by EPA. Therefore, EPA has concluded that the non-cancer POD for DINP is expected to adequately account for all chronic toxicity, including carcinogenicity.

Table 5-7. Summary of Non-Cancer PODs Selected for Use in Human Health Risk Characterization for Phthalates DCHP, DIBP, DEHP, DBP, BBP, DINP, and DIDP

Phthalate	Relevant Exposure Scenario(s)	Target Organ System	POD (HED) (mg/kg-day)	Benchmark MOE	Effect	Reference
DEHP	Acute, intermediate, chronic	Developing male reproductive system (phthalate syndrome-related effects)	NOAEL = 4.8 (1.1)	$UF_A = 3^a$ $UF_H = 10$ Total UF = 30	↑ Total reproductive tract malformations in F1 and F2 rat offspring	(U.S. EPA, 2025h)
BBP	Acute, intermediate, chronic	Developing male reproductive system (phthalate syndrome-related effects)	NOAEL = 50 (12)	$UF_A = 3^a$ $UF_H = 10$ Total UF = 30	Phthalate syndrome-related effects in rats (*e.g.*, ↓AGD; ↓ fetal testicular testosterone; ↓ reproductive organ weights; Leydig cell effects)	(U.S. EPA, 2025e)
DBP	Acute, intermediate, chronic	Developing male reproductive system (phthalate syndrome-related effects)	$BMDL_5$ = 9 (2.1)	$UF_A = 3^a$ $UF_H = 10$ Total UF = 30	↓ Fetal testicular testosterone in rats	(U.S. EPA, 2025f)
DIBP	Acute, intermediate, chronic	Developing male reproductive system (phthalate syndrome-related effects)	$BMDL_5$ = 24 (5.7)	$UF_A = 3^a$ $UF_H = 10$ Total UF = 30	↓ *ex vivo* fetal testicular testosterone production in rats	(U.S. EPA, 2025i)
DCHP	Acute, intermediate, chronic	Developing male reproductive system (phthalate syndrome-related effects)	NOAEL = 10 (2.4)	$UF_A = 3^a$ $UF_H = 10$ Total UF = 30	Phthalate syndrome-related effects in rats (*e.g.*, ↓ fetal testicular testosterone; ↓AGD; Leydig cell effects; ↓ mRNA and/or protein expression of steroidogenic genes; ↓INSL3)	(U.S. EPA, 2025g)
DINP	Acute, intermediate	Developing male reproductive system (phthalate syndrome-related effects)	$BMDL_5$ = 49 (12)	$UF_A = 3^a$ $UF_H = 10$ Total UF = 30	↓ Fetal testicular testosterone in rats	(U.S. EPA, 2025j)
	Chronic	Liver Toxicity	NOAEL = 15 (3.5)	$UF_A = 3^a$ $UF_H = 10$ Total UF = 30	↑ Liver weight, ↑ serum chemistry, histopathology (*e.g.*, focal necrosis, spongiosis hepatis)	
DIDP	Acute, intermediate, chronic	Developmental toxicity (decreased F2 offspring survival)	NOAEL = 38 (9.0)	$UF_A = 3^a$ $UF_H = 10$ Total UF = 30	Reduced F2 offspring survival on PND1 and PND4 in rats	(U.S. EPA, 2024a)

[a] EPA used allometric body weight scaling to the ¾-power to derive human equivalent doses (HEDs). Consistent with EPA Guidance (U.S. EPA, 2011), the UF_A was reduced from 10 to 3.

Table 5-8. Summary of Cancer Classifications for DEHP, BBP, DBP, DINP, and DIDP

Phthalate	EPA Cancer Classification (Section or Reference for Additional Information)
DEHP	*Not likely to be carcinogenic to humans* (Section 4.3.1.4)
BBP	*Not likely to be carcinogenic to humans* (Section 4.3.2.4)
DBP	*Not likely to be carcinogenic to humans* (Section 4.3.3.3)
DINP	*Not likely to be carcinogenic to humans* at doses below levels that do not result in PPARα activation (U.S. EPA, 2025a) (Section 4.3.4)
DIDP	*Not likely to be carcinogenic to humans* (U.S. EPA, 2024a) (Section 4.3.5)

5.10 Weight of Scientific Evidence Conclusions

Based on the weight of scientific evidence, EPA concludes that the lack of chronic toxicity and carcinogenicity bioassays for DIBP and DCHP do not suggest that there are significant remaining scientific uncertainties in the qualitative and quantitative risk characterization for either of these phthalates. Notably, this conclusion was supported by the SACC during their August 2025 phthalates peer review meeting (U.S. EPA, 2025v). EPA has concluded that the non-cancer PODs for DIBP and DCHP, based on effects on the developing male reproductive system consistent with a disruption of androgen action and phthalate syndrome that were selected for characterizing risk from acute, intermediate, and chronic exposure to DIBP and DCHP, are health-protective PODs—including for PESS. These conclusions are based on the following weight of scientific evidence considerations:

- The toxicological profiles of DCHP, DIBP, as well as DEHP, BBP, DBP, DINP, and DIDP were evaluated (Section 5).
- Following oral exposure, phthalates are rapidly absorbed, metabolized, systemically distributed and excreted in urine, and to a lesser extent in feces. Studies of rodents and humans have demonstrated near complete excretion within 72 to 96 hours. Based on the rapid elimination kinetics, phthalates are not considered bioaccumulative (Section 5.2).
- DIBP, DCHP, DEHP, BBP, DBP, DINP, and DIDP are not considered to be direct-acting genotoxicants or mutagens (Section 5.7).
- There is no evidence for immune suppression in experimental animal studies of DIBP, DCHP, DEHP, BBP, DBP, DINP, and DIDP (Section 5.6).
- DIBP, DCHP, DEHP, BBP, DBP, and DINP—but not DIDP—are antiandrogenic and can disrupt fetal testicular testosterone biosynthesis in rats leading to a spectrum of effects on the developing male reproductive system consistent with phthalate syndrome (Section 5.4).
- Intermediate and subchronic duration studies identify the liver as a target organ of phthalate toxicity, including for DIBP, DCHP, DEHP, BBP, DBP, DINP, and DIDP. Evidence of PPARα activation in the liver is also apparent (Sections 5.5 and 5.8).
- Of the five phthalates (DEHP, BBP, DBP, DINP, DIDP) that have chronic toxicity studies, in only one case (DINP) did a chronic toxicity study support a more sensitive POD for use in risk characterization than a POD derived from developmental toxicity studies. For DIDP, developmental toxicity (decreased F2 offspring survival) was identified as the most sensitive outcome and was used in characterize risk from acute, intermediate, and chronic duration exposures. For DEHP, BBP, DBP, DIBP, and DCHP, effects on the developing male reproductive system consistent with a disruption of androgen action were identified as the most sensitive and robust outcomes for use in risk characterization for acute, intermediate, and chronic exposure scenarios. For DINP, antiandrogenic effects were the most sensitive outcome for acute and intermediate exposure durations, while non-cancer liver effects were identified as the most sensitive effect for chronic exposure durations.
- EPA has determined that quantitative cancer risk assessment is not needed DEHP, BBP, DBP, DINP, or DIDP (Section 5.9).
- EPA has concluded that DIDP, DEHP, BBP, and DBP are *not likely to be carcinogenic to humans*. For DEHP, DBP, BBP, and DIDP, EPA did not quantitatively evaluate cancer risk. EPA concluded that DINP is *not likely to be carcinogenic to humans* at doses below levels that do not result in PPARα activation. For DINP, the non-cancer POD based on non-cancer liver toxicity

(DINP) is lower than the hazard values for PPARα activation; therefore, EPA has concluded that the non-cancer POD for DINP is expected to adequately account for all chronic toxicity, including carcinogenicity (Section 5.9).

6 CONCLUSIONS

Available studies indicate that phthalates DEHP, BBP, DBP, DIBP, DCHP, DINP, and DINP are not direct acting genotoxicants or mutagens (Section 2). Cancer bioassays are available for DEHP, BBP, DBP, DINP, and DIDP. EPA has previously concluded that DIDP is *not likely to be carcinogenic to humans* (U.S. EPA, 2024a). Herein, EPA has concluded that DEHP, BBP, and DBP are *not likely to be carcinogenic to humans* (Sections 4.3.1.4, 4.3.2.4 and 4.3.3.3). For DEHP, DBP, BBP, and DIDP, EPA did not quantitatively evaluate cancer risk.

For DINP (Section 4.3.4), treatment-related increases in hepatocellular adenomas and/or carcinomas have been consistently observed in rats and mice of both sexes. EPA has previously concluded that DINP causes liver tumors in rodents through a PPARα MOA (U.S. EPA, 2025a). Notably, this conclusion was supported by the SACC during their July 2024 peer review meeting (U.S. EPA, 2024d). Furthermore, EPA has previously concluded that (1) DINP is *not likely to be carcinogenic to humans* at doses below levels that do not result in PPARα activation; and (2) that the non-cancer POD based on liver toxicity will adequately account for all chronic toxicity, including carcinogenicity, which could potentially result from exposure to DINP (U.S. EPA, 2025a).

No chronic toxicity or cancer bioassays are available for DIBP or DCHP. Herein, EPA used elements of the ReCAAP weight of evidence framework as an organizational tool to evaluate the extent to which the lack of carcinogenicity studies imparts significant uncertainty on the human health risk assessments for DIBP and DCHP (Section 5). Human health hazards and toxicokinetic properties of DIBP and DCHP were evaluated and compared to DEHP, DBP, BBP, DINP, and DIDP. Overall, based on the weight of scientific evidence, EPA concludes that the lack of chronic toxicity and carcinogenicity bioassays for DIBP and DCHP do not suggest that there are significant remaining scientific uncertainties in the qualitative and quantitative risk characterization for either of these phthalates. Furthermore, EPA has concluded that the non-cancer PODs for DIBP and DCHP are health-protective, including for PESS. These PODs for DIBP and DCHP are based on effects on the developing male reproductive system consistent with a disruption of androgen action and phthalate syndrome that were selected for characterizing risk from acute, intermediate and chronic exposure to DIBP and DCHP. These conclusions are based on several key weight of scientific evidence considerations (discussed in Section 5). First, for the five phthalates used to support read-across, effects on the developing male reproductive system consistent with a disruption of androgen action and phthalate syndrome is a more sensitive and robust endpoint for deriving PODs for use in characterizing risk for acute, intermediate, and chronic exposure scenarios than PPARα-mediated effects on the liver. The one exception to this was for DINP, in which chronic non-cancer liver effects were identified as a more sensitive outcome than developmental toxicity for deriving a chronic POD. Second, EPA has determined that quantitative cancer risk assessment is not needed for DEHP, DBP, BBP, DINP, or DIDP.

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APPENDICES

Appendix A SUMMARY OF DEHP GENOTOXICITY STUDIES

Table_Apx A-1. Genotoxicity of DEHP *In Vitro* (Studies Considered by ATSDR (2022)) [a]

Species (Test System)	Endpoint	Result		Reference
		With Activation	Without Activation	
Prokaryotic organisms				
Salmonella typhimurium (TA98, TA100, TA1535, TA1538)	Gene mutation	–	–	(Agarwal et al., 1985)
typhimurium (NS)	Gene mutation	–	–	(Astill et al., 1986)
S. typhimurium (TA98, TA100, TA1535, TA1537, TA1538)	Gene mutation	–	–	(Kirby et al., 1983)
S. typhimurium (TA100)	Gene mutation	–	+	(Kozumbo et al., 1982)
S. typhimurium (TA98)	Gene mutation	–	–	(Sato et al., 1994)
S. typhimurium (TA102)	Gene mutation	–	–	(Schmezer et al., 1988)
S. typhimurium (TA98, TA100, TA1535, TA1537, TA1538)	Gene mutation	–	–	(Simmon et al., 1977)
S. typhimurium (TA100)	Gene mutation	–	–	(Seed, 1982)
S. typhimurium (TA100)	Gene mutation	+	NS	(Tomita et al., 1982)
S. typhimurium (TA98, TA100)	Gene mutation	–	–	(Yoshikawa et al., 1983)
S. typhimurium (TA98, TA1537)	Gene mutation	–	NS	(Kanode et al., 2017)
S. typhimurium (TA98, TA100, TA1535, TA1537)	Gene mutation	–	–	(Lee et al., 2019)
S. typhimurium (TA98, TA100, TA1535, TA1537)	Gene mutation	–	–	(Zeiger et al., 1985)
Escherichia coli PQ37	Gene mutation	–	–	(Sato et al., 1994)
E. coli WP2UVRA+	Gene mutation	–	–	(Yoshikawa et al., 1983)
E. coli WP2UVRA	Gene mutation	–	–	(Yoshikawa et al., 1983)
E. coli WP2UVRA	Gene mutation	–	–	(Lee et al., 2019)
S. typhimurium (TA1535/psk 1002)	DNA damage	+	–	(Okai and Higashi-Okai, 2000)
Bacillus subtilis (rec assay)	DNA damage	+	–	(Tomita et al., 1982)
S. typhimurium (TA100)	Azaguanine resistance	–	–	(Seed, 1982)
Eukaryotic organisms				
Saccharomyces cerevisae (XV185-14C, D7, RM52, D6, D5, D6-1)	Gene mutation	–	–	(Parry et al., 1985)
Saccharomyces cerevisiae (JD1, D7-144, D7)	Gene conversion	–	–	(Parry et al., 1985)
S. cerevisiae (D61M, D6)	Mitotic aneuploidy	+	+	(Parry et al., 1985)

Species (Test System)	Endpoint	Result		Reference
		With Activation	Without Activation	
S. cerevisiae (D61M, D6)	Mitotic segregation	–	–	(Parry et al., 1985)
Schizosaccharomyces pombe (P1)	Gene mutation	–	–	(Parry et al., 1985)
Aspergillus niger (P1)	Mitotic segregation	–	NS	(Parry et al., 1985)
Mammalian cells				
Mouse lymphoma cells	Mutagenicity	–	–	(Astill et al., 1986)
Mouse lymphoma cells	Mutagenicity	–	–	(Kirby et al., 1983)
Mouse lymphoma cells	Mutagenicity	± [b]	–	(Oberly et al., 1985)
Mouse lymphoma cells	Mutagenicity	–	–	(Tennant et al., 1987)
Human leukocytes	DNA damage	–	+	(Anderson et al., 1999)
Human lymphocytes	DNA damage	–	+	(Anderson et al., 1999)
Human HeLa cells	DNA damage	NS	+	(Park and Choi, 2007)
Human HepG2 cells	DNA damage	NS	+	(Choi et al., 2010)
Human LNCaP prostate adenocarcinoma cells	DNA damage	NS	+	(Erkekoglu et al., 2010b)
Human HepaRG cells	DNA damage	–	N/A	(Le Hégarat et al., 2014)
Human thyroid carcinoma	DNA damage	NS	+	(Kim et al., 2019)
Mouse MA-10 Leydig tumor cells	DNA damage	NS	+	(Erkekoglu et al., 2010a)
Mouse lung cells	DNA damage	NS	+	(Wang et al., 2014)
Rat hepatocytes	DNA damage	–	N/A	(Schmezer et al., 1988)
Hamster hepatocytes	DNA damage	–	N/A	(Schmezer et al., 1988)
CHO cells	DNA damage	–	–	(Douglas et al., 1986)
Human hepatocytes	DNA repair	–	N/A	(Butterworth et al., 1984)
Mouse hepatocytes	DNA repair	–	N/A	(Smith-Oliver and Butterworth, 1987)
Rat hepatocytes	DNA repair	–	N/A	(Astill et al., 1986)
Rat hepatocytes	DNA repair	–	N/A	(Butterworth, 1984)
Rat hepatocytes	DNA repair	–	N/A	(Hodgson et al., 1982)
Rat hepatocytes	DNA repair	–	N/A	(Kornbrust et al., 1984)
Rat hepatocytes	DNA repair	–	N/A	(Probst and Hill, 1985)
Chinese hamster V79 fibroblasts	DNA repair	–	N/A	(Kornbrust et al., 1984)
Human HepaRG cells	Micronuclei	–	N/A	(Le Hégarat et al., 2014)
Human TK6 lymphoblastoid cells	Micronuclei	NS	–	(Sobol et al., 2012)
Rat RL4 liver cells	Sister chromatid exchange	–	N/A	(Priston and Dean, 1985)
CHO cells	Sister chromatid exchange	NS	–	(Abe and Sasaki, 1977)

Species (Test System)	Endpoint	Result		Reference
		With Activation	Without Activation	
CHO cells	Sister chromatid exchange	–	–	(Douglas et al., 1986)
CHO cells	Sister chromatid exchange	NS	–	(Phillips et al., 1982)
CHO cells	Sister chromatid exchange	NS	+	(Tennant et al., 1987)
Human hepatocytes	Chromosomal aberrations	–	N/A	(Turner et al., 1974)
Human leucocytes	Chromosomal aberrations	–	N/A	(Stenchever et al., 1976)
Rat RL4 liver cells	Chromosomal aberrations	–	N/A	(Priston and Dean, 1985)
CHO cells	Chromosomal aberrations	NS	–	(Phillips et al., 1982)
CHO cells	Chromosomal aberrations	NS	–	(Tennant et al., 1987)
Chinese hamster lung (CHL/OU)	Chromosomal aberrations	–	–	(Lee et al., 2019)
SHE cells	Chromosomal aberrations	–	–	(Tsutsui et al., 1993)
CH SV40-transformed liver cells	Selective DNA amplification	–	N/A	(Schmezer et al., 1988)
Mouse JB6 epidermal cells	Cell transformation	+	N/A	(Diwan et al., 1985)
Mouse C3H/10T1/2 fibroblasts	Cell transformation	NS	–	(Sanchez et al., 1987)
Mouse BALB 3T3 cells	Cell transformation	–	–	(Astill et al., 1986)
SHE cells	Cell transformation	NS	+	(Mauthe et al., 2001; Leboeuf et al., 1996)
SHE cells	Cell transformation	NS	+	(Mikalsen et al., 1990)
SHE cells	Cell transformation	NS	+	(Pant et al., 2010)
SHE cells	Cell transformation	NS	+	(Sanner and Rivedal, 1985)
SHE cells	Cell transformation	+	±	(Tsutsui et al., 1993)
Rat hepatocytes	DNA binding	–	N/A	(Gupta et al., 1985)
Human fetal pulmonary cells	Aneuploidy	–	N/A	(Stenchever et al., 1976)
Rat RL4 liver cells	Polyploidy	–	N/A	(Priston and Dean, 1985)

– = negative result; + = positive result; ± = equivocal result; CHO = Chinese hamster ovary; N/A = not applicable to mammalian cell cultures with endogenous metabolic activity; NS = not specified; SHE = Syrian hamster embryo

[a] Adapted from Table 2-18 of ATSDR (2022).

[b] Mutagenic effect coincident with cytotoxicity.

Table_Apx A-2. Genotoxicity of MEHP *In Vitro* (Studies Considered by ATSDR (2022)) [a]

Species (Test System)	Endpoint	Result		Reference
		With Activation	Without Activation	
Prokaryotic organisms				
S. typhimurium (TA98, TA100, TA1535, TA1538)	Gene mutation	−	−	(Agarwal et al., 1985)
S. typhimurium (NS)	Gene mutation	−	−	(Astill et al., 1986)
S. typhimurium (TA97, TA98, TA100, TA102)	Gene mutation	−	−	(Dirven et al., 1991)
S. typhimurium (TA98, TA100, TA1535, TA1537, TA1538)	Gene mutation	−	−	(Kirby et al., 1983)
S. typhimurium (TA98, TA100, TA1535, TA1537, TA1538)	Gene mutation	−	−	(Ruddick et al., 1981)
S. typhimurium (TA100, TA102)	Gene mutation	−	−	(Schmezer et al., 1988)
S. typhimurium (TA100)	Gene mutation	−	±	(Tomita et al., 1982)
S. typhimurium (TA98, TA100)	Gene mutation	−	−	(Yoshikawa et al., 1983)
S. typhimurium (TA98, TA100, TA1535, TA1537)	Gene mutation	−	−	(Zeiger et al., 1985)
Escherichia coli (WP2 B/r)	Gene mutation	NS	± [b]	(Tomita et al., 1982)
E. coli (WP2 *try*− [*UvrA+ and UvrA*−])	Gene mutation	−	−	(Yoshikawa et al., 1983)
Bacillus subtilis (H17, M45)	DNA damage (Rec assay)	NS	+	(Tomita et al., 1982)
Mammalian cells				
Mouse lymphoma cells L5178Y (tk+/tk−)	Mutagenicity	−	−	(Kirby et al., 1983)
CHO cells	Mutagenicity	NS	−	(Phillips et al., 1982)
CHO cells (AS52)	Mutagenicity	NS	+	(Chang et al., 2017)
Human leukocytes	DNA damage	NS	+	(Anderson et al., 1999)
Human LNCaP prostatic cancer cells	DNA damage	NS	+	(Erkekoglu et al., 2010b)
Mouse MA-10 Leydig tumor cells	DNA damage	NS	+	(Erkekoglu et al., 2010a)
Human peripheral lymphocytes	DNA damage	NS	+	(Kleinsasser et al., 2004)
Human nasal mucosa cells	DNA damage	NS	+	(Kleinsasser et al., 2004)
CHO cells (AS52)	DNA damage	NS	+	(Chang et al., 2017)
Human HepG2 cells	Oxidative DNA damage	NS	+	(Yang et al., 2012)
Human primary hepatocytes	DNA repair	−	N/A	(Butterworth et al., 1984)
Rat primary hepatocytes	DNA repair	−	N/A	(Cattley et al., 1986)
Mouse primary hepatocytes	DNA repair	−	N/A	(Smith-Oliver and Butterworth, 1987)
Hamster SV40 transformed cells	DNA amplification	NS	−	(Schmezer et al., 1988)

Species (Test System)	Endpoint	Result		Reference
		With Activation	Without Activation	
Chinese hamster V79 fibroblasts	Sister chromatid exchange	NS	+	(Tomita et al., 1982)
Rat RL4 liver cells	Chromosomal aberrations	NS	+	(Phillips et al., 1986)
CHO cells	Chromosomal aberrations	+	+	(Phillips et al., 1986)
CHO cells	Chromosomal aberrations	NS	+	(Phillips et al., 1982)
SHE cells	Chromosomal aberrations	+	–	(Tsutsui et al., 1993)
CHO transformed cells	Gene mutation	NS	+	(Chang et al., 2017)
Mouse BALB 3T3 cells	Cell transformation	–	–	(Astill et al., 1986)
Mouse C3H/10T1/2 fibroblasts	Cell transformation	NS	–	(Sanchez et al., 1987)
SHE cells	Cell transformation	NS	+	(Mikalsen et al., 1990)
SHE cells	Cell transformation	+	–	(Tsutsui et al., 1993)

– = negative result; + = positive result; ± = equivocal result; N/A = not applicable to mammalian cell cultures with endogenous metabolic activity; NS = not specified
[a] Adapted from Table 2-19 of ATSDR (2022).
[b] Mutagenic effect coincident with cytotoxicity.

Table_Apx A-3. Genotoxicity of DEHP *In Vivo* (Studies Considered by ATSDR (2022)) [a]

Species (Exposure Route)	Endpoint	Result	Reference
Mammals			
Mouse (subcutaneous)	Dominant lethal test	+	(Autian, 1982)
Mouse (gavage)	Dominant lethal test	–	(Rushbrook et al., 1982)
Mouse (intraperitoneal)	Dominant lethal test	+	(Singh et al., 1974)
Rat (*gpt* delta transgenic) (diet)	Gene mutation in liver	–	(Kanki et al., 2005)
Mouse (lacZ transgenic) (NS)	Gene mutation in liver	+	(Boerrigter, 2004)
Mouse (lacZ transgenic) (NS)	Gene mutation in kidney or spleen	–	(Boerrigter, 2004)
Hamster embryo (gavage; via placenta)	8AG/6TG-resistant mutation	+	(Tomita et al., 1982)
Mouse (NS)	Micronuclei in bone marrow	–	(Astill et al., 1986)
Mouse (intraperitoneal)	Micronuclei in bone marrow	–	(Douglas et al., 1986)
Mouse (Oral)	Micronuclei in bone marrow	–	(Lee et al., 2019)
Human (unknown)	DNA damage in sperm and granulosa cells	+	(Al-Saleh et al., 2019)

Species (Exposure Route)	Endpoint	Result	Reference
Human (unknown)	DNA damage in peripheral blood cells	–	(Franken et al., 2017)
Rat (gavage, diet)	DNA damage in liver	–	(Butterworth et al., 1984)
Rat (diet)	DNA damage in liver	–	(Tamura et al., 1991)
Rat (diet)	DNA damage in liver	–	(Pogribny et al., 2008)
Rat (gavage)	DNA damage in sperm	+	(Hsu et al., 2016)
Rat (gavage)	DNA damage in blood lymphocytes and sperm	+	(Karabulut and Barlas, 2018)
Rat (gavage)	DNA damage in thyroid	+	(Kim et al., 2019)
Mouse (pipette)	Oxidative DNA damage in brain	+	(Barakat et al., 2018)
Mouse (gavage)	Oxidative DNA damage in oocytes	+	(Lu et al., 2019)
Rat (diet)	DNA base modification in liver	–	(Cattley and Glover, 1993)
Rat (diet)	DNA base modification in liver	+	(Takagi et al., 1990)
Rat (gavage, diet)	DNA repair in liver	–	(Butterworth et al., 1984)
Rat (diet)	DNA repair in liver	–	(Cattley et al., 1988)
Rat (gavage, diet)	DNA repair in liver	–	(Kornbrust et al., 1984)
Rat (gavage)	DNA repair in liver	+	(Hayashi et al., 1998)
Mouse (gavage, diet)	DNA repair in liver	–	(Smith-Oliver and Butterworth, 1987)
Rat (diet)	DNA binding in liver	+	(Albro et al., 1982)
Rat (gavage)	DNA binding in liver	–	(Gupta et al., 1985)
Rat (gavage, diet)	DNA binding in liver	–	(Lutz, 1986; von Däniken et al., 1984)
Human (occupational)	Chromosomal aberrations in leucocytes	–	(Thiess and Fleig, 1978)
Rat (gavage)	Chromosomal aberrations in bone marrow	–	(Putman et al., 1983)
Hamster embryo (gavage; via placenta)	Chromosomal aberrations	+	(Tomita et al., 1982)
Hamster embryo (gavage; via placenta)	Cell transformation	+	(Tomita et al., 1982)
Rat embryo (intraperitoneal; via placenta)	Mitotic recombination	+	(Fahrig and Steinkamp-Zucht, 1996)
Rat (diet)	Tetraploid nuclei in liver	+	(Ahmed et al., 1989)
Host-mediated assay			
Salmonella typhimurium (TA100); (rat host-meditated)	Gene mutation	–	(Kozumbo et al., 1982)
Eukaryotic organisms			
Drosophila melanogaster (feeding)	Mitotic recombination	–	(Vogel and Nivard, 1993)
D. melanogaster (injection)	Sex linked recessive lethal	–	(Yoon et al., 1985)

– = negative result; + = positive result; DNA = deoxyribonucleic acid; *gpt* = guanine phosphoribosyltransferase
[a] Adapted from Table 2-20 of ATSDR (2022)

Table_Apx A-4. Genotoxicity of MEHP *In Vivo* (Studies Considered by ATSDR (2022)) [a]

Species (Exposure Route)	Endpoint	Result	Reference
Rat (gavage)	DNA damage in liver	−	(Elliott and Elcombe, 1987)
Rat (gavage)	Chromosomal aberrations in bone marrow	−	(Putman et al., 1983)
Hamster embryo (gavage; via placenta)	Chromosomal aberrations	+	(Tomita et al., 1982)
Hamster embryo (gavage; via placenta)	Cell transformation	+	(Tomita et al., 1982)
Hamster embryo (gavage; via placenta	8AG/6TG-resistant mutation	+	(Tomita et al., 1982)

− = negative result; + = positive result
[a] Adapted from Table 2-21 of ATSDR (2022).

Table_Apx A-5. Summary of NTP Genotoxicity Testing of DEHP (as Reported in NTP (2021b))

Species (Test System)	Result
In vitro studies	
Bacterial gene mutations: *Salmonella typhimurium* strains TA100, TA1535, TA1537, TA97, TA98 treated with 100 to 1,000 µg DEHP per plate with and without exogenous metabolic activation systems (*i.e.*, induced hamster, rat, or mouse liver S9)	Negative with and without S9 in 6 independent assays
Mouse lymphoma gene mutation assay with L5178Y $tk^{+/-}$ cells with 0.125 to 3.0 µL/mL DEHP with and without induced rat liver S9	Negative with and without S9 in 1 assay
In vitro CHO cell chromosomal aberration test with and without induced rat liver S9	Negative with and without S9 in 3 independent studies at concentrations up to 5,000 µg/mL
In vitro CHO cell sister chromatid exchange test with and without induced rat liver S9	Positive in 4, equivocal in 3, and negative in 2 out of 9 studies without rat liver S9 Positive or equivocal results were only observed at concentrations of DEHP that induced severe cell cycle delay that necessitated longer incubation times. Cytotoxicity and longer incubation times may have contributed to increased SCE levels, rather than direct interactions of DEHP with chromosomal DNA.
	Negative in 9 out of 9 studies with rat liver S9
In vivo studies	
In vivo chromosome aberration test with female B6C3F1 mice fed diets containing 3,000 to 12,000 ppm DEHP for 14 days	No increase in chromosomal aberrations in bone marrow cells
In vivo micronucleus test in mice	Equivocal overall result in B6C3F1 females exposed to 3,000–12,000 ppm DEHP in feed for 14 days
	Equivocal in male TgAC (FVB/N) mice and positive in female mice exposed to 1,500–6,000 ppm DEHP in feed for 26 weeks
	Negative in male and female TgAC (FVB/N) mice exposed dermally to 100–400 mg/kg-day DEHP for 26 weeks
Drosophila melanogaster sex-linked recessive lethal test	Negative (adult injection)
	Negative (larval feeding)

Appendix B RODENT CARCINOGENICITY STUDY SUMMARIES

B.1 Di(2-ethylhexyl) Phthalate (DEHP)

B.1.1 Mice – Oral Exposure Studies

B.1.1.1 Two-Year Dietary Study of B6C3F1 Mice (NTP, 1982a)

NTP (1982a) reports the results of a 2-year dietary study of male and female B6C3F1mice. Male and female mice (50 per sex per dose) were administered diets containing 0, 3,000, or 6,000 ppm DEHP (equivalent to ≈673 and 1,325 mg/kg-day for males and 799 and 1,821 mg/kg-day for females) for 103 weeks. Terminal body weight was reduced 7 and 10 percent in low- and high-dose males, respectively, and 21 and 33 percent in low- and high-dose females, respectively. Average daily feed consumption per rat was 100 and 96 percent of controls for low-dose males and females, respectively, and 96 and 100 percent of controls for high-dose males and females, respectively. No compound-related clinical signs were reported. No significant effects on survival were observed for males; however, survival was significantly reduced for low-dose females (survival of control, low- and high-dose: 34/50, 38/50, 35/50 for males; 39/50, 25/50, 33/50 for females). Dose-related, statistically significant increases in hepatocellular carcinoma were observed in high-dose male mice, while combined hepatocellular carcinoma and adenoma were significantly increased in low- and high-dose male mice compared to controls (Table_Apx B-1). Similarly, statistically significant increases in hepatocellular carcinoma and combined hepatocellular carcinoma and adenoma were observed in low- and high-dose female mice (Table_Apx B-1). No other tumor types were significantly increased in male or female mice at any dose.

Under the conditions of the study, NTP concluded that DEHP was carcinogenic for B6C3F1 mice, causing increased incidence of male and female mice with hepatocellular carcinomas.

Table_Apx B-1. Incidence of Liver Tumors in Male and Female B6C3F1 Mice Fed Diets Containing DEHP for 2 Years (NTP, 1982a) [a]

Tissue: Tumor Type	Control	3,000 ppm	6,000 ppm
Male mice			
Liver: Hepatocellular carcinoma	9/50 (18%)	14/48 (29%)	19/50 (38%)*
Liver: Hepatocellular adenoma	6/50 (12%)	11/48 (23%)	10/50 (20%)
Liver: Hepatocellular carcinoma or adenoma	14/50 (28%)	25/48 (52%)*	29/50 (58%)*
Female mice			
Liver: Hepatocellular carcinoma	0/50	7/50 (14%)*	17/50 (34%)*
Liver: Hepatocellular adenoma	1/50 (2%)	5/50 (10%)	1/50 (2%)
Liver: Hepatocellular carcinoma or adenoma	1/50 (2%)	12/50 (24%)*	18/50 (36%)*

[a] Asterisk (*) indicates statistically significant pairwise comparison to controls by Fisher exact test ($p < 0.05$) when the Cochran-Armitage test was statistically significant ($p < 0.05$). Data from Tables 15 and 16 of (NTP, 1982a).

B.1.1.2 Two-Year Dietary Study of B6C3F1 Mice (David et al., 2000a; David et al., 1999)

David et al. (2000a; 1999) reports the results of a 2-year dietary study of male and female B6C3F1 mice. Briefly, male and female mice (65−70 per sex per dose) were administered diets containing 0, 100, 500, 1,500, or 6,000 ppm DEHP for up to 104 weeks (equivalent to 19, 99, 292, and 1,266 mg/kg-day for males; 24, 117, 354, 1,458 mg/kg-day for females). An additional recovery group was included in which male and female mice (55/sex) were fed diets containing 6,000 ppm DEHP for 78 weeks and then control diet for an additional 26 weeks. Survival was significantly reduced for high-dose males. Adjusted survival rates at study termination were 75, 80, 71, 71, and 31 percent for males and 63, 66, 73, 72, and 61 percent for females across dose groups. The most common cause of death was hepatocellular neoplasia, which was most frequently observed in mice fed diets containing 1,500 and 6,000 ppm DEHP. Mean body weight gain was significantly lower in high-dose males compared to controls (mean body weight change for control and high-dose males: 10.5 ± 2.7 vs. 5.8 ± 2.5 g) but was not significantly affected for females in any dose group. Incidence of combined hepatocellular adenomas and carcinomas were statistically significantly increased in a dose-related manner in male mice at 500 ppm DEHP and above and in female mice at 1,500 ppm DEHP and above (Table_Apx B-2). No other tumor types were significantly increased in male or female mice at any dose.

Table_Apx B-2. Incidence of Liver Tumors in Male and Female B6C3F1 Mice Fed Diets Containing DEHP for 2 Years (David et al., 2000a; David et al., 1999) [a]

Tissue: Tumor Type	0 ppm	100 ppm	500 ppm	1,500 ppm	6,000 ppm	Recovery	Historical
Male mice							
Liver: Hepatocellular carcinoma	4/70 (6%)	5/60 (8%)	9/65 (14%)	14/65 (22%)	22/70 (31%)	12/55 (22%)	
Liver: Hepatocellular adenoma	4/70 (6%)	10/60 (17%)	13/65 (20%)	14/65 (22%)	19/70 (27%)	3/55 (5%)	
Liver: Hepatocellular carcinoma or adenoma	8/70 (11%)	14/60 (23%)	21/65* (32%)	27/65* (42%)	37/70* (53%)	14/55* (26%)	41/149
Female mice							
Liver: Hepatocellular carcinoma	3/70 (4%)	2/60 (3%)	3/65 (5%)	10/65 (15%)	6/70 (23%)	23/55 (42%)	
Liver: Hepatocellular adenoma	0/70	2/60 (3%)	4/65 (6%)	9/65 (14%)	34/70 (49%)	13/55 (24%)	
Liver: Hepatocellular carcinoma or adenoma	3/70 (4%)	4/60 (6%)	7/65 (11%)	19/65* (29%)	44/70* (63%)	30/55* (55%)	11/151

[a] Asterisk indicates statistically significant pairwise comparison to the control by Fisher exact test ($p \leq 0.05$) as determined by original study authors. Data from Table 6 of (David et al., 1999).

B.1.2 Rats – Oral Exposure Studies

B.1.2.1 Two-Year Dietary Study of F344 Rats (NTP, 1982a)

NTP (1982a) reports the results of a 2-year dietary study of male and female F344 Rats. Male and female rats (50 per sex per dose) were administered diets containing 0, 6,000, or 12,000 ppm DEHP (equivalent to ≈322 and 674 mg/kg-day for males; 394 and 774 mg/kg-day for females) for 103 weeks. Terminal body weight was reduced 11 and 15 percent in low- and high-dose males, respectively, and 5

and 20 percent in low- and high-dose females, respectively. Average daily feed consumption per rat was 86 and 85 percent of controls for low-dose males and females, and 86 and 75 percent of controls for high-dose males and females, respectively. No compound-related clinical signs were reported. No significant effects on survival were observed (survival of control, low- and high-dose: 30/50, 28/50, and 33/50 for males; 36/50, 34/50, and 38/50 for females). No significant increases in MNCL or pancreatic acinar cell adenomas were observed in either sex. Compared to controls, the incidence of testicular interstitial cell tumors was significantly decreased in high-dose male rats; however, the spontaneous background rate of this tumor type was high (96%) in control males (Table_Apx B-3). Dose-related, statistically significant increases in combined neoplastic nodules and hepatocellular carcinomas were observed in high-dose male rats (incidence: 12/49 compared to 3/50 for controls). Similarly, statistically significant increases in hepatocellular carcinoma and neoplastic nodules were observed in high-dose females, while the incidence of combined hepatocellular carcinomas and neoplastic nodules was significantly increased in low- and high-dose females (combined incidence: 0/50, 6/49, and 13/50) (Table_Apx B-3).

Under the conditions of the study, NTP concluded that DEHP was carcinogenic for F344 rats, causing increased incidence of female rats with hepatocellular carcinomas, and inducing an increased incidence of male rats with either hepatocellular carcinomas or neoplastic nodules.

Table_Apx B-3. Incidence of Tumors in Male and Female F344 Rats Fed Diets Containing DEHP for 2 Years (NTP, 1982a) [a]

Tissue: Tumor Type	Control	6,000 ppm	12,000 ppm
Male rats			
Testis: Interstitial cell tumor	47/49 (96%)	42/44 (95%)	11/48 (23%)*
Liver: Hepatocellular carcinoma	1/50 (2%)	1/49 (2%)	5/49 (10%)
Liver: Neoplastic nodule	2/50 (4%)	5/49 (10%)	7/49 (14%)
Liver: Hepatocellular carcinoma or neoplastic nodule	3/50 (6%)	6/49 (12%)	12/49 (24%)*
Female rats			
Liver: Hepatocellular carcinoma	0/50	2/49 (2%)	8/50 (16%)*
Liver: Neoplastic nodule	0/50	4/49 (8%)	5/50 (10%)*
Liver: Hepatocellular carcinoma or neoplastic nodule	0/50	6/49 (12%)*	13/50 (26%)*

[a] Asterisk (*) indicates statistically significant pairwise comparison to the control by Fisher exact test ($p < 0.05$) when the Cochran-Armitage test was statistically significant ($p < 0.05$). Data from Tables 11 and 12 of (NTP, 1982a).

B.1.2.2 Two-Year Dietary Study of F344 Rats (David et al., 2000b; David et al., 1999)

David et al. (2000b; 1999) report the results of a 2-year dietary study of male and female F344 Rats. Briefly, male and female rats (55−80 per sex per dose) were administered diets containing 0, 100, 500, 2,500, or 12,500 ppm DEHP for up to 104 weeks (equivalent to 6, 29, 147, and 780 mg/kg-day for males; 7, 36, 182, and 939 mg/kg-day for females). An additional recovery group was included in which male and female rats (55/sex) were fed diets containing 12,500 ppm DEHP for 78 weeks and then control diet for an additional 26 weeks. Survival was not significantly affected by treatment with DEHP, though there was trend toward lower survival for high-dose rats. Adjusted survival rates at study termination were 82, 78, 78, 70, and 73 percent for males and 80, 86, 80, 76, and 70 percent for females

across dose groups, respectively. The most frequent cause of death was reported to be due to MNCL. Mean body weights for high-dose male and female rats were significantly lower than the control for the duration of the study. From study week 1 to 105, mean body weight gain was 226 vs. 192 g for control and high-dose males, respectively, and 149 vs. 126 g for control and high-dose females, respectively. For females, the only tumor type significantly increased compared to concurrent controls was incidence of combined hepatocellular adenomas and carcinomas in the 100 ppm, 12,500 ppm, and recovery group. However, the effect on incidence of liver tumors in female rats was only dose-related at the high-dose group (Table_Apx B-4). In male rats, a treatment related increase in incidence of pancreatic acinar cell adenomas was observed in the high-dose group (incidence: 0/60 vs. 5/59 in control and high-dose group, respectively) (Table_Apx B-4). Additionally, in the two highest dose groups (*i.e.,* 2,500 and 12,500 ppm) incidence of MNCL and combined hepatocellular adenomas and carcinomas was statistically significantly increased compared to concurrent controls (Table_Apx B-4). Incidence of interstitial cell tumor in the testis was significantly decreased compared to concurrent controls (Table_Apx B-4).

Table_Apx B-4. Incidence of Tumors in Male and Female F344 Rats Fed Diets Containing DEHP for 2 Years (David et al., 2000b; David et al., 1999) [a]

Tissue: Tumor Type	0 ppm	100 ppm	500 ppm	2500 ppm	12,500 ppm	Recovery	Historical
Male rats							
Liver: hepatocellular carcinoma	1/80 (1%)	0/50	1/55 (2%)	3/65 (5%)	24/80 (34%)	7/55 (13%)	
Liver: hepatocellular adenoma	4/80 (5%)	5/50 (10%)	3/55 (6%)	8/65 (12%)	21/80 (30%)	12/55 (22%)	
Liver: hepatocellular carcinoma or adenoma	5/80 (7%)	5/50 (10%)	4/55 (7%)	11/65* (17%)	34/80* (43%)	18/55* (33%)	11/323
Testis: interstitial cell tumor	59/64 (92%)	45/50 (90%)	50/55 (91%)	60/65 (92%)	20/64* (31%)	–	
Pancreas: acinar cell adenoma	0/60	0/17	0/14	0/18	5/59* (8%)	–	
MNCL	15/65 (23%)	13/50 (26%)	16/55 (27%)	32/65* (49%)	27/65* (42%)	–	
Female rats							
Liver: hepatocellular carcinoma	0/80	1/50 (2%)	0/55	1/65 (2%)	14/80 (20%)	4/55 (7%)	
Liver: hepatocellular adenoma	0/80	3/50 (6%)	1/55 (2%)	2/65 (3%)	8/80 (10%)	6/55 (11%)	
Liver: hepatocellular carcinoma or adenoma	0/80	4/50* (8%)	1/55 (2%)	3/65 (5%)	22/80* (31%)	10/55* (18%)	4/320
Pancreas: acinar cell adenoma	0/60	0/7	0/10	0/14	2/60 (3%)	–	
MNCL	14/65 (22%)	17/50 (34%)	11/55 (20%)	16/65 (25%)	17/65 (26%)	–	

[a] Asterisk (*) indicates statistically significant pairwise comparison to the control by Fisher exact test ($p \leq 0.05$) as determined by original study authors. Data from Table 5 of (David et al., 1999) and Tables 6 and 7 of (David et al., 2000b).

B.1.2.3 Ninety-Five Week Dietary Study of Male F344 Rats (Rao et al., 1987)

Male F344 rats were fed diets containing 0 or 2 percent DEHP for 95 weeks (n = 8 and 10 rats in control and DEHP dose group, respectively). No liver tumors were observed in any control rats. Four of 10 rats treated with DEHP had one or more hepatocellular carcinomas, while 2 of 10 rats treated with DEHP had neoplastic nodules. Six out of 10 rats treated with DEHP had neoplastic nodules or hepatocellular carcinomas (combined) ($p < 0.005$ by X^2 test).

B.1.2.4 Two-Year Dietary Study of Male F344 Rats (Rao et al., 1990)

Male F344 rats were fed diets containing 0 or 2 percent DEHP for 108 weeks (n = 10 and 14 rats in control and DEHP dose group, respectively). All rats in both groups survived until scheduled necropsy. Terminal body weight of rats fed diets containing DEHP was significantly lower than that of controls (276 vs. 378 g). Liver tumors were observed in a single male control rat, where a tumor (classified as a hepatocellular carcinoma) of 15 mm in size was observed (Table_Apx B-5). Livers of 11 of 14 rats (79%) treated with DEHP contained grossly visible nodules measuring 1 to 15 mm in size (Table_Apx B-5). Grossly visible lesions less than 3 mm in size showed features consistent with altered areas or neoplastic nodules, while tumors 3 to 5 mm in size showed features consistent with neoplastic nodules and/or hepatocellular carcinoma. All tumors greater than 5 mm showed features consistent with well differentiated hepatocellular carcinoma.

Table_Apx B-5. Quantification of Liver Tumors by Size in Male F344 Rats Exposed to DEHP in the Diet for 108-Weeks (Rao et al., 1990) [a]

Group	Total No. Rats	# of Rats with Tumors			# of Nodules per Liver		
		<3 mm	3–5 mm	>5 mm	<3 mm	3–5 mm	>5 mm
Control	10	0	0	1	0	0	1
2% DEHP	14	8	2	5	1.14 ± 0.32[b] (0–3) [c]	1.14 ± 0.32 (0–1)	1.14 ± 0.32 (0–2)

[a] Adapted from Table 2 in (Rao et al., 1990)
[b] Mean ± SEM
[c] Range of number of tumors per liver

B.1.2.5 Lifetime Dietary Study of Male Sprague-Dawley Rats (Voss et al., 2005)

Voss et al. (2005) fed male Sprague-Dawley (SD) rats diets containing 0 (n = 390), 600 (n = 180), 1,897 (n = 100), or 6,000 (n = 60) mg/kg DEHP. Rats were fed 5 g of DEHP-diet/100 g rat/day for 6 days per week and received DEHP-free food on the seventh day only after the rest of their DEHP diet had been consumed. On this basis, rats received doses of 0, 30, 95, or 300 mg/kg-day DEHP over the entire lifetime of the animals (up to 159 weeks). Treatment with DEHP did not affect median survival times compared to control animals. Weight gain was comparable across control and all treatment groups, except for a short period around study day 300, when body weight of rats in all DEHP-treated groups was lower than the control. However, body weight of DEHP treated rats recovered to that of control levels by around study day 500. No increase in hepatocellular adenomas and carcinomas (combined) was observed when incidence of tumors across all rats were compared (incidence: 35/390 [9.0%], 16/180 [8.9%], 5/100 [5%], 5/60 [8.3%]). However, histopathologic examination of the liver of only rats found in a moribund state and sacrificed demonstrated a statistically significant dose-related increase in the incidence of combined hepatocellular adenomas and carcinomas in high-dose rats (Table_Apx B-6). In addition to liver tumors, treatment-related, statistically significant increases in benign Leydig cell tumors were observed in high-dose male rats (Table_Apx B-7).

Table_Apx B-6. Incidence of Liver Tumors in Male SD Rats Chronically Fed Diets Containing DEHP (Voss et al., 2005) [a]

Tissue: Tumor Type	Control	30 mg/kg	95 mg/kg	300 mg/kg
Number examined microscopically	167	84	53	31
Hepatocellular adenomas	13/167 (7.8%)	3/84 (3.6%)	4/53 (7.5%)	6/31 (19.4%)
Hepatocellular carcinomas	2/167 (1.2%)	3/84 (3.6%)	0/53	3/31 (9.7%)
Hepatocellular adenomas and carcinomas (combined)	15/167 (9.0%)	6/84 (7.1%)	4/53 (7.5%)	9/31* (29%)

[a] Asterisk (*) indicates statistically significant pairwise comparison to the control ($p \leq 0.05$) as determined by original study authors. Data from Table 4 of (Voss et al., 2005).

Table_Apx B-7. Incidence of Testicular Tumors in Male SD Rats Chronically Fed Diets Containing DEHP (Voss et al., 2005) [a]

Tissue: Tumor Type	Control	30 mg/kg	95 mg/kg	300 mg/kg
Number examined microscopically	390	180	100	60
Leydig cell tumors (all)	64/390 (16%)	34/180 (19%)	21/100 (21%)	17/60* (28%)
Leydig cell tumors (unilateral)	51/390 (13%)	30/180 (17%)	17/100 (17%)	12/60 (20%)
Leydig cell tumors (bilateral)	13/390 (3%)	4/180 (2%)	4/100 (4%)	5/60 (8%)
Leydig cell tumors (multifocal)	16/390 (4%)	14/180 (8%)	5/100 (5%)	10/60* (17%)

[a] Asterisk (*) indicates statistically significant pairwise comparison to the control ($p \leq 0.05$) as determined by original study authors. Data from Table 6 of (Voss et al., 2005).

B.1.2.6 Two-Year Dietary Study of Sprague-Dawley Rats (Perinatal and Postweaning Exposure Study) (NTP, 2021b)

NTP (2021b) report the results of a chronic perinatal and postweaning exposure study of DEHP. Beginning on gestational day 6, time-mated SD rats (45/group) were fed diets containing 0, 300, 1,000, 3,000 or 10,000 ppm DEHP throughout gestation and lactation. Groups of 50 male and female F1 offspring were then fed diets containing the same respective DEHP concentration for 2 years. Mean received doses of DEHP in units of mg/kg-day for each phase of the study are shown in Table_Apx B-8.

Table_Apx B-8. DEHP Intake (mg/kg-day) During the Gestational, Perinatal, and 2-Year Phases of Chronic Dietary Study of DEHP with SD Rats (NTP, 2021b) [a]

Phase of Study	0 ppm	300 ppm	1,000 ppm	3,000 ppm	10,000 ppm
Gestational Day 6−21	0	21	68	206	626
Lactational Day 1−14	0	49	266	482	1,244
2-year study (F1 males)	0	18	58	189	678
2-year study (F1 females)	0	18	62	196	772

[a] Adapted from Table 4 of (NTP, 2021b).

Treatment with DEHP had no effect on maternal survival, maternal clinal observations, percentage of females that produced pups, gestation length, pup sex ratio. In the high-dose group, dam body weight was lower (up to 10%) compared to controls throughout gestation, with decreased body weight gain over the GD 6 to 9, GD 15 to 18, and GD 18 to 21 intervals. Overall, mean dam body weight gain in high-dose dams was reduced 27 percent over GD 6 to 21 compared to controls. Similarly, high-dose dam body weight gain was reduced 10 percent throughout the lactational period (PND 1−21). Food consumption was reduced by approximately 14 and 39 percent in high-dose dams throughout gestation and lactation, respectively. On PND 1, total litter size and total live litter size was significantly reduced in the 10,000 ppm group, which corresponded to a decreased number of live female offspring in the high-dose group. Offspring body weight gain was suppressed throughout PND 1 to 21. At weaning on PND 21, male and female offspring body weight was reduced by approximately 6 percent in the 1,000 and 3,000 ppm groups, while male and female offspring body weight in the 10,000 ppm group was reduced by 53 to 55 percent. Because pup survival was unaffected and no exposure-related clinical observations were observed, F1 offspring from the 10,000 ppm group were carried into the postweaning phase of the study. At study termination, no differences in overall survival were observed across treatment groups for male and female rats. However, terminal body weight was 30 to 32 percent lower for high-dose male and female rats compared to controls.

Liver

As can be seen from Table_Apx B-9, treatment with DEHP resulted in a statistically significant increase in hepatocellular adenoma (males at 10,000 ppm; females at 3,000 ppm), hepatocellular carcinoma (females at 10,000 ppm), and combined hepatocellular adenomas and carcinomas (males at 10,000 ppm; females at 3,000 ppm and above). Furthermore, there was a statistically significant positive trend in hepatocellular carcinoma for males. Hepatocellular tumors were accompanied by numerous non-neoplastic lesions in the liver of male and female rats (many of which occurred at lower doses that caused tumorigenesis)—including cytoplasmic alteration of hepatocytes, hepatocellular hypertrophy, increased pigment, necrosis, eosinophilic focus, basophilic focus, and bile duct hyperplasia (see Table 13 of (NTP, 2021b) for incidence data of these non-neoplastic liver lesions).

Table_Apx B-9. Incidence of Liver Tumors in SD Rats Chronically Exposed to DEHP (Perinatal and Postweaning Exposure Study) (NTP, 2021b) [l]

Tissue: Tumor Type	0 ppm	300 ppm	1,000 ppm	3,000 ppm	10,000 ppm
Male rats					
Hepatocellular adenoma (overall rate) [a e]	0/50	1/49 (2%)	0/50	3/50 (6%)	8/49 (16%)
Hepatocellular adenoma (rate per litter) [b]	0/25	1/25 (4%)	0/25	3/25 (12%)	7/25 (28%)
Hepatocellular adenoma (adjusted rate) [c]	0%	2.4%	0%	6.7%	22.3%
Rao-Scott-adjusted Poly-3 test [d]	p < 0.001	p = 0.578	(e)	p = 0.246	p = 0.018
Hepatocellular carcinoma (overall rate) [f]	1/50 (2%)	0/49	0/50	0/50	3/49 (6%)
Hepatocellular carcinoma (rate per litter)	1/25 (4%)	0/25	0/25	0/25	3/25 (12%)
Hepatocellular carcinoma (adjusted rate)	2.6%	0%	0%	0%	8.7%
Rao-Scott-adjusted Poly-3 test	p = 0.038	p = 0.589	p = 0.587	p = 0.587	p = 0.341
Hepatocellular adenoma or carcinoma (combined) (overall rate) [g]	1/50 (2%)	1/49 (2%)	0/50	3/50 (6%)	11/49 (22%)
Hepatocellular adenoma or carcinoma (combined) (rate per litter)	1/25 (4%)	1/25 (4%)	0/25	3/25 (12%)	9/25 (36%)

Tissue: Tumor Type	0 ppm	300 ppm	1,000 ppm	3,000 ppm	10,000 ppm
Hepatocellular adenoma or carcinoma (combined) (adjusted rate)	2.6%	2.4%	0%	6.7%	30.6%
Rao-Scott-adjusted Poly-3 test	p < 0.001	p = 0.750	p = 0.565	p = 0.429	p = 0.009
Female rats					
Hepatocellular adenoma (overall rate) [h]	1/49 (2%)	0/50	5/50 (10%)	9/50 (18%)	5/48 (10%)
Hepatocellular adenoma (rate per litter)	1/25 (4%)	0/25	4/35 (6%)	7/25 (28%)	5/25 (20%)
Hepatocellular adenoma (adjusted rate)	2.4%	0%	11.8%	20.9%	13.8%
Rao-Scott-adjusted Poly-3 test	p = 0.089	p = 0.587	p = 0.170	p = 0.033	p = 0.126
Hepatocellular carcinoma (overall rate) [i]	0/49	0/50	0/50	0/50	8/48 (17%)
Hepatocellular carcinoma (rate per litter)	0/25	0/25	0/25	0/25	7/25 (28%)
Hepatocellular carcinoma (adjusted rate)	0%	0%	0%	0%	21.8%
Rao-Scott-adjusted Poly-3 test	p < 0.001	(e)	(e)	(e)	p = 0.023
Hepatocellular adenoma or carcinoma (combined) (overall rate) [j]	1/49 (2%)	0/50	5/50 (10%)	9/50 (18%)	13/48 (27%)
Hepatocellular adenoma or carcinoma (combined) (rate per litter)	1/25 (4%)	0/25	4/25 (16%)	7/25 (28%)	11/25 (44%)
Hepatocellular adenoma or carcinoma (combined) (adjusted rate)	2.4%	0%	11.8%	20.9%	35.4%
Rao-Scott-adjusted Poly-3 test	p < 0.001	p = 0.568	p = 0.158	p = 0.028	p = 0.002

[a] Number of animals with neoplasm per number of animals necropsied.
[b] Number of litters with neoplasm-bearing animals per number of litters examined at site.
[c] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality.
[d] Beneath the control incidence is the p-value associated with the trend test. Beneath the exposed group incidence are the p-values corresponding to pairwise comparisons between the control group and that exposed group. The Rao-Scott test adjusts the Poly-3 test (which accounts for differential mortality in animals that do not reach study termination) for within-litter correlation.
[e] Historical control incidence for all routes of 2-year studies (mean ± standard deviation): 2/489 (0.44% ± 0.88%); range: 0−2%.
[f] Historical control incidence: 2/489 (0.45% ± 0.89%); range: 0−2%.
[g] Historical control incidence: 4/489 (0.89% ± 1.06%); range: 0−2%.
[h] Historical control incidence: 15/489 (2.65% ± 2.59%); range: 0−8%.
[i] Historical control incidence: 1/489 (0.22% ± 0.67%); range: 0−2%.
[j] Historical control incidence: 16/489 (2.87% ± 2.8%); range: 0−8%.
[k] (e) indicates that the value of the statistic could not be calculated.
[l] Adapted from Table 13 in (NTP, 2021b).

Pancreas

As can be seen from Table_Apx B-10, treatment with DEHP resulted in a statistically significant increase in pancreatic acinar adenoma and combined pancreatic acinar adenoma or carcinoma in males of the 3,000 and 10,000 ppm groups. Pancreatic acinar carcinoma were observed in 3/50 males at 3,000 ppm and 1/49 males at 10,000 ppm compared to 0/50 control males; however, the effect was not statistically significant. NTP also report that a clear morphological continuum from focal acinar hyperplasia to adenoma and to carcinoma was observed.

Table_Apx B-10. Incidence of Pancreatic Tumors in SD Rats Chronically Exposed to DEHP (Perinatal and Postweaning Exposure Study) (NTP, 2021b) [a]

Tumor Type	0 ppm	300 ppm	1,000 ppm	3,000 ppm	10,000 ppm
Male rats					
Acinus, hyperplasia [b]	13/50	9/49	16/50	25/50	15/50
Acinar adenoma (overall rate) [b f]	10/50 (20%)	7/49 (14%)	8/50 (16%)	36/50 (72%)	22/49 (45%)
Acinar adenoma (rate per litter) [c]	8/25 (32%)	5/25 (20%)	8/25 (32%)	24/25 (96%)	18/25 (72%)
Acinar adenoma (adjusted rate) [d]	26%	16.6%	16.9%	77.9%	62.5%
Rao-Scott-adjusted Poly-3 test [e]	p < 0.001	p = 0.209	p = 0.210	p < 0.001	p < 0.001
Acinar carcinoma (overall rate) [g]	0/50	0/49	0/50	3/50 (6%)	1/49 (2%)
Acinar carcinoma (rate per litter)	0/25	0/25	0/25	3/25 (12%)	1/25 (4%)
Acinar carcinoma (adjusted rate)	0%	0%	0%	6.6%	2.9%
Rao-Scott-adjusted Poly-3 test	p = 0.290	(e)[j]	(e)	p = 0.250	p = 0.534
Acinar adenoma or carcinoma (combined) (overall rate) [h]	10/50 (20%)	7/49 (14%)	8/50 (16%)	38/50 (76%)	22/49 (45%)
Acinar adenoma or carcinoma (combined) (rate per litter)	8/25 (32%)	5/25 (20%)	8/25 (32%)	25/25 (100%)	18/25 (72%)
Acinar adenoma or carcinoma (combined) (adjusted rate)	26%	16.6%	16.9%	81.2%	62.5%
Rao-Scott-adjusted Poly-3 test	p < 0.001	p = 0.209N	p = 0.210N	p < 0.001	p < 0.001
Female rats					
Acinus, hyperplasia	0/49	0/50	0/50	2/50	3/48
Acinar adenoma (overall rate) [i]	0/49	0/50	0/50	2/50	1/48
Acinar adenoma (rate per litter)	0/25	0/25	0/25	2/25	1/25
Acinar adenoma (adjusted rate)	0%	0%	0%	4.6%	2.8%
Rao-Scott-adjusted Poly-3 test	p = 0.307	(e)	(e)	p = 0.366	p = 0.561

[a] Adapted from Table 14 in (NTP, 2021b).
[b] Number of animals with neoplasm or lesion per number of animals necropsied.
[c] Number of litters with neoplasm-bearing animals per number of litters examined at site.
[d] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality.
[e] Beneath the control incidence is the p-value associated with the trend test. Beneath the exposed group incidence are the p-values corresponding to pairwise comparisons between the control group and that exposed group. The Rao-Scott test adjusts the Poly-3 test (which accounts for differential mortality in animals that do not reach study termination) for within-litter correlation.
[f] Historical control incidence for all routes of 2-year studies (mean ± standard deviation): 60/488 (11.58% ± 9.25%); range: 0−28%.
[g] Historical control incidence: 4/488 (0.8% ± 1.42%); range: 0−4%.
[h] Historical control incidence: 62/488 (12.03% ± 9.16%); range: 0−28%.
[i] Historical control incidence: 0/489.
[j] (e) indicates that the value of the statistic could not be calculated.

Male Reproductive Tract

Numerous treatment-related gross lesions were observed in the male reproductive tracts, including small testis, undescended testis, small size epididymis, incomplete preputial separation, and missing gubernaculum (see Table 15 of (NTP, 2021b) for incidence of lesions). Similarly, treatment-related non-

neoplastic histopathologic lesions were noted in the testis (*i.e.*, degeneration of germinal epithelium, seminiferous tubule dysgenesis) and epididymis (*i.e.*, hypospermia) (see Table 16 of (NTP, 2021b) for incidence of lesions). A significant treatment-related increase in focal hyperplasia of interstitial cells was also observed in high-dose male rats (incidence of hyperplasia across respective dose groups: 4/49, 3/49, 6/50, 5/50, and 30/49). However, the incidence of interstitial cell adenomas was not significantly affected by treatment with DEHP (incidence of interstitial adenoma across dose groups: 3/49, 1/49, 3/50, 5/50, and 5/49).

Uterus

A significant positive trend with increasing exposure to DEHP in uterus endometrium adenocarcinoma and combined uterus adenoma, adenocarcinoma, squamous cell carcinoma, or squamous cell papilloma was observed (Table_Apx B-11). However, pairwise comparisons to the control were not statistically significant. NTP characterized this as an equivocal finding.

Under the conditions of the study, NTP concluded the following:

> Under the conditions of the perinatal and postweaning feed study (Study 1), there was clear evidence of carcinogenic activity of di(2-ethylhexyl) phthalate (DEHP) in male [SD] rats based on the increased incidences of hepatocellular adenoma or carcinoma (combined) and acinar adenoma or carcinoma (combined) neoplasms (predominately adenomas) of the pancreas. There was clear evidence of carcinogenic activity of DEHP in female [SD] rats based on the increased incidence of hepatocellular adenoma or carcinoma (combined). The occurrence of pancreatic acinar adenoma or carcinoma (combined) was considered to be related to exposure. The occurrence of uterine (including cervix) adenoma, adenocarcinoma, squamous cell carcinoma, or squamous cell papilloma (combined) in female rats may have been related to exposure.

Table_Apx B-11. Incidence of Uterine Tumors in SD Rats Chronically Exposed to DEHP (Perinatal and Postweaning Exposure Study) (NTP, 2021b) [a]

Tissue: Tumor Type	0 ppm	300 ppm	1,000 ppm	3,000 ppm	10,000 ppm
Adenoma [b f]	0/50	1/50	0/50	0/50	0/48
Adenocarcinoma (overall rate) [b g]	3/50 (6%)	0/50	1/50 (2%)	3/50 (6%)	6/48 (13%)
Adenocarcinoma (rate per litter) [c]	3/25 (12%)	0/25	1/25 (4%)	3/25 (12%)	6/25 (24%)
Adenocarcinoma (adjusted rate) [d]	7%	0%	2.4%	7%	16.4%
Rao-Scott-adjusted Poly-3 test [e]	p = 0.008	p = 0.147	p = 0.325	p = 0.653	p = 0.184
Squamous cell carcinoma (includes multiple) [h]	0/50	1/50	0/50	0/50	1/48
Squamous cell papilloma (includes multiple) [i]	0/50	0/50	0/50	1/50	0/48
Adenoma, adenocarcinoma, squamous cell carcinoma, squamous cell papilloma (combined) (overall rate) [j]	3/50 (6%)	1/50 (2%)	1/50 (2%)	3/50 (6%)	7/48 (15%)
Adenoma, adenocarcinoma, squamous cell carcinoma, squamous cell papilloma (combined) (rate per litter)	3/25 (12%)	1/25 (4%)	1/25 (4%)	3/25 (12%)	7/25 (28%)

Tissue: Tumor Type	0 ppm	300 ppm	1,000 ppm	3,000 ppm	10,000 ppm
Adenoma, adenocarcinoma, squamous cell carcinoma, squamous cell papilloma (combined) (adjusted rate)	7%	2.4%	2.4%	7%	19%
Rao-Scott-adjusted Poly-3 test	p = 0.005	p = 0.325	p = 0.317	p = 0.651	p = 0.113

[a] Adapted from Table 17 in (NTP, 2021b).
[b] Number of animals with neoplasm or lesion per number of animals necropsied.
[c] Number of litters with neoplasm-bearing animals per number of litters examined at site.
[d] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality.
[e] Beneath the control incidence is the p-value associated with the trend test. Beneath the exposed group incidence are the p-values corresponding to pairwise comparisons between the control group and that exposed group. The Rao-Scott test adjusts the Poly-3 test (which accounts for differential mortality in animals that do not reach study termination) for within-litter correlation.
[f] Historical control incidence for all routes of 2-year studies (mean ± standard deviation): 1/350 (0.29% ± 0.76%); range: 0−2%.
[g] Historical control incidence: 20/350 (5.71% ± 3.35%); range: 2−10%.
[h] Historical control incidence: 2/350 (0.57% ± 1.51%); range: 0−4%.
[i] Historical control incidence: 0/350.
[j] Historical control incidence: 23/350 (6.57% ± 3.41%); range: 2−10%.

B.1.2.7 Two-Year Dietary Study of Sprague-Dawley Rats (Postweaning Exposure Study) (NTP, 2021b)

Male and female SD rats (50/sex/dose) were fed diets containing 0, 300, 1,000, 3,000, or 10,000 ppm DEHP for 2 years (mean received doses: 17, 54, 170, and 602 mg/kg-day for males and 17, 60, 177, and 646 mg/kg-day for females). Survival of male and female rats to study termination in all treatment groups was commensurate with or greater than that of control rats. At study termination, high-dose male and female rat body weight was approximately 16 and 22 percent lower than respective controls. Feed consumption by male and female rats was comparable to across treatment groups, with the exception of 21 percent lower feed consumption for high-dose males during study week 1. No exposure-related clinical findings were observed in any treatment groups.

Liver

As can be seen from Table_Apx B-12, treatment with DEHP resulted in a statistically significant increase in hepatocellular adenoma (males and females at 10,000 ppm), hepatocellular carcinoma (males at 10,000 ppm), and combined hepatocellular adenomas and carcinomas (males and females at 10,000 ppm). Hepatocellular tumors were accompanied by numerous non-neoplastic lesions in the liver of male and female rats (many of which occurred at lower doses that caused tumorigenesis)—including cytoplasmic alteration of hepatocytes, hepatocellular hypertrophy, increased pigment, necrosis, eosinophilic focus, and clear cell focus (see Table 25 of (NTP, 2021b) for incidence data of these non-neoplastic liver lesions).

Table_Apx B-12. Incidence of Liver Tumors in SD Rats Exposed to DEHP in the Diet for 2 Years (NTP, 2021b) [k]

Tissue: Tumor Type	0 ppm	300 ppm	1,000 ppm	3,000 ppm	10,000 ppm
Male rats					
Hepatocellular adenoma (overall rate) [a d]	0/50	1/50 (2%)	0/50	1/50 (2%)	6/50 (12%)
Hepatocellular adenoma (adjusted rate) [b]	0%	4.5%	0%	2.2%	12.9%
Poly-3 test [c]	p < 0.001	p = 0.251	(e)[j]	p = 0.514	p = 0.022
Hepatocellular carcinoma (overall rate) [e]	0/50 (0%)	0/50 (0%)	0/50 (0%)	0/50 (0%)	6/50 (12%)
Hepatocellular carcinoma (adjusted rate)	0%	0%	0%	0%	12.8%
Poly-3 test	p < 0.001	(e)	(e)	(e)	p = 0.022
Hepatocellular adenoma or carcinoma (combined) (overall rate) [f]	0/50 (0%)	2/50 (4%)	0/50 (0%)	1/50 (2%)	12/50 (24%)
Hepatocellular adenoma or carcinoma (combined) (adjusted rate)	0%	4.5%	0%	2.2%	25.6%
Poly-3 test	p < 0.001	p = 0.251	(e)	p = 0.514	p < 0.001
Female rats					
Hepatocellular adenoma (overall rate) [g]	0/50 (0%)	0/50 (0%)	1/50 (2%)	1/50 (2%)	13/49 (27%)
Hepatocellular adenoma (adjusted rate)	0%	0%	2.4%	2.3%	31.3%
Poly-3 test	p < 0.001	(e)	p = 0.495	p = 0.505	p < 0.001
Hepatocellular carcinoma (overall rate) [h]	0/50 (0%)	0/50 (0%)	0/50 (0%)	0/50 (0%)	2/49 (4%)
Hepatocellular carcinoma (adjusted rate)	0%	0%	0%	0%	4.9%
Poly-3 test	p = 0.018	(e)	(e)	(e)	p = 0.226
Hepatocellular adenoma or carcinoma (combined) (overall rate) [i]	0/50 (0%)	0/50 (0%)	1/50 (2%)	1/50 (2%)	14/49 (29%)
Hepatocellular adenoma or carcinoma (combined) (adjusted rate)	0%	0%	2.4%	2.3%	33.7%
Poly-3 test	p < 0.001	(e)	p = 0.495	p = 0.505	p < 0.001

[a] Number of animals with neoplasm per number of animals necropsied.
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality.
[c] Beneath the control incidence is the p-value associated with the trend test. Beneath the exposed group incidence are the p-values corresponding to pairwise comparisons between the control group and that exposed group. The Rao-Scott test adjusts the Poly-3 test (which accounts for differential mortality in animals that do not reach study termination) for within-litter correlation.
[d] Historical control incidence for all routes of 2-year studies (mean ± standard deviation): 2/489 (0.44% ± 0.88%); range: 0−2%.
[e] Historical control incidence: 2/489 (0.45% ± 0.89%); range: 0−2%.
[f] Historical control incidence: 4/489 (0.89% ± 1.06%); range: 0−2%.
[g] Historical control incidence: 15/489 (2.65% ± 2.59%); range: 0−8%.
[h] Historical control incidence: 1/489 (0.22% ± 0.67%); range: 0−2%.
[i] Historical control incidence: 16/489 (2.87% ± 2.8%); range: 0−8%.
[j] (e) indicates that the value of the statistic could not be calculated.
[k] Adapted from Table 25 in (NTP, 2021b).

Pancreas

As can be seen from Table_Apx B-13, treatment with DEHP resulted in a statistically significant increase in pancreatic acinar adenoma (males at 3,000 and 10,000 ppm), pancreatic acinar carcinoma (males at 10,000 ppm), and combined pancreatic acinar adenoma and carcinoma (males at 3,000 and 10,000 ppm). The increase in pancreatic tumors was accompanied by a statistically significant increase in focal hyperplasia of the acinus in males of 3,000 and 10,000 ppm groups. Pancreatic acinar adenomas were observed in 1/50 and 1/47 females at 3,000 and 10,000 ppm (not statistically significant), respectively, while pancreatic acinar carcinoma was observed in one high dose female (not statistically significant). No pancreatic tumors were observed in control females.

Table_Apx B-13. Incidence of Pancreatic Tumors in SD Rats Exposed to DEHP in the Diet for 2 Years (NTP, 2021b) [a]

Tumor Type	0 ppm	300 ppm	1,000 ppm	3,000 ppm	10,000 ppm
Male rats					
Acinus, hyperplasia [b]	7/49	8/50	9/50	24/50**	26/50**
Acinar adenoma (overall rate) [b e]	1/49 (2%)	4/50 (8%)	5/50 (10%)	23/50 (46%)	30/50 (60%)
Acinar adenoma (adjusted rate) [c]	2.4%	9%	10.7%	49.9%	64%
Poly-3 test [d]	p < 0.001	p = 0.202	p = 0.131	p < 0.001	p < 0.001
Acinar carcinoma (overall rate) [f]	49 (0%)	1/50 (2%)	0/50 (0%)	1/50 (2%)	5/50 (10%)
Acinar carcinoma (adjusted rate)	0%	2.3%	0%	2.2%	10.6%
Poly-3 test	p < 0.001	p = 0.513	(e) [i]	p = 0.515	p = 0.043
Acinar adenoma or carcinoma (combined) (overall rate) [g]	1/49 (2%)	5/50 (10%)	5/50 (10%)	23/50 (46%)	33/50 (66%)
Acinar adenoma or carcinoma (combined) (adjusted rate)	2.4%	11.2%	10.7%	49.9%	69.8%
Poly-3 test	p < 0.001	p = 0.119	p = 0.131	p < 0.001	p < 0.001
Female rats					
Acinus, hyperplasia	0/50	1/50	1/50	1/50	5/47*
Acinar adenoma (overall rate) [h]	0/50 (0%)	0/50 (0%)	0/50 (0%)	1/50 (2%)	1/47 (2%)
Acinar carcinoma (overall rate) [h]	0/50 (0%)	0/50 (0%)	0/50 (0%)	0/50 (0%)	1/47 (2%)
Acinar adenoma or carcinoma (combined (overall rate) [h]	50 (0%)	0/50 (0%)	0/50 (0%)	1/50 (2%)	2/47 (4%)

* Statistically significant at $p \leq 0.05$ by the Poly-3 test; **$p \leq 0.01$

[a] Adapted from Table 26 in (NTP, 2021b).

[b] Number of animals with neoplasm or lesion per number of animals necropsied.

[c] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality.

[d] Beneath the control incidence is the p-value associated with the trend test. Beneath the exposed group incidence are the p- values corresponding to pairwise comparisons between the control group and that exposed group. The Rao-Scott test adjusts the Poly-3 test (which accounts for differential mortality in animals that do not reach study termination) for within-litter correlation.

[e] Historical control incidence for all routes of 2-year studies (mean ± standard deviation): 60/488 (11.58% ± 9.25%); range: 0−28%.

[f] Historical control incidence: 4/488 (0.8% ± 1.42%); range: 0−4%.

[g] Historical control incidence: 62/488 (12.03% ± 9.16%); range: 0−28%.

[h] Historical control incidence: 0/489.

[i] (e) indicates that the value of the statistic could not be calculated.

Male Reproductive Tract

Treatment-related non-neoplastic histopathologic lesions were noted in the testis (*i.e.*, degeneration of germinal epithelium, edema, and interstitial cell hyperplasia) and epididymis (*i.e.*, hypospermia, exfoliated germ cells in the duct) (see Table 27 of (NTP, 2021b) for incidence of lesions). A positive trend in increasing incidence of interstitial cell adenomas was observed in male rats; however, pairwise comparisons to the control were not statistically significant (Table_Apx B-14).

Table_Apx B-14. Incidence of Testicular Tumors in SD Rats Exposed to DEHP in the Diet for 2 Years (NTP, 2021b) [a]

Tissue: Tumor Type	0 ppm	300 ppm	1,000 ppm	3,000 ppm	10,000 ppm
Interstitial cell, hyperplasia, focal (includes bilateral) [b]	1/50	1/50	0/50	4/50	4/50
Interstitial cell, adenoma (overall rate) [b e]	7/50 (14%)	3/50 (6%)	3/50 (6%)	6/50 (12%)	15/50 (30%)
Interstitial cell, adenoma (adjusted rate) [c]	16.7%	6.8%	6.5%	13.4%	32.2%
Poly-3 test [d]	p < 0.001	p = 0.135	p = 0.119	p = 0.451	p = 0.073

[a] Adapted from Table 27 in (NTP, 2021b).
[b] Number of animals with neoplasm or lesion per number of animals necropsied.
[c] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality.
[d] Beneath the control incidence is the p-value associated with the trend test. Beneath the exposed group incidence are the p-values corresponding to pairwise comparisons between the control group and that exposed group. The Rao-Scott test adjusts the Poly-3 test (which accounts for differential mortality in animals that do not reach study termination) for within-litter correlation.
[e] Historical control incidence for all routes of 2-year studies (mean ± standard deviation): 19/487 (4.06% ± 4.36%); range: 0−14%.

Uterus

As can be seen from Table_Apx B-15, treatment with DEHP causes a significant increase in incidence of uterine endometrial adenocarcinomas and combined uterine adenoma, adenocarcinoma, squamous cell carcinoma, and squamous cell papilloma in high-dose female rats. A significant positive trend in incidence of uterine squamous cell papilloma was also observed; however, pairwise comparisons to the control were not significant. Additionally, chronic uterine inflammation was observed in the 300, 1,000, and 10,000 ppm groups compared to controls.

Under the conditions of the study, NTP concluded the following:

> Under the conditions of the postweaning-only feed study (Study 2), there was clear evidence of carcinogenic activity of DEHP in male Hsd:Sprague Dawley® SD® rats based on the increased incidences of hepatocellular adenoma or carcinoma (combined) and acinar adenoma or carcinoma (combined) neoplasms (predominately adenomas) of the pancreas. The occurrence of testicular interstitial cell adenoma in male rats may have been related to exposure. There was clear evidence of carcinogenic activity of DEHP in female Hsd:Sprague Dawley® SD® rats based on the increased incidences of hepatocellular adenoma or carcinoma (combined) and uterine (including cervix) adenoma, adenocarcinoma, squamous cell carcinoma, or squamous cell papilloma (combined). The occurrence of pancreatic acinar adenoma or carcinoma (combined) in female rats was considered to be related to exposure.

Table_Apx B-15. Incidence of Uterine Tumors in SD Rats Chronically Exposed to DEHP in the Diet for 2 Years (NTP, 2021b) [a]

Tissue: Tumor Type	0 ppm	300 ppm	1,000 ppm	3,000 ppm	10,000 ppm
Inflammation, chronic [b]	2/50	9/50*	6/50*	8/50	8/49*
Adenoma [b e]	0/50	1/50	0/50	0/50	0/49
Adenocarcinoma (overall rate) [b]	2/50 (4%)	2/50 (4%)	1/50 (2%)	4/50 (8%)	10/50 (20%)
Adenocarcinoma (adjusted rate) [c f]	4.7%	4.9%	2.4%	9%	23.8%
Poly-3 test [d]	p < 0.001	p = 0.678	p = 0.508N	p = 0.352	p = 0.011
Squamous cell carcinoma (includes multiple) [g]	0/50	1/50	0/50	2/50	1/49
Squamous cell papilloma (includes multiple) [h]	0/50	0/50	0/50	0/50	2/49
Adenoma, adenocarcinoma, squamous cell carcinoma, squamous cell papilloma (combined) (overall rate) [i]	2/50 (4%)	4/50 (8%)	1/50 (2%)	6/50 (12%)	13/50 (26%)
Adenoma, adenocarcinoma, squamous cell carcinoma, squamous cell papilloma (combined) (adjusted rate)	4.7%	9.7%	2.4%	13.4%	30.7%
Poly-3 test	p < 0.001	p = 0.315	p = 0.508N	p = 0.145	p < 0.001

*Statistically significant at $p \leq 0.05$ by the Poly-3 test.
[a] Adapted from Table 28 in (NTP, 2021b).
[b] Number of animals with neoplasm or lesion per number of animals necropsied.
[c] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality.
[d] Beneath the control incidence is the p-value associated with the trend test. Beneath the exposed group incidence are the p-values corresponding to pairwise comparisons between the control group and that exposed group. The Rao-Scott test adjusts the Poly-3 test (which accounts for differential mortality in animals that do not reach study termination) for within-litter correlation.
[e] Historical control incidence for all routes of 2-year studies (mean ± standard deviation): 1/350 (0.29% ± 0.76%); range: 0−2%.
[f] Historical control incidence: 20/350 (5.71% ± 3.35%); range: 2−10%.
[g] Historical control incidence: 2/350 (0.57% ± 1.51%); range: 0−4%.
[h] Historical control incidence: 0/350
[i] Historical control incidence: 23/350 (6.57% ± 3.41%); range: 2−10%.

B.1.3 Hamsters – Inhalation and Intraperitoneal Studies

B.1.3.1 Inhalation Study (Schmezer et al., 1988)

Male and female Syrian golden hamsters (80/sex for the control; 65/sex for treatment group) were exposed continuously to vapor concentrations of 0 or 15 ± 5 µg/m^3 DEHP from 12 weeks of age until natural death (around 23 months for males; 17 months for females). Continuous exposure was maintained 5 days per week. Twice per week exposure was stopped for animal care. Treatment with DEHP had no effect on median survival, which was 709, 703, 507, and 522 days for control males, treated males, control females, and treated females, respectively. No significant increase in any tumor types were observed.

B.1.3.2 Intraperitoneal Injection Study (Schmezer et al., 1988)

Six-week-old male and female Syrian golden hamsters (25/sex/group) were administered 0 or 3 g DEHP per kilogram body weight via intraperitoneal injection. Animals were split into five treatment groups, including (1) untreated control group; (2) one injection of DEHP per week; (3) one injection of DEHP every 2 weeks; (4) one injection of DEHP every 4 weeks; and (5) one injection of DEHP every 4 weeks in combination of a single injection of 1.67 mg/kg N-nitrosodimethylamine (NDMA) per week. Treatment continued for life or until animals were found in a moribund state and sacrificed. Treatment with DEHP (groups 3, 4, and 5) alone had no effect on median survival times compared to untreated controls, though treatment with DEHP and NDMA in combination significantly reduced male and female median survival times. No significant difference in tumor incidence was observed between untreated controls and DEHP-treated animals.

B.1.4 Transgenic Mice – Oral Exposure Studies

B.1.4.1 Twenty-Six Week Dietary Study of Wild-Type and Transgenic RasH2 Mice (Toyosawa et al., 2001)

Groups of male and female transgenic RasH2 mice (15/sex/group) were fed diets containing 0, 1,500, 3,000, or 6,000 ppm for 26-weeks, while groups of male and female wild-type mice (15/sex/dose) were fed diets of 0 and 6,000 ppm DEHP for 26-weeks. No dose-related effects on survival were observed for either sex or strain. Food consumptions was comparable across treatment groups for both sexes and strains of mice. Body weight gain was decreased in high-dose rasH2 males starting around study week 12, and was decreased after 19 and 21 weeks of treatment with 6,000 ppm DEHP for wild-type male and female mice, respectively. At study termination, body weight was reduced approximately 10 percent in these treatment groups. Neoplastic findings attributable to DEHP exposure were limited to the liver of high-dose rasH2 male mice, and included a statistically significant increase in incidence of hepatocellular adenomas (Table_Apx B-16). No hepatocellular adenomas were observed in wild-type or female rasH2 mice, and no hepatocellular carcinomas were observed in any treatment group.

Table_Apx B-16. Summary of Neoplastic Lesions of the Liver Observed in RasH2 and Wild-Type Mice Fed Diets Containing DEHP for 26 Weeks (Toyosawa et al., 2001) [a]

Strain of Mice	Neoplastic Lesion	0 ppm	1500 ppm	3,000 ppm	6,000 ppm
Male - RasH2	Hepatocellular adenoma	0/15	1/15 (7%)	2/15 (13%)	4/15* (27%)
Female - RasH2	Hepatocellular adenoma	0/15	0/15	0/15	0/15
Male - Wild-type	Hepatocellular adenoma	0/15	N/A	N/A	0/15
Female - Wild-type	Hepatocellular adenoma	0/15	N/A	N/A	0/15

N/A = Not applicable, dose not tested for this strain.
Asterisk (*) indicates statistically significant difference compared to control at $p < 0.05$ as calculated by original study authors.
[a] Adapted from Table 6 of (Toyosawa et al., 2001).

B.1.4.2 Twenty-Six Week Dietary and 28-Week Topical Studies of Tg.AC Mice (Eastin et al., 2001)

The TG.AC transgenic mouse model carries the v-HA-*ras* oncogene fused to the promoter of the *zeta-globin* gene. Male and female Tg.AC mice (15/sex/dose) were exposed to DEHP topically and via oral administration. In the topical exposure study, 0, 100, 200, and 400 mg/kg DEHP was applied to a clipped area (≈8 cm^2) of dorsal skin of male and female Tg.AC mice. DEHP was dissolved in acetone

and volume doses of 3.3 mL/kg were applied to the shaved backs of mice 5 days per week for 28 weeks. Treatment with DEHP did not affect survival of female mice (11/15 or 73% of mice survived to scheduled necropsy in all groups); however, survival of high-dose males was reduced (survival: 13/15, 11/15, 13/15, and 7/15 for males across dose groups). Treatment with DEHP did not significantly increase the incidence of tumors at the site of application for either sex at any dose.

In the oral exposure study, male and female Tg.AC mice (15/sex/dose) were fed diets containing 0, 1,500, 3,000, or 6,000 ppm DEHP for 26 weeks (equivalent to 252, 480, and 1,000 mg/kg-day for males; 273, 545, and 1,143 mg/kg-day for females). Treatment with DEHP had no significant effect on terminal body weight or survival in males or females across dose groups (males that survived until scheduled necropsy: 13/15, 11/15, 13/15, and 9/15; females that survived until scheduled necropsy: 10/15, 13/15, 8/15, and 12/15). Treatment with DEHP did not significantly increase the incidence of proliferative changes in either sex at any dose.

B.1.4.3 Thirty-Nine Week Dietary Study of *Xpa*$^{-/-}$ Mice, C57BL/6 Mice, and *Xpa*$^{-/-}$/*P53*$^{+/-}$ Mice (Mortensen et al., 2002)

Male and female *Xpa*$^{-/-}$ mice (15/sex/dose) were fed diets containing 0, 1,500, 3,000, or 6,000 ppm DEHP (equivalent to 204, 408, and 862 mg/kg-day for males; 200, 401, and 827 for females) for 39 weeks. Similarly, male and female wild-type and *Xpa*$^{-/-}$/*p53*$^{+/-}$ mice (15/sex/dose) were fed diets containing 0 and 6,000 ppm DEHP for 39 weeks (equivalent to 879 and 872 mg/kg-day for male and female wild-type mice, respectively; 896 and 796 mg/kg-day for male and female *Xpa*$^{-/-}$/*p53*$^{+/-}$ mice, respectively). No significant increases in tumor responses were observed across various strains and treatment groups in response to exposure to DEHP.

B.1.4.4 Twenty-Two Month Dietary Study of Wild-Type and *PPARα*-Null Sv/129 Mice (Ito et al., 2007a)

Wild-type and *PPARα*-null male mice on a Sv/129 genetic background were fed diets containing 0, 0.01, 0.05 percent DEHP for 22 months. Mice were sacrificed by decapitation at approximately 23 months of age. Treatment with DEHP had no effect on survival, terminal body weight, or weight gain for either strain at any dose. In wild-type mice, hepatocellular adenomas were observed in two mice of each the 0.01 and 0.05 percent DEHP groups (Table_Apx B-17); however, the effect was not statistically significant. In *PPARα*-null mice hepatocellular adenomas, carcinomas, and cholangiocellular carcinomas were observed in the high-dose group (Table_Apx B-17). A statistically significant trend in increased total liver tumors was observed for *PPARα*-null mice

Table_Apx B-17. Summary of Liver Tumors in Wild-Type and *PPARα*-Null Mice Fed Diets Containing DEHP for 22 Months (Ito et al., 2007a) [a]

	Wild-Type			*PPARα*-Null		
	0%	0.01%	0.05%	0%	0.01%	0.05%
Number necropsied	24 (1) [b]	23 (2)	20 (1)	25 (1)	25 (3)	31 (3)
Hepatocellular adenoma	0	2	2	0	1	6
Hepatocellular carcinoma	0	0	0	1	0	1
Cholangiocellular carcinoma	0	0	0	0	0	1
Total liver tumors	0 (0%)	2 (8.7%)	2 (10%)	1 (4%)	1 (4%)	8* (25.8%)

[a] Adapted from Table 2 in (Ito et al., 2007a).
[b] Number in parentheses indicates the number of deaths prior to scheduled necropsy.

	Wild-Type			*PPARα*-Null		
	0%	0.01%	0.05%	0%	0.01%	0.05%
Asterisk (*) indicates a significant trend between control and 0.05% DEHP group in *PPARα*-null mice ($p < 0.05$) as calculated by original study authors.						

B.2 Butyl Benzyl Phthalate (BBP)

B.2.1 Studies of Mice

B.2.1.1 Two-Year Dietary Study of B6C3F1 Mice (NTP, 1982b)

NTP (1982b) reports the results of a 2-year dietary study of male and female B6C3F1 mice. Male and female mice (50/sex/dose) were administered diets containing 0, 6,000, and 12,000 ppm BBP (equivalent to ≈900 and 1,800 mg/kg-day) for 2 years. Survival across treatment groups was comparable, with 88, 88, and 84 percent of control, low-, and high-dose males, respectively, and 70, 70, and 72 percent of control, low-, and high-dose females, respectively, survival until scheduled necropsies at study weeks 105 to 106. No treatment-related or statistically significant increases in any tumor type in any tissue were observed. Under the conditions of the study, NTP concluded that BBP was "not carcinogenic for B6C3F1 mice of either sex."

B.2.2 Studies of Rats

B.2.2.1 Two-Year Dietary Study of F344/N Rats (NTP, 1982b)

NTP (1982b) reports the results of a 2-year dietary study of male and female F344/N rats. Male and female rats (50/sex/dose) were administered diets containing 0, 6,000, or 12,000 ppm BBP (equivalent to ≈300 and 600 mg/kg-day) for 2 years. Male rats died prematurely, with internal hemorrhaging being suspected at gross necropsy (but was not confirmed microscopically). At week 28, only 30 percent of high-dose males were still alive, and all male rats were sacrificed at study weeks 29 to 30, when 98, 80, and 30 percent of control, low-, and high-dose males were alive, respectively. Increased mortality was not encountered in female rats, with 62, 58, and 64 percent of control, low-, and high-dose females, respectively, surviving until scheduled necropsy at 105 to 106 weeks. The only tumor type statistically significantly increased was MNCL in high-dose females (Table_Apx B-18), which was observed in 18/50 (36%) high-dose females, compared to 7/49 (14%) of controls. Incidence of MNCL in high-dose females was outside the range of historical control data for female F344/N rats with "all leukemias" from the laboratory conducting the study (observed in 77/399 (19%); range 12–24%). No significant increase in urinary bladder transitional cell papillomas or carcinomas, or pancreatic adenomas or carcinomas were observed at any dose. Under the conditions of the study, NTP concluded that BBP was "probably carcinogenic for female F344/N rats, causing an increased incidence of mononuclear cell leukemias." Due to the high mortality observed in male rats, carcinogenicity of BBP could not be assessed.

Table_Apx B-18. Incidence of MNCL in Female F344 Rats Fed Diets Containing BBP for 2 Years (NTP, 1982b) [a]

Tissue: Tumor Type	Control	6,000 ppm (300 mg/kg-day)	12,000 ppm (600 mg/kg-day)
MNCL	7/49	7/49	18/50*
[a] Asterisk indicates statistically significant pairwise comparison to the control by Fisher exact test ($p < 0.05$) when the Cochran-Armitage test was statistically significant ($p < 0.05$). Data from Table A2 of (NTP, 1982b).			

B.2.2.2 Two-Year Dietary Study of F344/N Rats (NTP, 1997b)

Male F344/N rats (60/dose) were fed diets containing 0, 3,000, 6,000, or 12,000 ppm BBP and female F344/N rats (60/dose) were fed 0, 6,000, 12,000, or 24,000 ppm BBP for 2 years (equivalent to 120, 240, and 500 mg/kg-day for males; 300, 600, and 1,200 mg/kg-day for females) (NTP, 1997b). Survival rates were comparable across treatment groups for male (survival to study termination: 28/50, 20/50, 22/50, and 22/50) and female rats (survival: 25/50, 29/50, 29/50, and 29/50). No treatment-related clinical observations were reported for either sex in any dose group. Effects on food consumption were limited to females in the 24,000 ppm BBP treatment group. Food consumption was reduced in high-dose females at the start of the study but was similar to that of controls by study week 6. Body weights were reduced in high-dose male (4−10% less than controls throughout most of the study; terminal body weight on study week 101 was reduced 6%) and female rats (7−27% less than controls throughout most of the study; terminal body weight on study week 101 was reduced 27%).

In males, a statistically significant increase in focal hyperplasia of the pancreatic acinar cell was observed in high-dose males compared to concurrent study control group (Table_Apx B-19). This preneoplastic lesion was accompanied by a statistically significant increase in pancreatic acinar cell adenomas and pancreatic acinar cell adenomas and carcinoma (combined) in high-dose males (Table_Apx B-19). Incidence of acinar cell adenomas and adenomas and carcinoma (combined) were outside the range of historical controls from NTP 2-year feed studies (see footnotes b, c, and d in Table_Apx B-19). In female rats, no treatment-related increases in focal hyperplasia of the pancreatic acinar cell were observed. Pancreatic acinar cell adenomas were observed in two high-dose females; however, the effect was not statistically significant and fell within the range of historical controls from NTP 2-year feed studies (see footnote e in Table_Apx B-19). Because pancreatic neoplasms are rare in control animals and because a pancreatic tumor response was observed in males, NTP considered the low incidence of pancreatic acinar adenomas in female rats to be potentially treatment-related.

In high-dose female rats, mild to moderate transitional epithelium hyperplasia was observed in the urinary bladder (10/50 vs. 4/50 in controls) (Table_Apx B-19). Transitional epithelium papillomas were observed in two high-dose females. Although the incidence of papillomas in the urinary bladder was not statistically significant, the incidence of this neoplasm exceeded the range of NTP historical control data from 2-year feed studies (see footnote f in Table_Apx B-19). No transitional epithelium papillomas were observed in male rats.

MNCL was not significantly increased by exposure to BBP in male or female rats (Table_Apx B-19)

Overall, NTP concluded “Under the conditions of this 2-year feed study, there was some evidence of carcinogenic activity of butyl benzyl phthalate in male F344/N rats based on the increased incidences of pancreatic acinar cell adenoma and of acinar cell adenoma or carcinoma (combined). There was equivocal evidence of carcinogenic activity of butyl benzyl phthalate in female 344/N rats based on the marginally increased incidences of pancreatic acinar cell adenoma and of transitional epithelial papilloma of the urinary bladder.”

Table_Apx B-19. Summary of Neoplastic Findings in the Pancreas and Urinary Bladder in F344/N Rats Fed Diets Containing BBP for 2 Years (NTP, 1997b) [a]

	0 ppm	3,000 ppm	6,000 ppm	12,000 ppm	24,000 ppm
Male rats					
Number examined microscopically	50	49	50	50	N/A
Pancreas, acinus, focal hyperplasia	4/50	7/49	9/50	12/50*	N/A
Pancreas, acinus, adenoma [b]	3/50 (6%)	2/49 (4%)	3/50 (6%)	10/50* (20%)	N/A
Pancreas, acinus, carcinoma [c]	0/50	0/49	0/50	1/50 (2%)	N/A
Pancreas, acinus, adenoma, or carcinoma [d]	3/50 (6%)	2/49 (4%)	3/50 (6%)	11/50* (22%)	N/A
Urinary bladder, hyperplasia, transitional epithelium	0/50	0/49	0/50	2/50	N/A
Urinary bladder, papilloma, transitional epithelium	0/50	0/49	0/50	0/50	N/A
MNCL	31/50 (62%)	28/50 (56%)	34/50 (68%)	30/50 (60%)	N/A
Female rats					
Number examined microscopically	50	NA	50	50	50
Pancreas, acinus, focal hyperplasia	1/ 50	NA	4/50	2/50	0/50
Pancreas, acinus, adenoma [e]	0/50	NA	0/50	0/50	2/50 (4%)
Urinary bladder, hyperplasia, transitional epithelium	4/50	NA	0/50	1/50	10/50*
Urinary bladder, papilloma, transitional epithelium [f]	1/50	NA	0/50	0/50	2/50
MNCL	21/50 (42%)	NA	20/50 (40%)	21/50 (42%)	19/50 (38%)

N/A = not applicable (dose not tested for this sex)
Asterisk (*) indicates significant difference ($p \leq 0.05$) from the control by the logistic regression test, as calculated by NTP.
[a] Incidence data from Tables 9 and 10 in (NTP, 1997b).
[b] Historical incidence for 2-year NTP feed studies with untreated controls (acinus, adenoma, males): 19/1,191 (1.6% ± 2.4%); range 0−10%.
[c] Historical incidence (acinus, carcinoma, males): 0/1,919 (0.0%).
[d] Historical incidence (acinus, adenoma or carcinoma, males): 19/1,191 (1.6% ± 2.4%); range 0−10%.
[e] Historical incidence (acinus, adenoma, females): 2/1,194 (0.2% ± 0.8%); range 0−4%.
[f] Historical incidence (transitional epithelium papilloma): 4/1,182 (0.3% ± 0.8%); range 0−2%.

B.2.2.3 Two-Year Dietary Study of F344/N Rats – Study 1 (*Ad Libitum* and Weight-Matched Controls Protocol) (NTP, 1997a)

NTP (1997a) reports the results of three studies of BBP, including several diet restriction studies. In the first study (*Ad Libitum* and Weight-Matched Controls Protocol), male F344/N rats (60/dose) were fed diets containing 0 or 12,000 ppm BBP, while female F344/N rats (60/dose) fed 0 or 24,000 ppm BBP in feed that was available *ad libitum* for 104 weeks (equivalent to ≈500 mg/kg-day for males and 1,200 mg/kg-day for females). Two control groups were included, including a group in which food was

available *ad libitum* and a group in which control diet was restricted such that mean body weight matched the BBP treatment group. Survival rates were similar between male and female rats dosed with BBP and the *ad libitum* controls but were less than those of the weight-matched controls (survival [*ad libitum* control, weight-matched, BBP]: 28/60, 33/60, and 22/60 for males; 25/60, 41/60, and 29/60 for females). Feed consumption for BBP treated females was less than that of the *ad libitum* controls from study week 38 through the end of the study. Feed consumption for BBP treated males was comparable to that of the *ad libitum* controls. No treatment-related clinical findings were reported for either sex. Mean body weights for BBP treated males were reduced approximately 8 percent compared to *ad libitum* controls throughout the study. Mean body weights for BBP treated females were 80 percent that of *ad libitum* controls after one year and fell to 73 percent that of *ad libitum* controls by study termination.

Incidence of hyperplasia of the pancreatic acinus was increased in males treated with BBP compared to *ad libitum* and weight-matched controls (Table_Apx B-20). Furthermore, incidence of pancreatic acinar cell adenomas and pancreatic acinar cell adenomas and carcinomas (combined) were increased in male rats treated with BBP compared to both control groups. NTP further reported that the incidence of adenomas in BBP treated males exceeded the overall NTP historical control incidence of this tumor type in untreated male F344/N rats fed *ad libitum*. In female rats treated with BBP, there was no increase in hyperplasia of the pancreatic acinus, while pancreatic acinar cell adenomas were observed in 2 out of 50 female rats treated with BBP (not statistically significant) (Table_Apx B-20).

BBP-dosed females had higher incidence of hyperplasia of the urinary bladder transitional epithelium (10/50) compared to *ad libitum* (4/50) and weight-matched (0/50) control female rats (Table_Apx B-20). However, papilloma of the transitional epithelium was not significantly increased in BBP-treated females (2/50) compared to *ad libitum* (1/50) or weight-matched (0/50) controls (Table_Apx B-20).

Incidence of MNCL was comparable between ad libitum fed controls and BBP treated F344/N rats of both sexes (Table_Apx B-20), whereas weight-matched controls of both sexes had lower incidence of MNCL (Table_Apx B-20). Incidence of MNCL in BBP treated rats of both sexes was reported by NTP to be within the historical control ranges for leukemia (all types) in untreated F344/N rats.

Table_Apx B-20. Incidence of Neoplasms and Non-Neoplastic Lesions of the Pancreas, Urinary Bladder, and MNCL in F344/N Rats (*Ad Libitum* and Weight-Matched Controls Protocols) (NTP, 1997a) [a]

	Lesion / Tumor Type	*Ad Libitum*-Fed Control	Weight-Matched Control	12,000 ppm (Males) or 24,000 ppm (Females)
Male rats				
Number examined		50	50	50
Pancreas	Acinus, focal hyperplasia	4/50	2/50	12/50
	Acinus, adenoma	3/50 (6%)	0/50	10/50* (20%)
	Acinus, carcinoma	0/50	1/50 (2%)	1/50 (2%)
	Adenoma or carcinoma	3/50 (6%)	1/50 (2%)	11/50* (22%)
Urinary bladder	Hyperplasia, transitional epithelium	0/50	0/50	2/50
	Papilloma, transitional epithelium	0/50	0/50	0/50
MNCL	MNCL [b]	31/50 (62%)	15/50 (30%)	30/50* (60%)
Female rats				

	Lesion / Tumor Type	*Ad Libitum*-Fed Control	Weight-Matched Control	12,000 ppm (Males) or 24,000 ppm (Females)
Number examined		50	49	50
Pancreas	Acinus, focal hyperplasia	1/50 (2%)	0/49	0/50
	Acinus, adenoma	0/50	0/49	2/50 (4%)
Urinary bladder	Hyperplasia, transitional epithelium	4/50 (8%)	0/50	10/50 (20%)
	Papilloma, transitional epithelium	1/50 (2%)	0/50	2/50 (4%)
MNCL	MNCL [b]	21/50 (42%)	13/50 (26%)	19/50* (38%)

Asterisk (*) indicates significant difference ($p \leq 0.05$) from the control by the logistic regression test, as calculated by NTP.
[a] Incidence data from Tables 3, 4, B1a, and B3a of (NTP, 1997a).
[b] Incidence of MNCL significantly increased compared to weight-matched, but not *ad libitum* fed controls.

B.2.2.4 Two-Year Dietary Study of F344/N Rats – Study 2 (2-Year Restricted Feed Protocol) (NTP, 1997a)

Male F344/N rats (60/dose) were fed diets containing 0 or 12,000 ppm BBP, while female F344/N rats (60/dose) fed diets containing 0 or 24,000 ppm BBP for 104 weeks. Control animals were diet-restricted to limit the mean body weight of controls to approximately 85 percent of the *ad libitum* control rats in Study 1. Survival rates were similar between BBP treated males and controls (survival to 104 weeks: 34/50 vs. 31/50) and BBP treated females and controls (survival: 35/50 vs. 39/50). No clinical findings related to BBP treatment were observed. Mean body weights of BBP-treated males remained withing 10 percent of controls throughout the duration of the study. Mean body weights of BBP-treated females were 23 percent less than that of controls at study termination.

Evidence of carcinogenicity was limited to the urinary bladder in female rats (Table_Apx B-21). BBP-dosed females had higher incidence of hyperplasia of the urinary bladder transitional epithelium (14/50) compared to diet-restricted control female rats (0/50). Additionally, papilloma of the transitional epithelium was observed in two female rats treated with BBP (2/50); however, the increase was not statistically significant compared to the concurrent control. No carcinomas of the transitional epithelium in the urinary bladder were observed.

No statistically significant increase in MNCL was observed in male or female rats compared to the concurrent control (incidence: 21/50 [42%] vs. 27/50 [54%] in control and BBP-treated males, respectively; 16/50 [32%] vs. 18/50 [36%] in control and BBP-treated females, respectively).

B.2.2.5 Two-Year Dietary Study of F344/N Rats – Study 3 (Lifetime Restricted Feed Protocol) (NTP, 1997a)

Male F344/N rats (60/dose) were fed diets containing 0 or 12,000 ppm BBP, while female F344/N rats (60/dose) were fed diets containing 0 or 24,000 ppm BBP until survival fell to 20 percent. Control animals were diet-restricted to limit the mean body weight of controls to approximately 85 percent of the *ad libitum* control rats in Study 1. Survival was reduced to 20 percent during week 129 (≈30 months) for males and week 140 for females (≈32 months). No clinical findings related to BBP treatment were observed. Mean body weights of BBP-treated males remained withing 10 percent of controls throughout the duration of the study. Mean body weights of BBP-treated females were 29 percent less than that of controls at study termination.

Evidence of carcinogenicity was limited to the urinary bladder in female rats (Table_Apx B-21). BBP-dosed females had higher incidence of hyperplasia of the urinary bladder transitional epithelium (16/50) compared to diet-restricted control female rats (0/50). Papilloma and carcinoma of the transitional epithelium was observed in two and four female rats treated with BBP, respectively, while one control female rat had a papilloma at 32 months. Although a marginal increase in papillomas and carcinomas (combined) were observed in BBP-treated female rats (6/50) compared to control female rats (1/50), the increase was not statistically significant.

No statistically significant increase in MNCL was observed in male or female rats compared to the concurrent control (incidence: 39/50 [78%] vs. 36/50 [72%] in control and BBP treated males, respectively; 29/50 [58%] vs. 39/50 [78%] in control and BBP-treated females, respectively).

Table_Apx B-21. Incidence of Non-Neoplastic and Neoplastic Findings in F344/N Rats Treated with BBP (2-Year Restricted Feed and Lifetime Restricted Feed Protocols) (NTP, 1997a) [a]

	Lesion/ Tumor Type	2-Year Restricted Feed Protocol		Lifetime Restricted Feed Protocol	
		0 ppm	12,000 ppm (Males) or 24,000 ppm (Females)	0 ppm	12,000 ppm (Males) or 24,000 ppm (Females)
Male rats					
Number examined		50	50	50	50
Urinary bladder	Hyperplasia	1/50	2/50	0/50	1/50
	Papilloma	0/50	1/50 (2%)	0/50	1/50 (2%)
	Carcinomas	0/50	0/50	0/50	1/50 (2%)
Pancreas	Acinus, focal hyperplasia	0/50	3/50	0/50	2/50
	Acinus, adenoma	0/50	0/50	0/50	1/50 (2%)
MNCL	MNCL	21/50 (42%)	27/50 (54%)	39/50 (78%)	36/50 (72%)
Female rats					
Number examined		50	50	49	50
Urinary bladder	Hyperplasia	0/50	14/50*	0/49	16/50*
	Papilloma	0/50	2/50 (4%)	1/49 (2%)	2/50 (4%)
	Carcinomas	0/50	0/50	0/49	4/50 (8%)
	Papilloma or carcinoma (combined)	0/50	2/50 (4%)	1/49 (2%)	6/50 (12%)
Pancreas	Acinus, focal hyperplasia	0/50	3/50	0/50	1/50
	Acinus, adenoma	0/50	0/50	0/50	1/50 (2%)
MNCL	MNCL	16/50 (32%)	18/50 (36%)	29/50 (58%)	39/50 (78%)

Asterisk (*) indicates significant difference ($p \leq 0.05$) from the control by the logistic regression test, as calculated by NTP.
[a] Incidence date from Table 7, A1b, A3b, B1b, and B3b of (NTP, 1997a).

Appendix C SCIENTIFIC UNCERTAINTIES RELATED TO MONONUCLEAR CELL LEUKEMIA (MNCL) AND LEYDIG CELL TUMORS IN F344 RATS

MNCL is a spontaneously occurring neoplasm of the hematopoietic system that reduces lifespan and is one of the most common tumor types occurring at a high background rate in the F344 strain of rat (Thomas et al., 2007). Historical control data from NTP have demonstrated an increase in the spontaneous background incidence of MNCL in untreated male and female F344 rats from 7.9 and 2.1 percent in males and females, respectively, in 1971 to 52.5 and 24.2 percent in males and females, respectively, from 1995 through 1998 (Thomas et al., 2007). Spontaneous incidence of MNCL in other strains of rat appear to be rare. Brix et al. (2005) report the incidence of MNCL in female Harlan SD rats to be 0.5 percent in NTP 2-year studies. Furthermore, MNCL does not appear to occur naturally in mice (Thomas et al., 2007). Similarly, as discussed by King-Herbert et al. (2006), there is also a high background rate of spontaneous testicular Leydig cell tumors (also known as interstitial cell tumors) in control F344 and F344/N rats (ranging from 86−87%). Comparatively, the background rate of Leydig cell tumors is much lower in Wistar and SD strains of rats, ranging from 0.3 to 3.4 percent (King-Herbert and Thayer, 2006). The F344/N strain of rat was used in NTP 2-year chronic and carcinogenicity bioassays for nearly 30 years (King-Herbert et al., 2010; King-Herbert and Thayer, 2006). However, in the early 2000s NTP stopped using the F344/N strain of rat in part because of high background incidence of MNCL and testicular Leydig cell tumors, which decrease the ability of the F344 strain to detect exposure-related increases in MNCL and testicular Leydig cell tumors (King-Herbert and Thayer, 2006).

Another source of uncertainty is lack of MOA information for induction of MNCL in F344 rats. The MOA for induction of MNCL in F344 rats is unknown. Lack of MOA information makes it difficult to determine human relevancy. There is additional uncertainty related to the human correlate to MNCL in F344 rats. Some researchers have suggested that based on the biological and functional features in the F344 rat, MNCL is analogous to LGL in humans (Caldwell et al., 1999; Caldwell, 1999; Reynolds and Foon, 1984). There are two major human LGL leukemias, including CD3+ LGL leukemia and CD3− LGL leukemia with natural killer cell activity (reviewed in (Maronpot et al., 2016; Thomas et al., 2007)). Thomas et al. (2007) contend that MNCL in F344 rats shares some characteristics in common with ANKCL in humans, and that ANKCL may be a human correlate. However, Maronpot et al. (2016) point out that ANKCL is extremely rare with less than 98 cases reported worldwide, and its etiology is related to infection with Epstein-Barr virus, not chemical exposure. This is in contrast to MNCL in F344 rats, which is a more common form of leukemia and is not associated with a viral etiology. However, under EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), site concordance is not always assumed between animals and humans.

Given the limitations and uncertainties regarding MNCL in F344 rats discussed above, during the July 2024 peer review meeting of the DIDP and DINP human health hazard assessments, the SACC recommended that "the observation of an increased incidence of MNCL in a chronic bioassay employing the Fisher 344 rat should not be considered a factor in the determination of the cancer classification…" and "Most Committee members agreed that given the material presented in a retrospective review, MNCL and Leydig Cell Tumors, among other tumor responses in F344 rat carcinogenicity studies lack relevance in predicting human carcinogenicity (Maronpot et al., 2016)" (U.S. EPA, 2024d). Consistent with the recommendations of the SACC, *EPA is not further considering MNCL as a factor in the determination of the cancer classifications for phthalates*.

Appendix D SUMMARY OF STUDIES OF DEHP EVALUATING PPARα ACTIVATION

EPA reviewed the health effects section of ATSDR (2022) (including Table 2-2 of that report) for studies that report evaluation of biomarkers of PPARα activation (KE 1 in PPARα MOA). Identified studies were independently reviewed by EPA to determine effect levels (*i.e.*, NOAEL and LOAEL values) for PPARα activation in each study.

Overall, EPA identified 27 studies that evaluated various biomarkers of PPARα activation in the liver, including 18 studies of rats, 3 studies of mice, 3 studies of monkeys, 2 studies of hamsters, and 1 study of guinea pigs (Table_Apx D-1). As can be seen in Table_Apx D-1, the lowest identified NOAELs were 7.5 mg/kg-day for mice (Isenberg et al., 2000) and for 11 mg/kg-day for rats (Barber et al., 1987; BIBRA, 1985).

Table_Apx D-1. Summary of NOAEL and LOAEL Values for PPARα Activation from *In Vivo* Animal Toxicology Studies of DEHP [a]

Brief Study Details (Reference[s])	NOAEL/ LOAEL (mg/kg-day)	PPARα Biomarker at LOAEL	Comments
Male B6C3F1 mice (5/dose) exposed to 0, 500, or 6,000 ppm DEHP via diet for 2 or 4 weeks (equivalent to 0, 7.5, 900 mg/kg-day) (Isenberg et al., 2000) [b]	7.5 / 900	↑ PPARα-dependent enzyme activities (*e.g.*, PBOX at 2- and 6-weeks)	- ↓ hepatic GJIC at 2 weeks at 900 mg/kg-day (GJIC evaluated via *in situ* dye transfer assay)
Male and female F344 rats (5/sex/dose) exposed to 0, 11, 105, 667, 1,224, or 2,101 mg/kg-day DEHP [males] or 0, 12, 109, 643, 1,197, or 1892 mg/kg-day [females] for 21 days via feed (Barber et al., 1987; BIBRA, 1985)	11 / 105	↑ Peroxisome proliferation (electron microscopy quantification of periportal peroxisome sore)	- Coincided with ↓ serum lipids and ↑ liver weight at ≥105 mg/kg-day - 38–44% ↓ body weight and 48–60% ↓ food consumption at ≥1,892 mg/kg-day
Male and female B6C3F1 mice (60–70/sex/dose) exposed to 0, 19.2, 98.5, 292.2, or 1,266 mg/kg-day [males] or 0, 23.8, 116.8, 354.2, or 1,458 mg/kg-day DEHP [females] for 104 weeks via feed (David et al., 2000a; David et al., 1999)	19.2/ 98.5 (males) 23.8/ 116.8 (females)	↑ PPARα-dependent enzyme activities (*e.g.*, palmitoyl CoA oxidation activity)	- Coincided with ↑ liver weight and cytoplasmic eosinophilia at 1,266 mg/kg-day and hepatocellular neoplasms (≥98.5 mg/kg-day [males]; ≥354.2 mg/kg-day [females]) - hepatocellular neoplasia was the most common cause of death (≥500 mg/kg-day)
Male SD rats (5/group) exposed to 0, 25, 100, 250, or 1,000 mg/kg-day DEHP for 2 weeks via gavage (Lake et al., 1984)	25 / 100	↑ PPARα-dependent enzyme activities (*e.g.*, hepatic palmitoyl-CoA oxidation and carnitine	- Coincided with ↑ relative liver weight at ≥100 mg/kg-day and ↑ liver peroxisomes (qualitative

Brief Study Details (Reference[s])	NOAEL/ LOAEL (mg/kg-day)	PPARα Biomarker at LOAEL	Comments
		acetyltransferase)	histopathological assessment via 3,3′-diaminobenzidine staining) at ≥250 mg/kg-day.
Male and female F344 rats (50–80/sex/dose) exposed to 0, 5.8, 29, 147, or 789 mg/kg-day [males] or 0, 7.3, 36, 182, or 939 mg/kg-day DEHP [females] for 104 weeks via feed (David et al., 2000b; David et al., 1999)	29 / 147 (males) 36 / 182 (females)	↑ PPARα-dependent enzyme activities (*e.g.*, palmitoyl CoA oxidation)	- Coincided with ↑ absolute liver weight and hepatocellular tumors (≥147 mg/kg-day [males]; 939 mg/kg-day [females]) - 12% reduction in survival due to MNCL - 15% ↓ body weight gain; no changes in food consumption
Male and female Wistar albino strain rats (4–6/sex/dose) exposed to 0, 50, 200, or 1,000 mg/kg-day DEHP for 9 months via diet (Mitchell et al., 1985)	ND / 50	↑ Hepatic peroxisome proliferation (ultrastructural changes visualized by electron microscopy; males and females)	- ↓ body weight ≥ 200 mg/kg-day males (9−15%) and 1,000 mg/kg-day females (12%)
Male F344 rats (5/group) exposed to 0, 1,000, 6,000, 12,000, or 20,000 ppm DEHP via diet for 1-, 2-, 4-, or 6-weeks (equivalent to 0, 50, 300, 600, 1,000 mg/kg-day) (Isenberg et al., 2000) [b]	50 / 300	↑ PPARα-dependent enzyme activities at 1 and 2 weeks (*e.g.*, PBOX)	- ↓ hepatic GJIC at ≥300 mg/kg-day - Dose-dependent ↑ PBOX - GJIC significant only at the high dose (6,000 ppm) at 4-week timepoint - GJIC evaluated via *in situ* dye transfer assay - Coincided with ↑ liver weights (≥300 mg/kg-day, all timepoints)
Female F344 rats (18–20/group) were exposed to 0, 0.03, 0.1, or 1.2% DEHP for up to 2 years via diet (equivalent to 0, 15, 50, 600 mg/kg-day) (Cattley et al., 1987) [b]	50 / 600	↑ PPARα-dependent enzyme activities (*e.g.*, Carnitine acetyltransferase and cyanide insensitive palmitoyl CoA oxidase)	- Coincided with ↑ incidence of hepatic neoplasms in high dose (6/20 animals compared to 0/18 in control) - Sample size for enzyme activities was 11−16 /group.

Brief Study Details (Reference[s])	NOAEL/ LOAEL (mg/kg-day)	PPARα Biomarker at LOAEL	Comments
Male and female F344 rats (5/sex/dose) exposed to 0, 75, 470, or 950 mg/kg-day DEHP [males] or 0, 79, 490, or 930 mg/kg-day [females] for 3 weeks via feed followed by a 2-week recovery (Astill et al., 1986) [c]	75 / 470 (males)	↑ PPARα-dependent enzyme activities (*e.g.*, hepatic carnitine acetyltransferase)	- Coincided with ↓ serum lipids, ↑ liver weight at ≥75 mg/kg-day - Enzyme activity returns to control levels after recovery period
	79 / 490 (females)	↑ PPARα-dependent enzyme activities (*e.g.*, hepatic carnitine acetyltransferase)	- Coincided with ↓ serum lipids,↑ liver weight at ≥490 mg/kg-day - Enzyme activity returns to control levels after recovery period
Male and female marmoset monkeys (5−6/group) exposed to 0, 100, 500, or 2,500 mg/kg-day DEHP via gavage (oral) for 65 weeks from 3 months of age to sexual maturity (18 months) (Tomonari et al., 2006)	100 / 500	↑ PPAR-dependent enzyme activities (*e.g.*, lauric acid ω-1-hydrolase activity (females)	- No significant effects observed for hepatic palmitoyl CoA beta oxidation, carnitine acetyl transferase, and catalase; large variability across individual values in dose groups and controls.
Male SD rats (6/group) exposed to 0 or 500 mg/kg-day MEHP for 2 weeks via gavage (Lake et al., 1984)	ND / 500	↑ PPARα-dependent enzyme activities (*e.g.*, hepatic palmitoyl-CoA oxidation, carnitine acetyltransferase)	- Coincided with ↑ relative liver weight
Male Syrian hamsters (6/group) exposed to 0 or 500 mg/kg-day MEHP for 2 weeks via gavage (Lake et al., 1984)	ND / 500	↑ PPARα-dependent enzyme activities (*e.g.*, hepatic palmitoyl-CoA oxidation, carnitine acetyltransferase)	- Coincided with ↑ relative liver weight
Male F344 rats (4/group) exposed to 0, 11, 105, 667, 1,223, or 2100 mg/kg-day DEHP for 21 days via diet (Short et al., 1987)	105 / 667	↑ PPARα-dependent enzyme activities (*e.g.*, cyanide-insensitive palmitoyl-CoA oxidation and lauric acid hydroxylation) and ↑ peroxisome score (*i.e.*, "moderate increase – clear increase in peroxisome numbers and size range"; visualized via electron microscopy)	- Coincided with ↑ liver weight at ≥667 mg/kg-day - ↑ PPAR-dependent enzyme activities (≥105 mg/kg-day)

Brief Study Details (Reference[s])	NOAEL/ LOAEL (mg/kg-day)	PPARα Biomarker at LOAEL	Comments
Male F344 rats (5–10/group) exposed to 0, 23.8, 51.7, 115, 559, 1,093, or 2,496 mg/kg-day DEHP for 28 days via feed (BIBRA, 1990)	109 / 643	↑ Peroxisome proliferation (electron microscopy quantification of periportal peroxisome sore); ↑ PPAR-dependent enzyme activities (*e.g.*, palmitoyl-CoA oxidase)	- Coincided with ↓ serum lipids and ↑ liver weight at ≥646 mg/kg-day - 38–44% ↓ body weight and 48–60% ↓ food consumption at ≥1,892 mg/kg-day
Male F344 rats exposed to 0, 0.25, 0.5, 1, and 2% DEHP via diet for 30 days (equivalent to 0, 125, 250, 500, or 1,000 mg/kg-day) (Reddy et al., 1986) [b c]	125 / 250	↑ Indicators of peroxisomal proliferation (peroxisome number and density via electron microscopy) and ↑ PPAR-dependent enzyme activities (*e.g.*, PBOX, catalase)	- Coincided with ↑ liver weight (≥10% at all doses tested; no statistical analysis was performed)
Male Syrian Hamsters (5/group) exposed to 0, 25, 100, 250, or 1,000 mg/kg-day DEHP for 2 weeks via gavage (Lake et al., 1984)	250 / 1,000	↑ Liver peroxisomes (qualitative histopathological assessment via 3,3'-diaminobenzidine staining)	- Coincided with ↑ relative liver weight at 1,000 mg/kg-day and ↑ hepatic palmitoyl-CoA oxidation and carnitine acetyltransferase (≈200% ↑ in enzyme activity at 1,000 mg/kg-day).
Male and female SD rats (10/sex/dose) exposed to 0, 0.4, 3.7, 37.6, or 375.2 mg/kg-day [males] or 0, 0.4, 4.2, 42.2, or 419.3 mg/kg-day [females] DEHP for 13 weeks via feed (Poon et al., 1997)	ND / 375.2	↑ Liver peroxisomes (percent cell area; visualized via 3,3'-diaminobenzidine staining)	- Coincided with ↑ absolute and relative liver weight and mild hypertrophy (high dose only, both sexes) - Peroxisome staining was only evaluated in control and high-dose animals
Male CD-1 mice (6/group) were administered 0, 1.25, or 2.5 mmol/kg DEHP for 2 weeks (equivalent to 0, 488, or 976 mg/kg-day) (Ito et al., 2007b) [b]	ND / 488	↑ mRNA of PPARα-target gene (*PT)*	- Coincided with ↑ liver weights ≥488 mg/kg-day; ↑ mRNA at high dose *(MCAD)*; no change in *PPARa*
Male SD rats (3/group) were administered 0, 1.25, or 2.5 mmol/kg DEHP for 2 weeks (equivalent to 0, 488, or 976 mg/kg-day) (Ito et al., 2007b) [b]	ND / 488	↑ mRNA and protein of PPARα-target gene (*PT*)	- Coincided with ↑ liver weights ≥488 mg/kg-day; ↑ mRNA at high dose *(MCAD)*; no change in *PPARa*
Male F344 rats (3−10/group) exposed to 0 or 1.2% DEHP via diet for 1 year (equivalent to 0 or	ND / 600	↑ Peroxisomal volume and density (electron microscopy); ↑ PPARα-	- Coincided with ↑ absolute liver weights; ↓body weight gain in

Brief Study Details (Reference[s])	NOAEL/ LOAEL (mg/kg-day)	PPARα Biomarker at LOAEL	Comments
600 mg/kg-day) via diet (Marsman et al., 1988) [b]		dependent enzyme activities (*e.g.*, PBOX)	DEHP group; no macroscopic lesions of the liver were observed. - Sample size for peroxisomal volume density (electron microscopy) was 3/group; sample size for enzyme activity assays was 5−10/group)
Male cynomolgus monkeys (2/group) were exposed to 0, 100, or 500 mg/kg-day DEHP via gavage for 21 days. Monkeys were then administered radiolabeled DEHP (100 mg/kg-day) on day 23, 24, and 25, and were sacrificed on day 25 (Short et al., 1987)	500 / ND	N/A	- Low sample size - No changes in liver weight, no changes in PPAR-dependent enzyme activities (*e.g.*, cyanide-insensitive palmitoyl-CoA oxidation and lauric acid hydroxylation)
Male F344 rats (4−7/group) exposed to 0, 500, or 4,000 mg/kg-day DEHP for 1 week via feed (Reddy et al., 1976)	500 / 4,000	↑ PPARα-dependent enzyme activities (*e.g.*, hepatic catalase and carnitine acetyl transferase activity)	- Coincided with ↑ relative liver weight at 4,000 mg/kg-day
Male adult cynomolgus monkeys (4/group) exposed to 0 or 500 mg/kg-day DEHP via intragastric intubation (oral) for 14-days (Pugh et al., 2000)	ND / 500	↑ Indicators of peroxisomal proliferation (liver histopathology; diffuse hepatocellular vacuolation in one animal)	- No significant effects observed for hepatic GJIC or PBOX
Male F344 rats (8–10/group) exposed to 0 or 2% DEHP for 95 weeks via diet (equivalent to 0 or 600 mg/kg-day) (Rao et al., 1987) [b]	ND / 600	↑ Peroxisomes; ↑ PPARα-dependent enzyme activities (*e.g.*, PBOX, catalase)	- Coincided with ↑ hepatocellular carcinomas
Male F344 rats (5/group) exposed to 0 or 950 mg/kg-day DEHP for 4 days via gavage (Hasmall et al., 2000)	ND / 950	↑ PPARα-dependent enzyme activities (*e.g.*, PBOX)	- Coincided with significant ↑ liver weight (24%); no significant change in body weight
Dunkin Hartley guinea pigs (5/group) exposed to 0 or 950 mg/kg-day DEHP for 4 days via gavage (Hasmall et al., 2000)	950 / ND	N/A	- No significant effects observed for hepatic PBOX of liver weights; no significant change in body weight

Brief Study Details (Reference[s])	NOAEL/ LOAEL (mg/kg-day)	PPARα Biomarker at LOAEL	Comments
Male SD rats (3/group) were exposed to 0 or 2% DEHP for 2 weeks via diet (equivalent to 1,000 mg/kg-day DEHP) (Shin et al., 1999) [b]	1,000 / ND	↑ PPARα-dependent enzyme activities (*e.g.*, PBOX, catalase)	- Coincided with ↑ liver weights ↑ NAD+

DEHP = di-2-ethylhexyl phthalate; GJIC = Gap Junction Intercellular Communication; LOAEL = lowest-observed-adverse-effect level; MEHP = mono-2-ethylhexyl phthalate; NAD+ = nicotinamide adenine dinucleotide; ND = no data; NOAEL = no-observed-adverse-effect level; PBOX = peroxisomal beta oxidation; PPARα = peroxisome proliferator-activated receptor alpha; PT = keto-acyl-CoA thiolase; MCAD = medium-chain acyl-CoA dehydrogenase

[a] Studies identified from (ATSDR, 2022) unless otherwise stated.

[b] Study did not report received doses in mg/kg-day and food consumption were not reported. To estimate the mean received doses of DEHP in mg/kg-day, when given as % DEHP in diet, the following equation was applied: % DEHP in diet × (food factor) × 10,000 = mean dose in mg/kg-day, where food factor = 0.15 for mice, 0.05 for rats, 0.10 for young rats, 0.04 for guinea pigs, 0.05 for monkeys. To estimate the mean received doses of DEHP in mg/kg-day, when given as ppm DEHP in diet, the following equation was applied: DEHP in diet (ppm) × (food factor) = mean dose in mg/kg-day (WHO, 1987).

[c] Studies identified from (IARC, 2013).

Appendix E COMPARISON OF DEHP NON-CANCER POD TO THRESHOLD FOR PPARα ACTIVATION AND TUMORIGENISES

This appendix compares the DEHP non-cancer point of departure (POD) (NOAEL/LOAEL of 4.8/14 mg/kg-day) based on effects on the developing male reproductive system consistent with a disruption of androgen action and phthalate syndrome (see *Non-Cancer Human Health Hazard Assessment for Diethylhexyl Phthalate (DEHP)* (U.S. EPA, 2025h)) that was selected to characterize risk for acute, intermediate, and chronic exposures scenarios to the lowest identified thresholds for tumorigenesis and PPARα activation.

Overall, the DEHP non-cancer POD is expected to adequately account for all chronic toxicity, including carcinogenicity (assuming a threshold MOA), which could potentially result from exposure to DEHP. This conclusion is because the non-cancer POD (NOAEL/LOAEL of 4.8/14 mg/kg-day) is less than the lowest identified thresholds (*i.e.*, NOAEL/LOAEL or BMDL values) for tumorigenesis in the liver, pancreas and testis, and is less than the lowest identified threshold for PPARα activation. Identified thresholds are as follows:

- ***PPARα activation in the liver*.** EPA identified 27 studies that evaluated various biomarkers of PPARα activation (KE 1 in PPARα MOA) in the liver—including 18 studies of rats, 3 studies of mice, 3 studies of monkeys, 2 studies of hamsters, and 1 study of guinea pigs (Table_Apx D-1). As can be seen from Table_Apx D-1, the lowest identified NOAEL for PPARα activation in the liver were 7.5 mg/kg-day for mice (Isenberg et al., 2000) and for 11 mg/kg-day for rats (Barber et al., 1987; BIBRA, 1985). These NOAELs are greater than the identified non-cancer POD (NOAEL/LOAEL of 4.8/14 mg/kg-day) based on effects on the developing male reproductive system.

  EPA also identified a recent gene expression study conducted by NTP that evaluated biomarkers of PPARα activation in the liver and conducted BMD modeling of gene expression changes. Gwinn et al. (2020) conducted a transcriptomic dose-response study of DEHP in which male SD rats were gavaged with 0, 8, 16, 31.25, 62.5, 125, 250, 500, or 1,000 mg/kg-day DEHP for 5 days. Animals were sacrificed 24 hours after the last exposure, and then gene expression changes in the liver and kidney were evaluated using high-throughput transcriptomics with the rat Biospyder S1500+ platform. BMD modeling of transcriptional changes was performed using BMD Express 2.2 and a predefined analysis process that was previously peer-reviewed (NTP, 2018). Transcriptional BMDs were determined based on a benchmark response of 1 control standard deviation (1 SD). Table_Apx E-1 summarizes transcriptional BMD_{1SD} and $BMDL_{1SD}$ values in the liver for genes known to be regulated by PPARα. The lowest $BMDL_{1SD}$ was 8.6 mg/kg-day for enoyl-CoA hydratase and 3-hydroxyacyl CoA dehydrogenase (*Ehhadh*), which is above the non-cancer POD of 4.8 mg/kg-day.

- ***Hepatocellular adenoma and carcinoma (combined)*.** The lowest identified NOAELs/LOAELs were 29/147 mg/kg-day in male F344 rats (David et al., 2000b; David et al., 1999) and 19/99 mg/kg-day in male B6C3F1 mice (David et al., 2000a; David et al., 1999). Notably, in the studies by David et al. biomarkers of PPARα activation (*i.e.*, palmitoyl CoA oxidase activity) were significantly increased at doses equivalent to or less than those that resulted in tumorigenesis. These NOAELs are greater than the identified non-cancer POD (NOAEL/LOAEL of 4.8/14 mg/kg-day) based on effects on the developing male reproductive system.

- ***Pancreatic acinar cell adenoma and carcinoma (combined).*** The lowest NOAEL/LOAEL was 54/170 mg/kg-day in male SD rats exposed to DEHP in the feed for 2 years (postweaning only exposure study) (NTP, 2021b). NTP also conducted benchmark dose (BMD) modeling of pancreatic acinar cell adenoma and carcinoma (combined) incidence data from the perinatal and postweaning and postweaning only carcinogenicity studies of DEHP with male SD rats. The lowest BMD and BMDL associated with a 10 percent tumor response were 31 mg/kg-day and 20 mg/kg-day, respectively, in male rats in the postweaning only exposure study of DEHP (see Table 30, Table 31, and Appendix F in (NTP, 2021b)). This NOAEL and BMDL is greater than the identified non-cancer POD (NOAEL/LOAEL of 4.8/14 mg/kg-day) based on effects on the developing male reproductive system.
- ***Leydig cell tumors.*** The lowest NOAEL/LOAEL for Leydig cell tumors in male SD rats was 95/300 mg/kg-day (Voss et al., 2005). This NOAEL is greater than the identified non-cancer POD (NOAEL/LOAEL of 4.8/14 mg/kg-day) based on effects on the developing male reproductive system.

Table_Apx E-1. Summary of Transcriptional BMD and BMDL Values for Genes Regulated by PPARα in the Liver of Male SD Rats Gavaged with DEHP for 5 Days (Gwinn et al., 2020) [a]

Gene Name	Gene Symbol	Entrez Gene ID	BMD_{1SD} (mg/kg-day)	$BMDL_{1SD}$ (mg/kg-day)
Enoyl-CoA hydratase and 3-hydroxyacyl CoA dehydrogenase	Ehhadh	171142	11	8.6
Cytochrome P450, family 4, subfamily a, polypeptide 1	Cyp4a1	50549	12	9.0
Acyl-CoA thioesterase 1	Acot1	50559	13	9.5
CD36 molecule	Cd36	29184	30	18
Acyl-CoA oxidase 1	Acox1	50681	44	28
Fatty acid binding protein 1	fabp1	24360	77	32
Apolipoprotein A1	Apoa1	25081	120	58
Catalase	Cat	24248	124	86
Fibroblast growth factor 21	Fgf21	170580	815	614

[a] Rat $S1500^+$ gene expression data and BMDs can be found in NTP's Chemical Effects in Biological Systems (CEBs) database (accessed December 4, 2025).