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*Preliminary Materials*
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# Preliminary Materials for the Integrated Risk Information System (IRIS) Toxicological Review of Diisononyl Phthalate (DINP)

(CASRNs 28553-12-0, 68515-48-0, 71549-78-5, and 14103-61-8)

August 2014

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National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Washington, DC

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# ABBREVIATIONS

| | |
|---|---|
| AGD | anogenital distance |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| AOP | adverse outcome pathway |
| AST | aspartate aminotransferase |
| BBP | butyl benzyl phthalate |
| BMI | body mass index |
| BUN | blood urea nitrogen |
| BW | body weight |
| CalEPA | California Environmental Protection Agency |
| CASRN | Chemical Abstracts Service Registry Number |
| CHAP | Chronic Hazard Advisory Panel |
| CI | confidence interval |
| CPSC | Consumer Product Safety Commission |
| CPSIA | Consumer Product Safety Improvement Act |
| DBP | dibutyl phthalate |
| DEP | di-ethyl phthalate |
| DEHP | di(2-ethylhexyl)phthalate |
| DHEAS | Dehydroepiandrosterone |
| DIBP | diisobutyl phthalate |
| DIDP | di-isodecyl phthalate |
| DINP | diisononyl phthalate |
| DNA | deoxyribonucleic acid |
| DPP | dipentyl phthalate |
| ED | estrous day |
| EPA | Environmental Protection Agency |
| FIFRA | Federal Insecticide, Fungicide, and Rodenticide Act |
| FSH | follicle stimulating hormone |
| GD | gestational day |
| Hct | hematocrit |
| HERO | Health and Environmental Research Online |
| Hgb | hemoglobin |
| IgE | immunoglobulin E |
| ICC | intra-class correlation coefficient |
| IRIS | Integrated Risk Information System |
| LH | luteinizing hormone |
| LOD | level of detection |
| LOQ | level of quantification |
| MBzP | mono-benzyl phthalate |
| MEP | monoethyl phthalate |
| MBP | monobutyl phthalate |
| MCIOP | mono-carboxyisooctyl phthalate |
| MCNP | monocarboxyisononyl phthalate |
| MCOP | mono-carboxyoctyl phthalate |
| MCPP | mono(3-carboxypropyl) phthalate |
| MECCP | mono-2-ethyl-carboxypentyl |
| MEHP | mono-(2-ethylhexyl) phthalate |
| MEHHP | mono-2-ethyl-5-hydroxyhexyl phthalate |
| MEOHP | mono-2-ethyl-oxohexyl phthalate |
| MHINP | mono-hydroxyisononyl phthalate |
| MIBP | monoisobutyl phthalate |
| MINP | monoisononyl phthalate |
| MNCL | mononuclear cell leukemia |
| MOA | mode of action |
| MOINP | oxo-(mono-oxoisononyl) phthalate |
| NCEA | National Center for Environmental Assessment |
| NHANES | National Health and Nutrition Examination Survey |
| NRC | National Research Council |
| NTP | National Toxicology Program |
| OR | odds ratio |
| ORD | Office of Research and Development |
| PCOS | polycystic ovarian syndrome |
| PND | postnatal day |
| PNW | postnatal week |
| PVC | polyvinyl chloride |
| RBC | red blood cell |
| SD | standard deviation |
| SHBG | sex-hormone binding globulin |
| T3 | triiodothyronine |
| T4 | thyroxine |
| TSCA | Toxic Substances Control Act |
| TSH | thyroid stimulating hormone |
| WHO | World Health Organization |

# PREFACE

This draft document presents preliminary materials for an assessment of diisononyl phthalate (DINP) prepared by the U.S. Environmental Protection Agency's (EPA's) Integrated Risk Information System (IRIS) Program. These preliminary materials include a planning and scoping summary, information on the approaches used to identify pertinent literature, results of the literature search, approaches for selection of studies for hazard identification, presentation of critical studies in evidence tables and exposure-response arrays, and mechanistic information for DINP. This material is being released for public review and comment prior to a public meeting, providing an opportunity for the IRIS Program to engage in early discussions with stakeholders and the public on data that may be used to identify adverse health effects and characterize dose-response relationships.

The planning and scoping summary includes information on the uses of DINP, occurrence of DINP in the environment, and the rationale and scope for the development of the assessment. This information is responsive to recommendations in the 2009 National Research Council (NRC) report *Science and Decisions: Advancing Risk Assessment* (NRC, 2009) related to planning and scoping in the risk assessment process.

The preliminary materials are also responsive to the 2011 NRC report *Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde* (NRC, 2011). The IRIS Program's implementation of the NRC recommendations is following a phased approach that is consistent with the NRC's "Roadmap for Revision" as described in Chapter 7 of the formaldehyde review report. The NRC stated that "the committee recognizes that the changes suggested would involve a multi-year process and extensive effort by the staff at the National Center for Environmental Assessment and input and review by the EPA Science Advisory Board and others." Phase 1 of implementation has focused on a subset of the short-term recommendations, such as editing and streamlining documents, increasing transparency and clarity, and using more tables, figures, and appendices to present information and data in assessments. Phase 1 also focused on assessments near the end of the development process and close to final posting. Phase 2 of implementation is focused on assessments that are in the beginning stages of assessment development. The IRIS DINP assessment is in Phase 2 and represents a significant advancement in implementing the NRC recommendations. In the development of this assessment, many of the recommendations are being implemented in full, while others are being implemented in part. Achieving full and robust implementation of certain recommendations will be an evolving process with input and feedback from the public, stakeholders, and independent external peer review. Phase 3 of implementation will incorporate the longer-term recommendations made by the NRC, including the development of a standardized approach to describe the strength of evidence for noncancer effects. In May 2014, the NRC released their report reviewing the IRIS assessment

development process. As part of this review, the NRC reviewed current methods for evidence-based reviews and made several recommendations with respect to integrating scientific evidence for chemical hazard and dose-response assessments. In their report, the NRC states that EPA should continue to improve its evidence-integration process incrementally and enhance the transparency of its process. The committee did not offer a preference but suggests that EPA consider which approach best fits its plans for the IRIS process. The NRC recommendations will inform the IRIS Program's efforts in this area going forward. This effort is included in Phase 3 of EPA's implementation plan.

The literature search strategy, which describes the processes for identifying scientific literature, screening studies for consideration, and identifying primary sources of health effects data, is responsive to NRC recommendations regarding the development of a systematic and transparent approach for identifying the primary literature for analysis. The preliminary materials also describe EPA's approach for the selection of critical studies to be included in the evidence tables, as well as the approach for evaluating methodological features of studies that will be considered in the overall evaluation and synthesis of evidence for each health effect. The development of these materials is in response to the NRC recommendation to thoroughly evaluate critical studies with standardized approaches that are formulated and based on the type of research (e.g., observational epidemiology or animal bioassays). In addition, NRC recommendations for standardized presentation of key study data are addressed by the development of the preliminary evidence tables and preliminary exposure-response arrays for primary health effect information.

EPA welcomes all comments on the preliminary materials in this document, including the following:

- the clarity and transparency of the materials;
- the approach for identifying pertinent studies;
- the selection of critical studies for data extraction to preliminary evidence tables and exposure-response arrays;
- any methodological considerations that could affect the interpretation of or confidence in study results; and
- any additional studies published or nearing publication that may provide data for the evaluation of human health hazard or dose-response relationships.

The preliminary evidence tables and exposure-response arrays should be regarded solely as representing the data on each endpoint that have been identified as a result of the draft literature search strategy. They do not reflect any conclusions as to hazard identification or dose-response assessment.

After obtaining public input and conducting additional study evaluation and data integration, EPA will revise these materials to support the hazard identification and dose-response assessment in a draft Toxicological Review that will be made available for public comment.

# 1. INTRODUCTION

This introduction contains a planning and scoping summary for the Integrated Risk Information System (IRIS) assessment of diisononyl phthalate (DINP). The planning and scoping summary includes information on the properties, sources, and uses of DINP, occurrence and fate of DINP in the environment, potential for human exposure, and the rationale for the development of this assessment.

## 1.1. DINP IN THE ENVIRONMENT

### 1.1.1. Production and Use

DINP (Chemical Abstract Service Registry Numbers (CASRNs) 68515-48-0, 28553-12-0, 71549-78-5, 14103-61-8), is not a pure compound, but rather a mixture of isomers with an average side chain length of nine carbons (Figure 1-1).

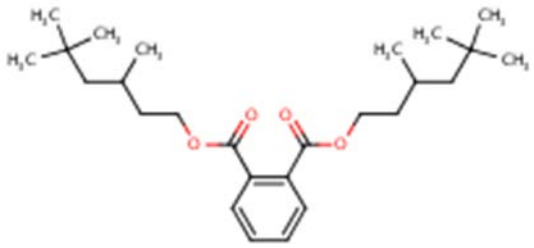

**Figure 1-1. Chemical structure of DINP (HSDB, 2009).**

Between 100 and 500 million pounds of DINP was imported or manufactured in US in 2006 (US.EPA 2014). It is used in the production of plastics to increase flexibility and is commonly present in products such as toys, vinyl swimming pools, vinyl containing furniture and clothes, flooring, gloves, drinking straws, garden hoses and sealants used in food packaging (CDC, 2014; HSDB, 2009). Most DINP is used in PVC products, with less than 10% used in non-PVC products such as different types of rubber, inks, pigments, paints, lacquers, adhesives, and sealants (Cal/EPA, 2013). The use of di-2-ethylhexyl phthalate (DEHP) has largely been replaced by DINP, though not in medical products. In 2008, the Consumer Product Safety Improvement Act (CPSIA) placed an interim ban on DINP in children's toys and certain child care articles at concentrations greater than 0.1 percent. The Chronic Hazard Advisory Panel (CHAP) recommended that the interim ban on

DINP be made permanent in children's toys and child care products at level greater than 0.1% (CHAP, 2014).

DINP has been sold in varying commercial formulations, such as DINP-1, DINP-2, and DINP-3, which are produced with different C8–C10 alcohol feedstocks (Gill et al., 2001). Production of the DINP-3 formulation was discontinued in 1995 (ECPI, 2010; Gill et al., 2001). The exact composition of the commercial DINP formulations is not well defined. Gas chromatographic analysis of these mixtures is difficult due to the large number of isomers present at low concentrations and the co-elution of isomers present at higher concentrations (Gill et al., 2001). Based on the available estimates of alkyl chain content, the compositions of DINP-1 and DINP-2 can be expected to be similar, while DINP-3 contained larger proportions of methyl ethyl hexanols than the other formulations (BASF, 2013; Evonik Industries, 2009; ECJRC, 2003; ExxonMobil, 2001). The correspondence between DINP formulations and CASRNs is as follows:

- DINP-1: CASRN 68515-48-0.
- DINP-2 and DINP-3: CASRN 28553-12-0
- Santicizer 900 and DINP-A: CASRN 71549-78-5;
- Bis(3,5,5-trimethylhexyl) phthalate: CASRN 14103-61-8

As noted above, DINP-2 and DINP-3 were assigned the same CASRN, and, thus, the specific formulation used in some studies was not readily distinguishable. Throughout this document, the general term, DINP, will be used to describe the test materials used and evidence tables will provide the specific formulation in the reference design column if this information is available.

### 1.1.2. Environmental Fate

As noted by Wormuth et al. (2006), the major portion of phthalates that are found in the environment comes from their slow releases from plastics and other phthalate containing articles. The presence of phthalates in food is due to their use in packaging materials and food preparation. Certain waste streams, sludges, and contaminated sites may contain higher levels of phthalates.

Based on its vapor pressure, DINP, if released to air, is expected to exist in both the vapor and particulate phases. Vapor-phase DINP will be photolytically degraded with a half-life of less than a day. Particulate-phase diisononyl phthalate will be removed from the atmosphere by wet or dry deposition. Once in soil, DINP will be tightly sorbed given a high organic carbon partition coefficient, $K_{oc}$. DINP's binding to soil limits its volatilization. Similarly, if released into water, DINP binds to suspended solids and sediment. Biodegradation is expected to occur in both soil and water over of period of days to months, depending on environmental conditions. DINP has a low potential for bioaccumulation given measured bioconcentration factor of 3 (HSDB, 2009).

### 1.1.3. Human Exposure Pathways

The ways that humans are exposed to phthalates along with the magnitude of the exposures have changed over time as the quantities and uses of phthalates have changed. As noted above, the Consumer Product Safety Improvement Act (CPSIA) of 2008 placed an interim ban on DINP in children's toys and certain child care articles at concentrations greater than 0.1 percent and the CHAP recommended that the interim ban on DINP be made permanent in children's toys and child care products at level greater than 0.1% (CHAP, 2014). In December 2013, California EPA added DINP to the Proposition 65 list as a carcinogen. These recommendations and statements reflect the changing levels of phthalates in different products and exposure sources.

Diet is currently understood to be the greatest source of exposure to DINP. DINP has been found in beverages, dairy, fish, grain, poultry, other meats, and vegetables (CHAP, 2014; Schecter et al., 2013). It was not detected in infant formula (Schecter et al., 2013; Clark, 2010). Lesser exposures to DINP may occur through inhalation and dermal contact with products containing DINP. In background settings, DINP has been measured in dust and soil, but not found in air (CHAP, 2014). In association with contaminated settings, it has been found in sludge and sludge amended soil and in wastewater (Clark, 2010; Vikelsøe et al., 1999).

Calafat et al. (2011) identified monocarboxyisooctyl phthalate (MCIOP) as the most appropriate metabolite of DINP to characterize exposure to DINP. Zota et al. (2014) looked at the temporal trends of phthalate metabolites in NHANES from 2001 to 2010. For MCIOP, they found an increasing trend in concentrations, with geometric means at about 5.1 ng/mL in the 2005/2006 cycle, 7.0 ng/mL in the 2007/2008 cycle, and 13.4 ng/mL in the 2009/2010 cycle.

Intake exposures can be estimated on a pathway-basis by combining exposure media concentrations and contact rates. Using this approach, Clark et al. (2011) estimated a median intake of DINP between 0.7 and 2.1 µg/kg-day for various lifestages as defined by the author: adults (20–70 years of age), teens (12–19 years of age), children (5–11 years of age), toddlers (ages 0.5–4 years of age), and infants (0–0.5 years of age). Toddlers had the highest intake noted. Pathways the authors assessed include ingestion of food, drinking water, dust/soil, and inhalation of air. For the adult, teen, child, and toddler, ingestion of food accounts for 61–71% of intake, depending on the age group. The remainder of the exposure for these age groups (and all of the exposure to the infant) is due to ingestion of dust. Infant and toddler intakes with toys and teethers have been estimated to range from 1.7 to 120 µg/kg-day by RIVM (1998), Health Canada (1998), Wormuth et al. (2006), U.S. Consumer Product Safety Commission (CPSC, 1998) and (Babich et al., 2004). Estimates of mean total intakes using a pathway-based approach were provided by the CPSC (CHAP, 2014): 5.1 µg/kg-day for women, ages 15-45, and 20.7 µg/kg-day for infants (0 - <1 yr), 30.8 µg/kg-day for toddlers (1 to <3 yr), and 14.3 µg/kg-day for children (3-12 yr). For all age categories, diet dominated the estimates, at over 90% for adult women to 67% for toddlers (with "child care" products explaining most of the remainder).

An estimate of total exposure by all pathways can be determined based on urine concentrations of phthalate metabolites. Kransler et al. (2012) reviewed the literature on general

population intakes of DINP and found reported mean intakes in the range of 1–2 μg/kg-day. They reviewed pathway-based estimates as well as intakes determined from surveys of MCOP in urine. On a body weight basis, they found the highest intakes for children ages 6–11 at about 3 μg/kg-day, with all other ages in the 1–2 μg/kg-day range. Qian et al. (2014); using NHANES 2007/2008, a median intake of 1.1 μg/kg-day and a 95$^{th}$ percentile intake of 9.4 μg/kg-day was found. Christensen et al. (2014) combined the data from NHANES 2005–2008 and found similar results to Qian et al. (2014), with a median over that time span of 1.3 μg/kg-day and a 95$^{th}$ percentile intake of 11.7 μg/kg-day. The CPSC (CHAP, 2014) found median and 99% percentile intakes of 1.1 and 35.0 μg/kg-day, respectively, for adults aged 15-45, using data from NHANES 2005-06.

## 1.2. SCOPE OF THE ASSESSMENT

The National Research Council has recommended, "Cumulative risk assessment based on common adverse outcomes is a feasible and physiologically relevant approach to the evaluation of the multiplicity of human exposures and directly reflects EPA's mission to protect human health (NRC 2009, p12)." They envisioned facilitating the process by "defining the groups of agents that should be included for a given outcome" (NRC 2009, p13). In humans, the NRC cited results from the National Health and Nutrition Examination Survey that demonstrate exposure to multiple phthalates in most people (NRC 2009, p23). A recent review of human exposure to eight phthalates estimated DINP to have the second-highest concentrations in dust and soil (CPSC 2014, p E1-11). Thus, an evaluation of the human health hazards of DINP is necessary to future cumulative risk assessments that assess effects on human health outcomes that might be associated with DINP.

In order to evaluate the potential health effects resulting from exposure to DINP, the IRIS Program is developing an IRIS assessment for this chemical. Once final, the assessment of DINP will help to inform EPA programs and regions and other groups. DINP has not been assessed previously by the IRIS Program.

# 2. METHODS FOR IDENTIFYING AND SELECTING STUDIES

The NRC (2011) recommended that the U.S. Environmental Protection Agency (EPA) develop a detailed search strategy utilizing a graphical display documenting how initial search findings are narrowed to the final studies that are selected for further evaluation on the basis of inclusion and exclusion criteria. Following these recommendations, a literature search and screening strategy was applied to identify literature related to characterizing the health effects of diisononyl phthalate (DINP). This strategy consisted of a search of online scientific databases and other sources, casting a wide net in order to identify all potentially pertinent studies. In subsequent steps, references were screened to exclude papers not pertinent to an assessment of the health effects of DINP, and remaining references were sorted into categories for further evaluation. Section 2.1 describes the literature search and screening strategy in detail. The NRC (2011) further recommended that after studies are identified for review by utilizing a transparent search strategy, the next step is to summarize the details and findings of the most pertinent studies in the evidence tables. The NRC suggested that such tables should provide a link to the references, and include details of the study population, methods, and key findings. This approach provides for a systematic and concise presentation of the evidence. The NRC also recommended that the methods and findings should then be evaluated with a standardized approach. The approach that was outlined identified standard issues for the evaluation of epidemiological and experimental animal studies. Section 2.2 describes the approach taken for DINP for selecting studies to be included in the preliminary evidence tables and exposure-response arrays. Section 3 presents the selected studies in preliminary evidence tables and exposure-response arrays, arranged by health effect.

## 2.1. DRAFT LITERATURE SEARCH AND SCREENING STRATEGY

The literature search for DINP was conducted in four online scientific databases (PubMed, Web of Science, Toxline, and TSCATS2) in June of 2013; the search was repeated in January 2014. This document is complete through January 2014. Additional updates will be performed at regular (e.g., 6-month) intervals. The detailed search approach, including the search strings and number of citations identified per database, is presented in Table 2-1. This search of online databases identified 542 citations (after electronically eliminating duplicates). The computerized database searches were also supplemented by a manual search of citations from other regulatory documents (Table 2-2); 85 citations were obtained using these additional search strategies. In total, 604 citations were identified using online scientific databases and additional search strategies.

**Table 2-1. Database search strategy for DINP**

| Database (search date) | Keywords[a] |
|---|---|
| PubMed<br>01/2014<br>06/2013 | (28553-12-0 OR ("Diisononyl phthalate" OR "1,2-Benzenedicarboxylic acid diisononyl ester" OR "Isononyl alcohol phthalate" OR "Phthalic acid diisononyl ester" OR "1,2-Benzenedicarboxylic acid 1,2-diisononyl ester " OR "Di isononyl phthalate" OR Diisononylphthalate OR "di-isononylphthalate") OR ("alpha-Dinonyl phthalate"[tw] OR " 1,2-Benzenedicarboxylic acid bis(3,5,5-trimethylhexyl) ester"[tw] OR "Bis(3,5,5-trimethylhexyl) phthalate"[tw] OR "Di-3,5,5-trimethylhexyl phthalate"[tw] OR "Phthalic acid bis(3,5,5-trimethylhexyl) ester"[tw] OR "Di(C8-10, C9 rich) branched alkyl phthalates"[tw] OR ("1,2-Benzenedicarboxylic acid" AND "di-C8-10-branched alkyl esters" AND "C9-rich")[tw] OR ( "1,2-Benzenedicarboxylic acid" AND "di-C8-C10-branched alkyl ester" AND "C9-rich")[tw] OR "Branched dinonyl phthalate"[tw] OR "Di-(C9-branched alkyl) phthalate"[tw] OR "1,2-Benzenedicarboxylic acid 1,2-dinonyl ester"[tw] OR "1,2-Benzenedicarboxylic acid dinonyl ester"[tw] OR "Di(C8-C10) branched alkyl phthalate"[tw] OR "BIS(7-METHYLOCTYL) PHTHALATE"[tw]) OR (("diisononyl phthalate"[Substance Name] OR "diisononyl phthalate"[All Fields]) OR (Palatinol[All Fields] AND DN[All Fields]) OR (Palatinol[All Fields] AND N[All Fields])) OR (dinp AND (phthalic OR phthalate* OR isononyl* OR benzenedicarboxylic OR diisononyl)) |
| **Web of Science**<br>01/2014<br>06/2013 | TS=”1 2 benzenedicarboxylic acid” OR TS=”1 2 benzenedicarboxylic acid 1 2 dinonyl ester” OR TS=”1 2 benzenedicarboxylic acid 1 2 diisononyl ester” OR TS=”1 2 benzenedicarboxylic acid diisononyl ester” OR TS=”1 2 benzenedicarboxylic acid dinonyl ester” OR TS=”alpha dinonyl phthalate” OR TS=”baylectrol 4200” OR TS=”branched dinonyl phthalate” OR TS=”c9 rich” OR TS=”di 3 5 5 trimethylhexyl phthalate” OR TS=”di c8 10 branched alkyl esters” OR TS=”diisononyl phthalate” OR TS=”di isononylphthalate” OR TS=”di isononyl phthalate” OR TS=”diisononylphthalate” OR TS=”dinp” OR TS=”dinp2” OR TS=”dinp3” OR TS=”enj 2065” OR TS=”isononyl alcohol phthalate” OR TS=”palatinol dn” OR TS=”palatinol n” OR TS=”phthalic acid diisononyl ester” OR TS=”sansocizer dinp” OR TS=”vestinol 9” OR TS=” vinylcizer 90” OR TS=”vestinol nn” OR TS=”witamol 150” OR TS=”28553-12-0” OR TS=”68515-48-0” OR TS=”71549-78-5” OR TS=”14103-61-8” OR TS=”1 2 benzenedicarboxylic acid bis 3 5 5 trimethylhexyl ester” OR TS=”bis 3 5 5 trimethylhexyl phthalate” OR TS=”phthalic acid bis 3 5 5 trimethylhexyl ester” OR TS=”di c8 10 c9 rich branched alkyl phthalates” OR TS=”di c8 c10 branched alkyl phthalate” OR TS=”di c9 branched alkyl phthalate” OR TS=”bis 7 methyloctyl phthalate”) OR (TS=”1 2 benzenedicarboxylic acid" AND TS=“ester*” AND (TS=“diisononyl” OR TS="di isononyl" OR TS=“branched” OR TS=“dinonyl” OR TS=“trimethylhexyl”)) OR (TS="phthalic acid" AND TS=“ester*” AND (TS=“diisononyl” OR TS="di isononyl" OR TS=“branched” OR TS=“dinonyl” OR TS=”trimethylhexyl”)) |
| **Toxline**<br>01/2014<br>06/2013 | (( "diisononyl phthalate" OR "vestinol nn" OR "sansocizer dinp" OR "palatinol dn" OR "palatinol n" OR dinp OR 28553-12-0 [rn] ) OR (68515-48-0 [rn]) OR ( 71549-78-5 [rn] ) OR ( "alpha dinonyl phthalate" OR 14103-61-8 [rn] ) OR ( "diisononyl phthalate" OR "1 2 benzenedicarboxylic acid diisononyl ester" OR "isononyl alcohol phthalate" OR "phthalic acid diisononyl ester" OR "1 2 benzenedicarboxylic acid 1 2 diisononyl ester" OR "di isononyl phthalate" OR diisononylphthalate OR "di isononylphthalate" ) OR ( "alpha dinonyl phthalate" OR " 1 2 benzenedicarboxylic acid bis ( 3 5 5 trimethylhexyl ) ester" OR "bis ( 3 5 5 trimethylhexyl ) phthalate" OR "di 3 5 5 trimethylhexyl phthalate" OR "phthalic acid bis ( 3 5 5 trimethylhexyl ) ester" OR "di ( c8 10 c9 rich ) branched alkyl phthalates" ) OR ( "1 2 benzenedicarboxylic acid" AND "di c8 10 branched alkyl esters" AND "c9 rich" ) OR ( "branched dinonyl phthalate" OR "di ( c9 branched alkyl ) phthalate" OR "1 2 benzenedicarboxylic acid 1 2 dinonyl ester" OR "1 2 benzenedicarboxylic acid dinonyl ester" OR "di ( c8 c10 ) branched alkyl phthalate" OR "bis ( 7 methyloctyl ) phthalate" ) OR ( "enj 2065" OR "baylectrol 4200" OR dinp OR dinp2 OR dinp3 OR "palatinol dn" OR "palatinol n" OR "vestinol 9" OR "vestinol nn" OR "vinylcizer 90" OR "witamol 150" ) OR ( di AND isononyl AND phthalate ) OR ( "1 2 |

| | |
|---|---|
| | benzenedicarboxylic acid" AND ester* AND ( diisononyl OR "di isononyl" OR branched OR dinonyl OR trimethylhexyl ) ) OR ( "phthalic acid" AND ester* AND ( diisononyl OR "di isononyl" OR branched OR dinonyl OR trimethylhexyl ) )) NOT PubMed [org] NOT pubdart [org] NOT tscats [org] |
| **TSCATS2**<br>01/2014<br>10/2013 | (2000-) 28553-12-0, 68515-48-0, 71549-78-5, 14103-61-8 |

[a]The search strings did not include DINP metabolites; a PubMed search using metabolites of DINP did not capture any additional pertinent studies.

**Table 2-2. Summary of additional search strategies for DINP**

| Approach used | Source(s) | Date performed | Number of additional citations identified |
|---|---|---|---|
| Manual search from reviews conducted by other international and federal agencies | CPSC (2010). Toxicity review of Diisononyl Phthalate (DINP). Bethesda, MD. | 08/2013 | 17 citations |
| | ECJRC (2003). European Union risk assessment report: 1,2-Benzenedicarboxylic acid, di-C8-10-branched alkyl esters, C9-rich - and di-"isononyl" phthalate (DINP). (EUR 20784 EN). Luxembourg, Belgium: Office for Official Publications of the European Communities. http://bookshop.europa.eu/en/european-union-risk-assessment-report-pbEUNA20784/. | 08/2013 | 31 citations |
| | CPSC (2001). Report to the U.S. Consumer Product Safety Commission by the Chronic Hazard Advisory Panel on diisononyl phthalate (DINP). Bethesda, MD. | 08/2013 | 7 citations added |
| | NTP-CERHR (2003). NTP-CERHR monograph on the potential human reproductive and developmental effects of di-isononyl phthalate (DINP) (pp. i-III90). Research Triangle Park, NC: National Toxicology Program Center for the Evaluation of Risks to Human Reproduction. http://cerhr.niehs.nih.gov/chemicals/phthalates/dinp/DiNP_Monograph_Final.pdf. | 08/2013 | 0 citations added |
| Electronic forward Search through Web of Science[1] | Lington et al. (1997). Chronic toxicity and carcinogenic evaluation of diisononyl phthalate in rats. Fundam Appl Toxicol 36: 79-89. http://dx.doi.org/10.1093/toxsci/36.1.79. | 08/2013 | 0 citations |
| | Masutomi et al. (2003). Impact of dietary exposure to methoxychlor, genistein, or diisononyl phthalate during the perinatal period on the development of the rat endocrine/reproductive systems in later life. Toxicology 192: 149-170. http://dx.doi.org/10.1016/S0300-483X(03)00269-5. | 08/2013 | 0 citations |
| References obtained during the assessment process | DINP references obtained from submissions, full study reports from HERO, or in previous assessment | 08/2013 | 15 citations added |

| Approach used | Source(s) | Date performed | Number of additional citations identified |
|---|---|---|---|
| Background Check | Searched a combination of CASRNs and synonyms on the following databases:<br>ACGIH (http://www.acgih.org/home.htm)<br>ATSDR (http://www.atsdr.cdc.gov/substances/index.asp)<br>CalEPA Office of Environmental Health Hazard Assessment (http://www.oehha.ca.gov/risk.html)<br>CalEPA OEHHA Toxicity Criteria Database (http://www.oehha.ca.gov/tcdb/index.asp)<br>CalEPA Biomonitoring California-Priority Chemicals (http://www.oehha.ca.gov/multimedia/biomon/pdf/PriorityChemsCurrent.pdf)<br>CalEPA Biomonitoring California-Designated Chemicals (http://www.oehha.ca.gov/multimedia/biomon/pdf/DesignatedChemCurrent.pdf)<br>CalEPA Cal/Ecotox database (http://www.oehha.ca.gov/scripts/cal_ecotox/CHEMLIST.ASP)<br>CalEPA OEHHA Fact Sheets (http://www.oehha.ca.gov/public_info/facts/index.html)<br>CalEPA Non-cancer health effects Table (RELs) and Cancer Potency Factors (Appendix A and Appendix B) (http://www.oehha.ca.gov/air/hot_spots/index.html)<br>CPSC (http://www.cpsc.gov)<br>eChemPortal (http://www.echemportal.org/echemportal/participant/page.action?pageID=9)<br>Environment Canada − Search entire site if not found below: (http://www.ec.gc.ca/default.asp?lang=En&n=ECD35C36)<br>Toxic Substances Managed under CEPA (http://www.ec.gc.ca/toxiques-toxics/Default.asp?lang=En&n=98E80CC6-1)<br>Screening Assessment reports<br>Risk Management reports<br>Final Assessments (http://www.ec.gc.ca/lcpe-cepa/default.asp?lang=En&xml=09F567A7-B1EE-1FEE-73DB-8AE6C1EB7658)<br>Draft Assessments (http://www.ec.gc.ca/lcpe-cepa/default.asp?lang=En&xml=6892C255-5597-C162-95FC-4B905320F8C9)<br>EPA Acute Exposure Guideline Levels (http://www.epa.gov/oppt/aegl/pubs/chemlist.htm)<br>EPA − IRISTrack/New Assessments and Reviews<br>EPA NSCEP (http://www.epa.gov/ncepihom/)<br>EPA RfD/RfC and CRAVE meeting notes<br>EPA Science Inventory (http://cfpub.epa.gov/si/)<br>FDA (http://www.fda.gov/)<br>Federal Docket (www.regulations.gov)<br>Health Canada First Priority List Assessments (http://www.hc-sc.gc.ca/ewh-semt/pubs/contaminants/psl1-lsp1/index-eng.php) | 1/2013 | 15 citations added |

| Approach used | Source(s) | Date performed | Number of additional citations identified |
|---|---|---|---|
| | Health Canada Second Priority List Assessments (http://www.hc-sc.gc.ca/ewh-semt/pubs/contaminants/psl2-lsp2/index-eng.php)<br>IARC (http://monographs.iarc.fr/htdig/search.html)<br>ITER (TERA database) (http://iter.ctcnet.net/publicurl/pub_search_list.cfm)<br>NAP – Search Site (http://www.nap.edu/)<br>NRC – AEGLs via NAP search for "Acute Exposure Guideline Level" and the chemical<br>NCI (http://www.cancer.gov)<br>NCTR (http://www.fda.gov/AboutFDA/CentersOffices/OC/OfficeofScientificandMedicalPrograms/NCTR/default.htm)<br>National Institute for Environmental Health Sciences (NIEHS) http://www.niehs.nih.gov/<br>NICNAS (PEC only covered by eChemPortal) (http://www.nicnas.gov.au/industry/aics/search.asp)<br>NIOSH (http://www.cdc.gov/niosh/topics/)<br>NIOSHTIC 2 (http://www2a.cdc.gov/nioshtic-2/)<br>NTP - RoC, status, results, and management reports (http://ntpsearch.niehs.nih.gov/query.html)<br>OSHA (http://www.osha.gov/dts/chemicalsampling/toc/toc_chemsamp.html)<br>RTECS http://www.ccohs.ca/search.html | | |

These citations were screened using the title, abstract, and in limited instances, full text for pertinence to examining the health effects of DINP exposure. The citations were then screened using inclusion criteria (Table 2-3) describing specific information to help identify primary source health effect data and mechanistic and/or genotoxic data, as well as resources useful in preparation of the DINP package. The process for screening the literature search is described below and is shown graphically in Figure 2-1:

- 38 references were identified as animal studies with health effects data and were considered for data extraction to evidence tables and exposure-response arrays.
- 51 references were identified as supporting studies; of these, 9 were toxicokinetic studies and 42 were mechanistic and genotoxicity studies.
- 75 references were identified as secondary literature (e.g., reviews and editorials, risk assessments, and regulatory documents); these references were kept as additional resources for development of the Toxicological Review.
- 416 references were excluded because these studies did not include the primary source data evaluating DINP in relation to any kind of toxicity or health endpoint, and did not provide either supporting information (e.g., toxicokinetic or mechanistic/genotoxic data) or secondary literature information (see Figure 2-1 and Table 2-3 for inclusion categories and criteria).

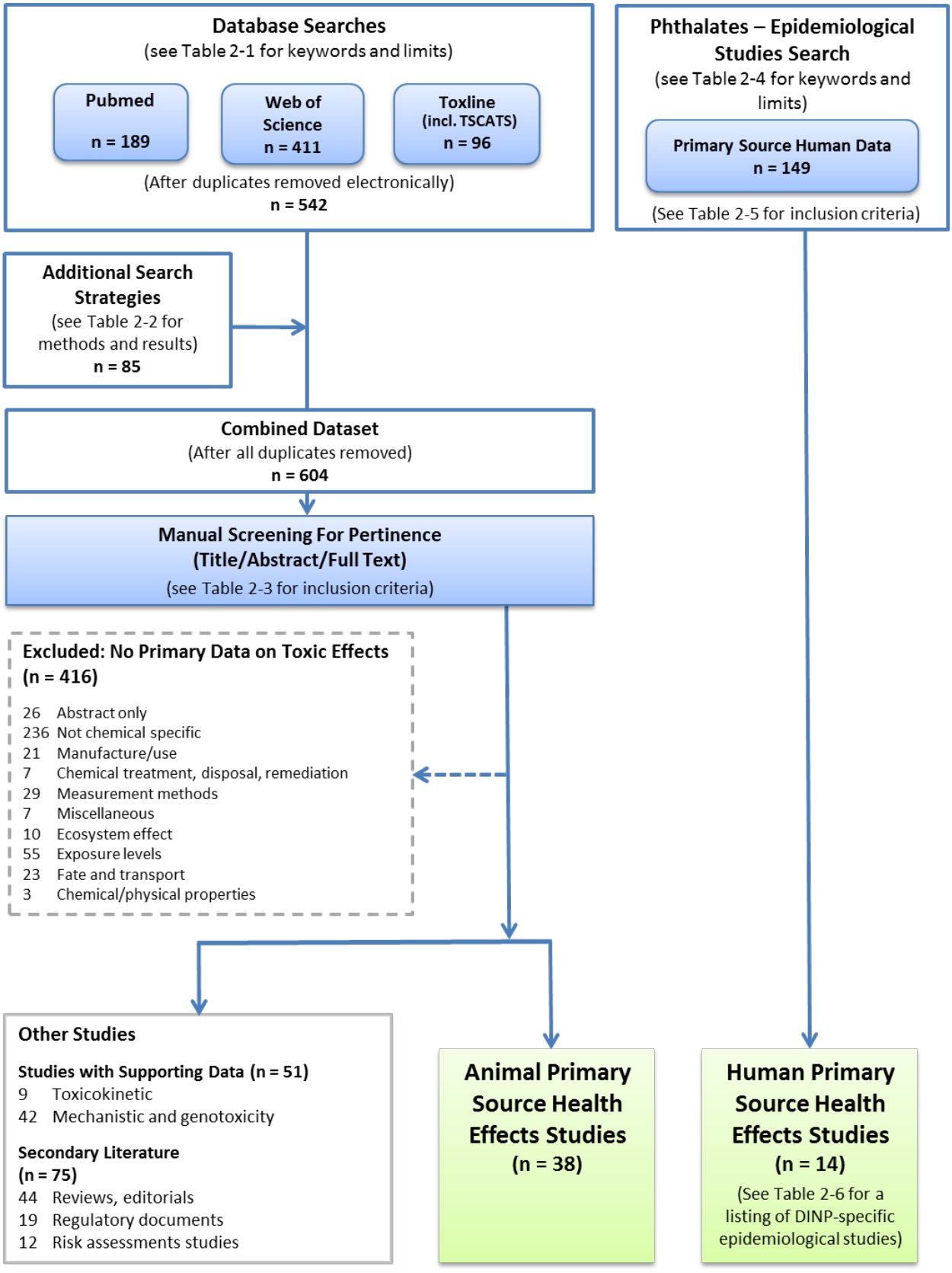


**Figure 2-1. Literature search approach for DINP.**

**Table 2-3. Inclusion criteria used to identify animal studies of health-related endpoints, supporting data, or secondary literature**

| Inclusion criteria[a] |
|---|
| • Did the study evaluate effects of DINP or its metabolites known to be formed in humans?<br>• Did the study evaluate effects in a tissue (organ) or cells derived from a tissue (organ)?<br>• Did the study evaluate cellular, biochemical or molecular effects relevant to any mode of action?<br>or<br>• Does the study include information from other agencies, risk assessments, or reviews that would aid in the development of a toxicological review of DINP? |

[a]If the answer is ''no'' to any of these criteria questions, the study was placed under "No Primary Data on Toxic Effects."

Eight human studies were also identified from the initial literature search using the search strings presented in Table 2-1. However, work being done concurrently on the development of other phthalate preliminary materials revealed that this set of DINP epidemiology studies was incomplete. Epidemiology studies frequently examine multiple compounds (e.g., metabolites of several different phthalates). The indexing terms and abstracts may not include a comprehensive list of all of the specific phthalates examined, resulting in the inappropriate exclusion of studies and the potential for introduction of bias in the selection process. Specifically, "negative" studies (i.e., studies that did not demonstrate an association between exposure and disease) are potentially more likely to be missed than "positive" studies. This issue did not arise in the search process for experimental (animal toxicology) studies, for which the test compound is virtually always identified through search terms or key word searches of abstracts.

Another issue encountered in the development of the search and screening process for the phthalate epidemiology studies relates to the duplication of efforts involved in the development of EPA's health assessments for several individual phthalates (e.g., dibutyl phthalate [DBP], DINP, butyl benzyl phthalate [BBP], di(2-ethylhexyl)phthalate [DEHP], di-ethyl phthalate [DEP], dipentyl phthalate [DPP], and diisobutyl phthalate [DIBP]). In contrast to animal toxicology studies, most of the epidemiology studies examine more than one phthalate, resulting in considerable overlap in the sets of studies identified using individual-phthalate search terms. Full text screening of the same studies identified in multiple searches results in an inefficient use of resources.

For these reasons, EPA developed a process for identifying epidemiological studies evaluating phthalates by performing a single broad search to create a listing of epidemiological studies of all phthalates mentioned above, from which the selection of studies examining potential health effects of an individual phthalate could be drawn. This list records each of the phthalates included in the study, based on information in the methods section of the paper, and the outcome(s) examined. This literature search for epidemiological studies examining phthalates in relation to

health-related endpoints (from which the DINP studies were drawn) was conducted in PubMed, Web of Science, and ToxNet databases in June 2013, using keywords and limits described in Table 2-4; the search was updated in December 2013. For this search, "phthalate" (and related terms) rather than names of specific phthalates was used as the foundation of the search, along with terms designed specifically to identify epidemiological studies. These terms were based on terms used in previously identified epidemiology studies of six different phthalates.

**Table 2-4. Summary of search terms: targeted epidemiology search**

| Database, search date | Terms | Hits |
|---|---|---|
| **June 2013 search**<br>PubMed<br>06/2013<br>No date restriction | (phthalate OR phthalates OR phthalic acid) AND (human OR case-control OR pregnancy OR cohort OR workers OR children OR survey) | Imported: 2,505<br>After duplicates deleted: 2,482 |
| Web of Science<br>06/2013<br>No date restriction | (TS="phthalic acid" OR TS="phthalate" OR TS="phthalates") AND (TS="humans" OR TS="human" OR TS="case-control" OR TS="pregnancy" OR TS="cohort" OR TS="workers" OR TS="child" OR TS="children" OR TS="survey") | Imported: 1,840<br>After duplicates deleted: 1,836 |
| ToxNet<br>06/2013<br>No date restriction | (phthalate OR phthalates OR phthalic acid) AND (human OR case-control OR pregnancy OR cohort OR workers OR children OR survey) | Imported: 2,505<br>After duplicates deleted: 2,426 |
| Merged Reference Set | Merged dataset, with duplicates eliminated through electronic screen<br>**Epidemiology articles meeting inclusion criteria** | 4,127<br>127 |
| **December 2013 search** | PubMed<br>Web of Science<br>ToxNet<br>Merged Reference Set<br>**Additional epidemiology articles meeting inclusion criteria** | 155<br>249<br>114<br>350<br>**22** |

More than 4,000 citations were identified through this search. These were then screened using inclusion criteria describing specific population (i.e., human), exposure measures, comparison, and health effects (Table 2-5). Note that other studies obtained in the search, for example mechanistic and pharmacokinetic studies, are excluded from consideration with respect to the specific objective of this search (i.e., identification of epidemiology studies), but could be included in other steps in the assessment. Duplicate citations of the same article were excluded and articles written in a language other than English were retained for subsequent review.

**Table 2-5. Inclusion criteria used to identify epidemiology studies of health-related endpoints**

| Inclusion criteria |
|---|
| • Is the study population humans?<br>and<br>• Is exposure to one or more phthalate (parent compound or metabolite(s)[a]...<br>- measured in air, dust, or biological tissue?<br>- based on knowledge of industrial hygiene (occupational settings)?<br>- based on knowledge of specific contamination sites or accidental exposure?<br>and<br>• Does the study compare a health effect in higher versus lower or no exposure?<br>and<br>• Does the study include a measure of one or more primary health effect endpoints relating to[b]…<br>- sexual differentiation measures (e.g., male genital malformations, anogenital distance, gender-related play behavior)<br>- male reproductive effects (e.g., steroidal and gonadotropin hormone levels, measures of male-mediated infertility)?<br>- female reproductive effects (e.g., steroidal and gonadotropin hormone levels, measures of female-mediated infertility, gynecological conditions)?<br>- pregnancy outcomes (e.g., birth weight, gestation age)?<br>- puberty (male and female) (e.g., timing of development, precocious puberty, gynecomastia)?<br>- neurodevelopment (infants and children) (e.g., standardized tests of reflexes, behavior, and intelligence)?<br>- thyroid effects (e.g., thyroid stimulating hormone and thyroid hormones, subclinical and clinical thyroid disease)?<br>- immune system effects (e.g., asthma, allergies, immunoglobulin E (IgE) levels, skin prick tests)?<br>- pulmonary function (e.g., standardized test of lung volume, diffusing capacity)?<br>- neurological effects (adults) (e.g., peripheral neuropathy, vision or hearing or other sensory tests)?<br>- liver effects (e.g., cholestasis, biomarkers of liver function)?<br>- kidney effects (e.g., end stage renal disease, biomarkers of kidney function)?<br>- diabetes and measures of insulin resistance?<br>- obesity (and other measures of adiposity)?<br>- cardiovascular disease (cause-specific incidence or mortality)?<br>- cardiovascular risk factors (e.g., triglyceride and lipid levels, blood pressure or hypertension)?<br>- cancer (cause-specific incidence or mortality)?<br>or<br>• Does the study include a measure of one or more secondary health effect endpoints (to be considered within context of mechanistic evidence) relating to…<br>- oxidative stress?<br>- inflammation?<br>- gene expression? |

[a]For DINP, metabolites would include MINP (monoisononyl phthalate), MCOP (mono-carboxyoctyl phthalate), MCIOP (mono-carboxyisooctyl phthalate), MOINP (mono-oxoisononyl phthalate), and MHINP (mono-hydroxyisononyl phthalate).

One hundred and forty-nine epidemiological studies examining one or more phthalate in relation to one or more endpoints were identified by the searches conducted through December 2013 (127 in the initial search and 22 in the December 2013 update). Fourteen studies analyzed one or more health effects in relation to a measure of DINP (Table 2-6; eight had been identified in the DINP-specific search described in Table 2-1 and Figure 2-1).

**Table 2-6. Primary source epidemiological studies examining health effects of DINP**

| Outcome category | Reference[a] | DINP measure |
|---|---|---|
| Sexual differentiation measures | Main et al. (2006) | MINP (urine) |
| Male reproductive | Joensen et al. (2012)<br>Jurewicz et al. (2013) | Sum 4 DINP metabolites (urine)<br>MINP (urine) |
| Female reproductive | Buck Louis et al. (2013)<br>Hart et al. (2013) | MINP (urine)<br>Sum 2 DINP metabolites (urine) |
| Pregnancy-related outcomes | Philippat et al. (2012)<br>Meeker et al. (2009) | Sum 4 DINP metabolites (urine)<br>MINP (urine)<br>MINP (urine)<br>MINP (urine) |
| Male pubertal development | Mieritz et al. (2012) | Sum 4 DINP metabolites (urine) |
| Female pubertal development | Frederiksen et al. (2012)<br>Hart et al. (2013) | Sum 4 DINP metabolites (urine)<br>Sum 2 DINP metabolites (urine) |
| Thyroid hormones, children | Boas et al. (2010)<br><br>Wu et al. (2013)[b] | Sum 2 DINP metabolites (+ 2 others in supplemental material) (urine)<br>Accidental contamination (with DEHP) |
| Immune | Hoppin et al. (2013)<br>Bertelsen et al. (2013)<br>Bornehag et al. (2004) | MCOP (urine)<br>MCOP (urine)<br>DINP (dust) |
| Obesity | Hart et al. (2013) | Sum 2 DINP metabolites (urine) |

[a]Suzuki et al. (2010) and Weinberger et al. (2014), measured a DINP metabolite (MINP), but levels were reported to be too low for analysis; these studies are not included in the listing of DINP-related studies.
[b]Wu et al. (2013) is not included in the evidence tables because the exposure was characterized by food-contamination with both DEHP and DINP, without separate measures of these exposures.

Additional strategies are also being used to supplement this broad search for epidemiology studies of phthalates (Table 2-7); the screening process for the publications identified through these methods is currently underway.

**Table 2-7. Summary of additional search strategies for epidemiology studies of phthalate exposure in relation to health-related endpoints**

| Approach used | Date performed | Number of additional citations identified |
|---|---|---|
| Testing and refinement of search terms based on terms used for the identified articles within each category | June 2014 | 7: review in process |
| Review of references cited in the identified list of epidemiology studies ("backward" search) | July 2014 | 3: review in process |
| Electronic forward search through Web of Science of one to three studies within each health endpoint category (early studies within each category generally selected to maximize potential for citation in subsequent publications)[a] | July 2014 | 5: review in process |

[a]The following studies were used to conduct the forward searches: (Trasande et al. (2013); James-Todd et al. (2012); Lind and Lind (2011); Boas et al. (2010); Cho et al. (2010); Engel et al. (2010); Lopez-Carrillo et al. (2010); Wolff et al. (2010); Adibi et al. (2009); Chou et al. (2009); Hatch et al. (2008); Wolff et al. (2008); Meeker et al. (2007); Stahlhut et al. (2007); Hauser et al. (2006); Reddy et al. (2006); Jonsson et al. (2005); Swan et al. (2005); Bornehag et al. (2004); Hoppin et al. (2004); Aschengrau et al. (1998); Heineman et al. (1992); Nielsen et al. (1989); Nielsen et al. (1985)).

The literature for both epidemiological and animal studies will be regularly monitored for the publication of new studies; regular updates of the searches are planned at 6-month intervals. The documentation and results for this supplementary search can be found on the Health and Environmental Research On-line (HERO) website[1] (http://hero.epa.gov/DINP) and (http://hero.epa.gov/phthalates-humanstudies).

## 2.2. SELECTION OF CRITICAL STUDIES IN EARLY STAGES OF DRAFT DEVELOPMENT

### 2.2.1. General Approach

Each study retained following the literature search and screen was evaluated for aspects of design, conduct, or reporting that could affect the interpretation of results and the overall contribution to the synthesis of evidence for determination of hazard potential. Much of the key

[1]HERO is a database of scientific studies and other references used to develop EPA's risk assessments aimed at understanding the health and environmental effects of pollutants and chemicals. It is developed and managed in EPA's Office of Research and Development (ORD) by the National Center for Environmental Assessment (NCEA). The database includes more than 1,400,000 scientific articles from the peer-reviewed literature. New studies are added continuously to HERO.

Note: The HERO database will be regularly updated as additional references are identified during assessment development. Therefore, the numbers of references (by tag) displayed on the HERO webpage for DINP may not match the numbers of references identified in Figure 2-1 (current through January 2014).

information for conducting this evaluation can generally be found in the study's methods section and in how the study results are reported. Importantly, this evaluation does not consider study results or, more specifically, the direction or magnitude of any reported effects. For example, standard issues for evaluation of experimental animal data identified by the NRC and adopted in this approach include consideration of the species and sex of animals studied, dosing information (dose spacing, dose duration, and route of exposure), endpoints considered, and the relevance of the endpoints to the human endpoints of concern. Similarly, observational epidemiologic studies in this approach for evaluation should consider the following:

- Approach used to identify the study population and the potential for selection bias.
- Study population characteristics and the generalizability of findings to other populations.
- Approach used for exposure assessment and the potential for information bias, whether differential (nonrandom) or nondifferential (random).
- Approach used for outcome identification and any potential bias.
- Appropriateness of analytic methods used.
- Potential for confounding to have influenced the findings.
- Precision of estimates of effect.
- Availability of an exposure metric that is used to model the severity of adverse response associated with a gradient of exposures.

To facilitate the evaluation outlined above, evidence tables are constructed that systematically summarize the important information from each study in a standardized tabular format as recommended by the NRC (2011). In general, the evidence tables include all studies that inform the overall synthesis of evidence for hazard potential. At this early stage of study evaluation, the goal is to be inclusive. Exclusion of studies may unnecessarily narrow subsequent analyses by eliminating information that might later prove useful. Premature exclusion might also give a false sense of the consistency of results across the database of studies by unknowingly reducing the diversity of study results. However, there may be situations in which the initial review of the available data will lead to a decision to focus on a particular set of health effects and to exclude others from further evaluation.

### 2.2.2. Exclusion of Studies

After the literature search was manually screened for pertinence, studies were excluded if fundamental flaws were identified in their design, conduct, or reporting. The DINP experimental animal database consists of studies designed to examine repeat-dose oral toxicity (including chronic, subchronic, and short-term duration studies) and endpoint-specific toxicities (including reproductive and developmental toxicity). All studies involved administration of DINP in the diet

or via gavage administration. Acute studies are generally less pertinent for characterizing health hazards associated with chronic exposure; there are 10 acute and short-term studies that are not summarized in the preliminary evidence tables. Nevertheless, these studies will still be evaluated as possible sources of supporting health effects information during assessment development. Experimental animal studies that were sources of subchronic or chronic health effects were evaluated for potential flaws in their design, reporting, or conduct. As a result, one study was removed from consideration in the assessment. Bio Dynamics (1982b) had a malfunction in delivery of water to the rats (Sprague-Dawley) that resulted in water deprivation. The authors did not provide information on the number of animals that may have been affected by this issue, and, therefore, there is uncertainty in the results.

The remaining studies are all sources of health effects data that may be used in the assessment. The studies summarized in the evidence tables are considered the "critical" studies from which the study methods and results are presented in preliminary evidence tables and exposure-response arrays (Section 3).

## 2.3. STUDY CHARACTERISTICS THAT WILL BE CONSIDERED IN THE FUTURE EVALUATION AND SYNTHESIS OF THE CRITICAL EPIDEMIOLOGICAL STUDIES FOR DINP

Several considerations will be used in EPA's evaluation of epidemiological studies of human health effects of DINP. The evaluation of these studies considered aspects of the study design affecting the internal or external validity of the results (e.g., population characteristics and representativeness, exposure and outcome measures, confounding, data analysis), focusing on specific types of bias (e.g., selection bias; information bias due to exposure misclassification), and other considerations that could otherwise influence or limit the interpretation of the data. A study is externally valid if the study results for the study population can be extrapolated to external target populations. An internally valid study is free from different types of biases, and is a prerequisite for generalizing study results beyond the study population. These issues are outline in the IRIS Preamble, and are described below.

### *Study Population*

Evaluation of study population characteristics (including key socio-demographic variables and study inclusion criteria) can be used to evaluate external validity (i.e., generalizability) and to facilitate comparison of results across different study populations. Some aspects of the selection process may also affect the interval validity of a study, resulting in a biased effect estimate.

The general considerations for evaluating issues relating to the study population include adequate documentation of participant recruitment, including eligibility criteria and participation rates, as well as missing data, and loss to follow-up. This information is used to evaluate internal study validity related to selection bias. Several different types of selection bias that may occur include the healthy worker effect, differential loss to follow up, Berkson's bias, and participation bias. It is important to note that low participation rates, or differences in participation rates

between exposed and non-exposed groups or between cases and controls, are not evidence of selection bias. Rather, selection bias arises from a differential pattern of participation with respect to both the exposure and the outcome, i.e., patterns of participation that would result in a biased effect estimate. This could occur, for example, if people with high exposure and the outcome of interest are more likely to participate than people with low exposure and the outcome.

The available DINP studies have generally examined metabolites from many different phthalates within the context of research on environmental exposures. Most of these studies rely on objective exposure measures (e.g., biomonitoring data), some of which are collected prior to onset of the outcomes being examined (e.g., in the prospective pregnancy cohort studies). Study participants also typically do not have knowledge of the study hypothesis or their exposure to DINP and thus, knowledge of exposure or exposure level is unlikely to result in differential participation with respect to outcomes. These study features should minimize the potential for selection bias. However, EPA will consider the possibility that a particular concern about the specific sources of DINP (e.g., polyvinyl chloride [PVC] applications including toys, flooring, wall coverings (ECHA, 2013)), in conjunction with knowledge of specific health outcomes, may motivate people to participate in a study or to continue participation throughout a follow-up period. In the absence of evidence that any of these scenarios is likely to occur in a study, EPA will not consider selection bias as a limitation of a study.

***Exposure Considerations***

General considerations for evaluating exposure include: (1) how exposure and dose can occur (e.g., exposure sources, routes and media); (2) appropriate critical exposure period(s) for the outcomes under study; (3) variability in the exposure metrics of interest (e.g., temporal and spatial variability for environmental measures or inter-individual variability for biomonitoring data) which can impact the choice of exposure metric (e.g., cumulative, average, or peak exposure); (4) analytical methodology employed (e.g., choice of biological matrix, sampling protocol, quantification approach, etc.); (5) choice of exposure surrogate evaluated (e.g., constituent chemical or group/mixture); and (6) classification of individuals into exposure categories. These considerations help determine how accurate and precise the exposure estimates are, and how likely measurement error is with respect to the exposure metrics that were used. Nondifferential misclassification of exposure categories, for example, can also result from measurement error and is expected to predominantly result in attenuated effect estimates.

Some common sources of exposure to DINP include PVC applications, children's toys, flooring, and wall covering materials (Zota et al., 2014), with the primary route of exposure occurring through ingestion and some exposure via inhalation and dermal routes (see Section 1.1.3). Exposure to DINP may be increasing, as it (along with DiDP) is increasingly being used as a substitute for DEHP (Zota et al., 2014; Koch and Angerer, 2007). Although temporal analyses based on National Health and Nutrition Examination Survey (NHANES) biomonitoring data from the U.S. general population are limited because repeated measures are not collected on the same individuals, a recent study of the U.S. general population found that urinary concentrations of the

DINP metabolite, MCOP, have increased since 2005 (geometric mean concentration of MCOP was 13.4 ng/mL in 2009–2010 compared to 5.1 ng/mL in 2005–2006) (Zota et al., 2014).

Urine provides an integrated measure of phthalate exposure from all sources. Measurement of DINP metabolites, rather than the parent compound, is preferred because the parent compound is metabolized very quickly. The most commonly reported DINP metabolites measured in epidemiology studies include the simple monoester metabolite MINP (monoisononyl phthalate), and the oxidative metabolites, MCOP (mono-carboxyoctyl phthalate) and MCIOP (mono-carboxyisooctyl phthalate); other less commonly measured metabolites may include MOINP (mono-oxoisononyl phthalate) and MHINP (mono-hydroxyisononyl phthalate) (Silva et al., 2006). Table 2-8 shows synonyms for the most commonly measured DINP metabolites.

**Table 2-8. DINP metabolites and their synonyms**

| Metabolite name | Synonyms |
|---|---|
| **Simple monoester metabolite** | |
| MINP (monoisononyl phthalate) | MiNP |
| MCOP (mono-carboxyoctyl phthalate) | MCiOP |
| MCiOP (mono-carboxyisooctyl phthalate) | CX-MiNP<br>7cx-MMeHP (Mono(4-methyl-7-carboxyheptyl) phthalate)<br>Mono(2,6-dimethyl-6-carboxyhexyl) phthalate |
| MOINP (mono-oxoisononyl phthalate) | OXO-MiNP<br>7oxo-MMeOP (Mono(4-methyl-7-oxo-octyl) phthalate) |
| MHINP (mono-hydroxyisononyl phthalate) | OH-MiNP<br>7OH-MMeOP (Mono(4-methyl-7-hydroxyoctyl) phthalate) |

These metabolites vary in terms of validity as surrogates of DINP exposure in epidemiology studies. Two controlled human dosing studies evaluated what fraction of the total DINP ingested produced MINP (the simple monoester metabolite) via excretion. One was conducted in a single volunteer (Koch and Angerer, 2007), and the other among 20 volunteers (Anderson et al., 2011); both found that MINP represented only a small fraction of the total DINP ingested (2–3%), while the secondary metabolites accounted for larger proportions (9–18%). MINP often falls below the limit of detection, making accurate measurement difficult. The correlations among secondary DINP metabolites are generally high, ranging from 0.73 to 0.83 for MCIOP, MHINP, and MOINP (Silva et al., 2006), while correlations between these secondary metabolites and MINP have not been reported. The oxidative metabolites have been recommended for use as biomarkers in epidemiology studies (Koch and Angerer, 2007; Silva et al., 2006). Based on these considerations, EPA considers measures of DINP based solely on MINP to be less informative (i.e., subject to greater measurement error) than measures that include at least one of the oxidative metabolites. Although a summation of two or more metabolites could offer some advantages over a single metabolite, EPA does not consider use of a single oxidative metabolite to be a major limitation.

Although urine measures are most commonly used in epidemiological studies of phthalate exposure, measures in serum, semen, and breast milk have also been used. One study reported that none of the three secondary DINP metabolites examined were above the limit of detection in breast milk samples from 30 women, and the detection rate in cord blood (n = 30) ranged from 3 to 13%; the correlation when comparing the summation of DINP metabolites in maternal urine and breast milk could not be calculated, and the correlation between maternal urine and cord blood was Pearson r = 0.35 (Lin et al., 2011). Another study conducted among 60 men ages 18–26 years found that while 43.3% of serum samples had MCIOP concentrations above the limit of detection, only 10% of serum samples had detectable MINP concentrations, and both metabolites were detected at low levels in semen samples (MINP: 12.1%, MCIOP: 1.7%) (Frederiksen et al., 2010). In this latter study, the Spearman correlation coefficient between MCIOP levels measured in urine and serum was r = 0.37) (Frederiksen et al., 2010). The lower detection rate in tissues other than urine reduces EPA's confidence in DINP metabolite measures in these biological matrices.

Given their first-order kinetics with half-lives on the order of hours [~3–5 hours for MINP, and ~5–18 hours for oxidized metabolites in (Koch and Angerer, 2007), ~4–8 hours for both MINP and oxidized metabolites in (Anderson et al., 2011)], urinary phthalate metabolite concentrations peak shortly after exposure. Thus, for single-time exposure scenarios (rather than multi-source, multiple time exposure scenarios), urine sampled during this time of peak concentration could lead to overestimates of average daily intake, and conversely, measurements made after concentrations have peaked and declined could lead to underestimates of intake. One study conducted among pregnant women in Puerto Rico included one of the DINP metabolites, however, and found that sampling time was not a significant predictor of urinary MCOP concentrations; that is, there was little difference in MCOP levels for women whose samples were collected in early morning, morning, early afternoon, or evening time periods (Cantonwine et al., 2014). Urinary measures of DINP metabolite concentrations in epidemiological studies are generally conducted using spot urine samples (i.e., collected at time of a clinic or study examination visit) rather than at a specified time (e.g., first morning void) or in 24-hour urine samples. Although the time of sample collection described above may affect the accuracy of an estimated intake for a single individual, studies of other phthalates (e.g., DEHP) have demonstrated that on a group level, spot urine samples provide a reasonable approximation of concentrations that would have been observed using full-day urine samples (Christensen et al., 2014) and that a single spot sample was reliable in ranking subjects according to tertile (Teitelbaum et al., 2008). Although neither of these studies included DINP metabolites, the general conclusions are expected to be similar. Based on this information, EPA does not consider the reliance on spot urine samples for exposure estimation (including ranking of individuals into different DINP categories) to be a major limitation for epidemiological studies. However because of the potential for greater inaccuracy of estimates in the "tails" of the distribution, EPA will include additional considerations (e.g., discussion of analysis of residuals, sample size, outliers) when evaluating analyses based on use of DINP metabolites as continuous measures.

Another potential limitation of measurement of DINP metabolites in urine is the reproducibility of phthalate metabolite concentrations over time; that is, how well does a single measure reflect the key exposure metric (average, peak) for the critical exposure window of interest. For many short-lived chemicals, considerable temporal variability in exposure level is expected, and thus, repeated measures in the critical exposure window are preferred over a single measurement. Reproducibility is usually evaluated with the intraclass correlation coefficient (ICC), a measure of the 'between-individual' variance divided by the total variance (between and within individuals). A higher ICC indicates greater reproducibility (i.e., lower within-person variance). Frederiksen et al. (2013) reported the ICC calculated for urine samples collected over a 3-month period among young Danish men, using a summed measure of DINP metabolites (comprising MINP, MHINP, MOINP, and MCIOP). This study reported ICCs of 0.26 for 24-hour urine samples and 0.25–0.29 for first-morning urine samples; the ICCs for spot samples were considerably lower (0.08–0.13). In a study of pregnant women in Puerto Rico, Cantonwine et al. (2014) reported an ICC of 0.29 for MCOP when comparing urine samples taken at 18, 22, and 26 weeks of gestation. No studies have evaluated temporal variability of DINP metabolites in children, limiting the ability to examine this source of uncertainty for certain endpoints such as timing of puberty. EPA considers the available data pertaining to reproducibility of DINP measures to be very limited; these results indicate a low level of reproducibility over periods of 1–3 months, and highlight the value of repeated exposure measures collected during the appropriate critical period for the outcome(s) under study.

EPA will also consider the potential for differential misclassification of biomarker measures of exposure, for example in situations in which a health outcome (e.g., diagnosis with diabetes or cancer) could result in changes in behavior that could affect DINP exposure. This type of scenario adds an additional challenge to the interpretation of the DINP metabolites as valid measures of exposure in a relevant time window(s) with respect to disease development.

Some researchers have hypothesized that the fraction of primary metabolites (i.e., percent of the total metabolites accounted for by the primary monoester, MINP) is better than concentration of a single (or summed) metabolite(s) as a measure of relevant exposure (Joensen et al., 2012). Because this idea is not currently established, EPA will focus on results reflecting measures of absolute metabolites concentrations rather than relative (percent of total) concentrations.

EPA also considers the distribution of exposure in evaluating individual studies and when comparing results among groups of studies. One consideration is the contrast of exposure levels (i.e., the difference between "high" and "low"): a study with a very narrow contrast may not have sufficient variability to detect an effect that would be seen over a broader range. Another consideration is the absolute level of exposure, as different effect estimates may be expected in studies examining different exposure levels even if they had similar exposure contrasts.

***Primary Outcome Measures***

The general considerations for evaluating issues relating to accuracy, reliability, and biological relevance of outcomes include adequate duration of exposure and follow-up in order to evaluate the outcomes of interest, and use of appropriate ascertainment methods to classify individuals with regard to the outcome (e.g., high sensitivity and specificity).

Issues relating to assessment of the specific primary health effects are discussed below and summarized in Table 2-9 at the end of Section 2.3.

Sexual differentiation

Cryptorchidism and hypospadias are two disorders of the development of the male reproductive system. Cryptorchidism, or undescended testes, can be present at birth (congenital cryptorchidism) or can occur later during infancy and childhood (acquired cryptorchidism). Surgical correction (orchiopexy) is recommended in cases of cryptorchidism that do not resolve during infancy because long-term complications include impaired sperm production and increased risk of testicular cancer (Virtanen et al., 2007). Retractile testes can move back and forth between the scrotum and the abdomen; this condition usually resolves by puberty and is not associated with reproductive or other complications. Classification criteria for cryptorchidism that involve testicular positioning are commonly used in clinical research (John Radcliffe Hospital Cryptorchidism Study Group, 1988; Scorer, 1964). EPA will consider the definition used and age range in interpreting studies of cryptorchidism or related outcomes.

In animal toxicology studies, anogenital distance (AGD) is a routine marker to assess endocrine disruption; this marker has only recently been adapted for use in epidemiological studies. One study in adult men reported associations between decreased AGD and measures relating to infertility (Eisenberg et al., 2011); most studies have used this measure in infants, however, as a marker of endocrine environment during development. It is important to consider general size, in addition to sex, in the evaluation of AGD, for example by incorporating birth weight or length (e.g., calculation of "anogenital index" by dividing anogenital distance by weight. With regard to reproducibility of this measure, a low degree of between-observer variability was found using a standardized protocol and trained observers (Romano-Riquera et al., 2007; Salazar-Martinez et al., 2004). Because of the importance of size and age in the interpretation of this measure, EPA has greater confidence in studies with measures taken at birth rather than among a group spanning a larger age range.

Reproductive (steroidal and gonadotropin) hormones

The details of the laboratory procedures, including information on the basic methods, level of detection, and coefficient of variation, are important considerations for hormone assays and measures of semen parameters. Timing within a menstrual cycle can also be an important consideration for interpretation of reproductive hormone concentrations in pre-menopausal women.

Much of the focus of the research on male steroidal and gonadotropin hormones in the DINP database concerns testosterone. One issue with respect to these measures is the estimation method used for free testosterone. Based on the analysis by Vermeulen et al. (1999), EPA will consider estimates based on total testosterone divided by immunoassay-derived sex-hormone binding globulin (SHBG) levels to be most reliable.

Other male reproductive outcomes

The World Health Organization (WHO) laboratory methods for analysis of sperm counts and semen parameters (see, for example, WHO, 1999) are generally recognized as standards in this field. EPA will consider studies that reference these methods, regardless of which revision used, to be reliable measures.

Other female reproductive outcomes

Endometriosis can be symptomless, or can lead to surgical intervention; it is often diagnosed as part of a work-up for infertility. Variability in clinical presentation and in access and use of health care services present considerable challenges to conducting epidemiological studies of this condition (Holt and Weiss, 2000). Confirmation of "case" and "control" status (i.e., presence or absence of endometriosis) by ultrasound or clinical evaluation is recommended to reduce outcome misclassification, and representation of the source population should be carefully considered.

Pregnancy outcomes

Gestational age and birth weight are two outcomes commonly used in reproductive epidemiology studies. These variables are sometimes defined as dichotomous outcomes (e.g., low birth weight, defined as <2,500 g or preterm birth, defined as <37 weeks of gestation). They can also be examined as continuous variables, often in analyses in which preterm or low birthweight births are excluded, so that the focus of the analysis is on variability within the "normal" range. EPA considers both types of analyses to be informative with respect to hazard identification, but will consider each separately as they address different issues. In the birth cohort studies included in the DINP database, data pertaining to birth weight are generally taken directly from medical records. EPA considers this to be a reliable source as this is a very accurate and precise measurement. Although more prone to measurement error than birth weight measures, gestational age can be estimated from several approaches. Some of these include ultrasonography, estimates based on date of last menstrual period based on maternal recall, or from clinical examination based on antenatal or newborn assessments (which may include an ultrasound). None of the currently available studies examined size for gestational age (e.g., small for gestational age) as an outcome; this outcome accounts for both fetal growth and gestational duration, and would thus be preferred over a measure of birthweight that includes preterm births.

Timing of male and female puberty, and conditions of unusual pubertal development

Pubertal development in humans is often assessed using timing of peak height velocity ("growth spurt") and secondary markers of sexual development. Secondary markers for females include breast development (thelarche) and pubic hair development (pubarche), and age at first period (menarche). Secondary markers for males include gonadal development (gonadarche) and pubic hair development, and age at first sperm emission (spermarche).

Evaluation of breast, pubic hair, and gonadal development is frequently performed using the Tanner stages (Marshall and Tanner, 1970, 1969), which places the individual in one of five stages, ranging from pre-pubertal (stage 1) to adult maturation (stage 5). However, the process of this staging is not straightforward, and is most reliable when performed by trained personnel (rather than by the individual or a parent, for example) (Slough et al., 2013; Schlossberger et al., 1992; Espeland et al., 1990). Age at menarche is considered to more reliable when assessed via self-report (Koprowski et al., 2001), although reliability may decrease with increasing time since menarche (Cooper et al., 2006). Additionally, hormone levels may sometimes be used to evaluate pubertal development. Individuals may vary widely in the timing of these developmental milestones.

Several clinical syndromes are known to disrupt the timing and order of markers of pubertal development. Considerations in the diagnosis of either precocious or delayed puberty include the diagnostic criteria used and the source of the information (e.g., whether collected from medical records or from self- or parental report). For females, precocious puberty is usually defined as the onset of puberty before the age of 8 years, while delayed puberty is usually defined as the lack of pubertal development by the age of 13 years (Marshall and Tanner, 1969); corresponding ages in male are before the age of 9 years for precocious puberty and lack of pubertal development by the age of 14 years for delayed puberty (Marshall and Tanner, 1970). Clinical evaluation would involve hormone assays to distinguish between gonadotropin dependent ("central"), gonadotropin independent ("peripheral"), or a combination of both (Traggiai and Stanhope, 2003) forms of these conditions.

Thyroid

Thyroid-related endpoints examined in epidemiological studies of DINP include thyroid hormones (triiodothyronine, T3, and thyroxine, T4) and thyroid stimulating hormone (TSH) (or thyrotropin) produced by the pituitary.

As with other hormone assays, the details of the laboratory procedures, including information on the basic methods, limit of detection, and coefficient of variation, are important considerations for the hormone assays. Thyroid hormones are generally measured in serum, although they may also be measured in dried blood spots, such as are collected from newborn infants in screening for congenital hypothyroidism as well as for genetic metabolic diseases such as phenylketonuria. Studies in older age groups have also shown a very high correlation ($r = 0.99$) between thyroid hormone levels measured in dried blood spots and levels in serum (Hofman et al., 2003).

With respect to thyroid hormones, time of day and season of sampling are two main potential sources of variability. For example, serum TSH measured shortly after midnight may be as much as twice as high as the value measured in late afternoon (Brabant et al., 1991; Weeke and Gundersen, 1978). The evidence with respect to seasonal variability is mixed (Plasqui et al., 2003; Nicolau et al., 1992; Simoni et al., 1990; Behall et al., 1984; Postmes et al., 1974) and this effect is likely to be smaller than that of time of day. The impact of these sources of variation will depend on whether they are also related to DINP (i.e., whether DINP levels vary diurnally or seasonally). If this is the case, failure to address these factors in the design or analysis could result in confounding of the observed association, with the direction of this bias determined by the direction of the association between these factors and DINP. If this is not the case, the lack of consideration of time of day or seasonality would result in greater variability in the hormone measures, and would thus result in more imprecise (but not biased) estimates was located. EPA has not found evidence of a seasonal variation in DINP levels, and only one study with information on diurnal variability (Cantonwine et al., 2014); in this study, MCOP levels did not vary by sampling time (e.g., early morning, morning, early afternoon, or evening time periods (Cantonwine et al., 2014). Based on these data, EPA does not consider the lack of consideration of time of day or season in the analysis of thyroid outcomes to be a likely source of bias, but recognizes the limited nature of the available data.

Immune

Skin prick testing is a standard method for assessing atopy (allergic disease) used in some epidemiologic studies. Other studies use an assessment protocol based on reported history of symptoms (e.g., rhinitis, hay fever) or specific types of allergies. These can be considered complementary types of measures: skin prick tests provide information on a defined set of potential antigens to which a person may be exposed, and symptom-based evaluations provide information on experiences of individuals and the variety of exposures they encounter. Studies comparing questionnaire responses with skin prick tests in children have reported relatively high specificity (89–96%) and positive predictive value (69–77%) for self-reported history of pollen or pet dander allergy or for answers to a combination of questions incorporating itchy eyes with nasal congestion in the absence of a cold or flu (Braun-Fahrländer et al., 1997; Dotterud et al., 1995). The validity was somewhat lower for a more restricted set of questions (nasal congestion in the absence of a cold or flu; specificity 83%, positive predictive value 52%) (Braun-Fahrländer et al., 1997). Based on these data, EPA considers allergy history based only on rhinitis symptoms to have a greater likelihood of outcome misclassification compared with those based on a combination of symptoms.

Epidemiologic studies of asthma typically use a questionnaire-based approach to define asthma based on symptoms relating to wheezing episodes or shortness of breath, reported history of asthma attacks, or use of asthma medication, usually for a period defined as "current" or in the past year. Much of this work is based upon the American Thoracic Society questionnaire (Ferris, 1978) or subsequent instruments that built upon this work, including the International Society of

Arthritis and Allergies in Children Questionnaire and the European Community Respiratory Health Survey. These questionnaire-based approaches have been found to have an adequate level of specificity and positive predictive value for use in etiologic research (Ravault and Kauffmann, 2001; Pekkanen and Pearce, 1999; Burney et al., 1989; Burney and Chinn, 1987). EPA considers outcomes defined over a recent time period (e.g., symptoms in the past 12 months) to be more relevant within the context of concurrent exposure measurements compared with outcomes defined over a lifetime (e.g., ever had asthma).

Obesity

The study of obesity measures in the DINP database is based on body mass index (BMI) using measurements taken as part of the data collection protocol. Although not relevant for the set of studies currently available, EPA notes that use of self-reported weight (e.g., report of pre-pregnancy weight) would not be considered to be as reliable as actual measurements.

***Confounding***

The general considerations for evaluating issues relating to potential confounding include consideration of which factors may be potential confounders (i.e., those which are strongly related to both the exposure and the outcome under consideration, and are not intermediaries on a causal pathway), adequate control for these potential confounders in the study design or analysis, and where appropriate, quantification of the potential impact of mismeasured or unmeasured confounders. Uncontrolled confounding by factors that are positively associated with both the exposure (e.g., DINP) and health endpoint of interest, and those that are inversely associated with both exposure and health endpoint, will result in an upward bias of the effect estimate. Confounding by factors that are positively associated with either exposure or the health endpoint, and inversely associated with the other axis, will result in a downward bias of the effect estimate.

Potential confounding by other phthalates

DINP has been used as a substitute for DEHP, and available data indicate a moderate correlation between metabolites of these two phthalates. In an analysis conducted by EPA of 5,109 samples from the 2005–2008 National Health and Nutrition Examination Survey (NHANES) participants aged ≥6 years, the pairwise Spearman correlation coefficient between MCOP (the only DINP metabolite measured in the NHANES) and DEHP metabolites (mono-2-ethyl-5-hydroxyhexyl phthalate [MEHHP], mono-2-ethyl-oxohexyl phthalate [MEOHP], or mono-2-ethyl-carboxypentyl phthalate [MECCP]) ranged from 0.40 to 0.60. The correlations between DINP metabolites and those of other phthalates are generally lower than seen with DEHP metabolites, with correlation coefficients between −0.1 and 0.2 reported for MEP, and correlation coefficients between 0.01 and 0.3 for monobutyl phthalate (MBP), monoisobutyl phthalate (MIBP), and mono-benzyl phthalate (MBzP) (Buck Louis et al., 2013; Hart et al., 2013; Jurewicz et al., 2013). Thus, EPA does not consider lack of adjustment for these other phthalate metabolites to be a limitation of a study; an

exception would be a situation in which an association with DEHP metabolites was considerably stronger than the association seen with DINP metabolites.

Potential confounding by demographic factors

Age, race/ethnicity, and sex are considered important explanatory factors for most types of outcomes measured in epidemiological research. In NHANES 2009–2010 data, urinary MCOP levels were similar among children ages 6–11 (geometric mean of 15.0 μg/L) and teenagers ages 12–19 (geometric mean of 16.1 μg/L), and both groups had higher levels compared to adults ≥20 years (geometric mean of 11.9 μg/L) (CDC, 2013). Variability by sex and by race or ethnicity was also observed, with higher levels in men compared with women (geometric means of 14.0 and 11.4 μg/L, respectively, in women and men) and lower levels in Mexican Americans (geometric mean of 10.0 μg/L) compared with non-Hispanic whites and non-Hispanic blacks (geometric means of 13.4 and 12.6 μg/L, respectively). EPA will consider these differences in assessing the potential influence of demographic factors on observed effect estimates for DINP.

Potential confounding by other factors

Some of the health effects under consideration may have strong associations with other risk factors. For example, smoking is associated with increased risk of low birth weight and preterm births, and with infertility. Abstinence time is strongly related to sperm concentration measures. In evaluating the potential for confounding by any of these factors, EPA will review evidence pertaining to the strength and direction of its association with DINP (or its metabolites).

***Data Analysis***

The general considerations for evaluating issues relating to data analysis include adequate documentation of statistical assumptions and analytic approach (including addressing skewness of exposure or outcome variable and shape of exposure-response), consideration of sample size and statistical power, and use of appropriate statistical methods for the study design.

One other issue specific to much of the DINP literature concerns the optimal approach to addressing urinary volume or dilution in the analysis of spot urine or first morning void samples. Options include use of creatinine- or specific-gravity-adjusted metabolite concentrations, or use of unadjusted concentrations. Although use of some kind of correction factor has been advocated for studies of obesity (Goodman et al., 2014), a simulation study reported that creatinine-adjusted exposure measures may produce biased effect estimates for outcomes that are strongly related to factors affecting creatinine levels, of which obesity is a prime example (Christensen et al., 2014). EPA recognizes the lack of consensus at this time, as well as the need for continued research into the potential bias introduced by different analytic approaches. Based on current understanding of this issue, EPA prefers results using unadjusted concentration for outcomes strongly related to creatinine levels; for other outcomes, EPA does not have a basis for preferring one type of analysis over another.

**Table 2-9. General and outcome-specific considerations for DINP study evaluation**

| | |
|---|---|
| **General considerations** | |
| **Study population** | • Study population and setting: geographic area, site, time period, age and sex distribution, other details as needed (may include race/ethnicity, socioeconomic status)<br>• Recruitment process; exclusion and inclusion criteria, knowledge of study hypothesis; knowledge of exposure and outcome<br>• Participation rates: total eligible; participation at each stage and for final analysis group and denominators used to make these calculations<br>• Length of follow-up, loss to follow-up<br>• Comparability: participant characteristic data by group, data on non-participants |
| **Exposure** | • Biological matrix or target tissue/organ (e.g., urine, serum, semen, breast milk)<br>• Level of detection (LOD) or level of quantitation (LOQ)<br>• Exposure distribution (e.g., central tendency, range), proportion < LOD |
| **Analysis** | • Consideration of data distribution including skewness of exposure and outcome measures<br>• Consideration of influence of "tails" in analysis based on continuous exposure measure<br>• Consideration of analytic approaches exploring different shapes of exposure-response<br>• Consideration of values below LOD or LOQ<br>• Consideration of creatinine or other approach to adjust for urine volume. Presentation of effect estimates, rather than statement regarding presence or absence of statistical significance |
| **Outcome-specific considerations** | |
| *Sexual differentiation*<br>**Measures** | • AGD: protocol, training procedures, standardization and inter-rater reliability<br>• Cryptorchidism: definition |
| **Consideration of confounding** | • AGD: variability by size (e.g., birth weight), sex, age; temporal trends in DINP exposure if study spans several years and includes a wide age range<br>• Cryptorchidism, preterm birth |
| **Relevant exposure time window(s)** | • In utero for outcomes assessed in infancy; for acquired cryptorchidism, other time window(s) during childhood may also be relevant |

| | |
|---|---|
| *Steroidal and gonadotropin hormones (adults; sex-specific)*<br>**Measures** | • Type of assay<br>• Sensitivity/detection limits, coefficient of variation; number of samples below LOD |
| **Consideration of confounding** | • Age, day or phase of menstrual cycle (if cycling) |
| **Relevant exposure time window(s)** | • Up to 6 mo preceding hormone sample collection |
| *Sperm parameters*<br>**Measures** | • Type of assay (e.g., WHO protocol) |
| **Consideration of confounding** | • Age, smoking, BMI, abstinence time (consider if these are related to exposure) |
| **Relevant exposure time window(s)** | • Up to 6 mo preceding semen sample collection; could also consider cycle-specific (or lagged cycle-specific) window |
| *Infertility*<br>**Measures** | • Definition, source of data |
| **Consideration of confounding** | • Age, smoking, alcohol use, heavy metal exposure, radiation time (consider if these are related to exposure) |
| **Relevant exposure time window(s)** | • Time preceding attempt to become pregnant |
| *Gestational age*<br>**Measures** | • Source of data (e.g., birth certificate) and estimation procedure (ultrasound; last menstrual period or clinical assessment) |
| **Consideration of confounding** | • Smoking, pregnancy complications, assisted reproduction technologies (consider if these are related to exposure) |
| **Relevant exposure time window(s)** | • In utero; particularly third trimester |
| *Birth weight*<br>**Measures** | • Source of data (e.g., medical records, birth certificate) |
| **Consideration of confounding** | • Gestational age, maternal age, ethnicity, infections, pregnancy complications (e.g., pre-eclampsia), nutritional intake, smoking, alcohol/drug use, weight gain during pregnancy; maternal height/BMI, heavy metal exposures (consider if these are related to exposure) |
| **Relevant exposure time window(s)** | • In utero; particularly third trimester |
| *Timing of puberty*<br>**Measures** | • Source of data (e.g., measures of sexual maturation [menarche; spermarche; breast, pubic hair, axillary hair, and genital development]; self-report, physician assessment, or other) |
| **Consideration of confounding** | • Age, sex, ethnicity, body size, nutritional status (consider if these are related to exposure) |
| **Relevant exposure time window(s)** | • In utero? Up to 12 mo preceding transition from one stage to another stage? |

| | |
|---|---|
| *Thyroid*<br>**Measures** | • Assay used and evidence from validation studies, if available<br>• Sensitivity/detection limits, coefficient of variation; number of samples below LOD<br>• Biological sample used (e.g., serum, dried whole blood spots)<br>• Time of day and season when samples for thyroid hormone (and TSH) collected |
| **Consideration of confounding** | • Age, sex, smoking, iodine, radiation exposure (consider if these are related to exposure) |
| **Relevant exposure time window(s)** | • Lifestage considerations (i.e., adults, children, etc) |
| *Immune*<br>**Measures** | • Number of allergens used in skin prick testing or allergen-specific IgE assay; sensitivity/specificity of specific questions used in history assessment |
| **Consideration of confounding** | • Age, family history (consider if these are related to exposure) |
| **Relevant exposure time window(s)** | • For current conditions (e.g., asthma in past 12 mo): up to 12 mo preceding outcome assessment |
| *Obesity*<br>**Measures** | • Source of data (e.g., measures of weight and height, if BMI used; self-report |
| **Consideration of confounding** | • Age, sex, ethnicity, caloric intake, physical activity (consider if these are related to exposure) |
| **Relevant exposure time window(s)** | • Not established (likely to be more than one) |

## 2.4. STUDY CHARACTERISTICS THAT WILL BE CONSIDERED IN THE FUTURE EVALUATION AND SYNTHESIS OF THE CRITICAL EXPERIMENTAL STUDIES FOR DINP

Beyond the initial methodological screening described above in Section 2.2.2, methodological aspects of a study's design, conduct, and reporting will be considered again in the overall evaluation and synthesis of the pertinent data that will be developed for each health effect. Some general questions that will be considered in evaluating experimental animal studies are presented in Table 2-10. These questions are, for the most part, broadly applicable to all experimental studies.

**Table 2-10. Questions and relevant experimental information for the evaluation of experimental animal studies**

| Methodological feature | Question(s) considered |
|---|---|
| Test animal | Based on the endpoint(s) in question, are concerns raised regarding the suitability of the species, strain, or sex of the test animals on study? |
| Experimental setup | Are the timing, frequency and duration of exposure, as well as animal age and experimental group allocation procedures/ group size for each endpoint evaluation, appropriate for the assessed endpoint(s)? |
| Exposure | Are the exposure conditions and controls informative and reliable for the endpoint(s) in question, and are they sufficiently specific to the compound of interest? |
| Endpoint evaluation procedures | Do the procedures used to evaluate the endpoint(s) in question conform to established protocols, or are they biologically sound? Are they sensitive for examination of the outcome(s) of interest? |
| Outcomes, data, and reporting | Were data reported for all pre-specified endpoint(s) and study groups, or were any data excluded from presentation/analyses? |

Note: "Outcome" refers to findings from an evaluation (e.g., steatosis), whereas "endpoint" refers to the evaluation itself (e.g., liver histopathology).

Evaluation of some specific methodological features identified in Table 2-10 such as exposure, is likely to be relatively independent of outcome. Other methodological features, in particular those related to experimental setup and endpoint evaluation procedures, are generally outcome specific (i.e., reproductive and developmental toxicity). In general, experimental animal studies will be compared against traditional assay formats (e.g., those used in guideline studies), with deviations from the protocol evaluated in light of how the deviations could alter interpretation of the outcome in question. A full evaluation of all critical studies will be performed as part of the critical review and synthesis of evidence for hazard identification for each of the health endpoints identified in the evidence tables presented in Section 3.

# 3. PRELIMINARY EVIDENCE TABLES AND EXPOSURE-RESPONSE ARRAYS

## 3.1. DATA EXTRACTION FOR EPIDEMIOLOGICAL AND ANIMAL STUDIES: PREPARATION OF PRELIMINARY EVIDENCE TABLES

The evidence tables present data from studies related to a specific outcome or endpoint of toxicity. At a minimum, the evidence tables include the relevant information for comparing key study characteristics such as study design, exposure metrics, and dose-response information. Evidence tables will also provide the specific formulation of diisononyl phthalate (DINP) in the reference design column if this information is available. Evidence tables will serve as an additional method for presenting and evaluating the suitability of the data to inform hazard identification for DINP during the analysis of hazard potential and utility of the data for dose-response evaluation. For each critical study selected, key information on the study design, including characteristics that inform study quality, and study results pertinent to evaluating the health effects from subchronic and chronic oral exposure to DINP are summarized in preliminary evidence tables.

Epidemiological studies are presented first where each study per table is listed in reverse chronological order. Animal studies are then presented where each study per health endpoint is presented in alphabetical order by study author, followed by species and strain. Most results are presented as the percent change from the control group; an asterisk (*) indicates a result that has been calculated and reported by study authors to be statistically significant compared to controls ($p < 0.05$). Unless otherwise noted in a footnote, doses presented in the animal evidence tables were those reported by the study authors.

The information in the preliminary evidence tables is also displayed graphically in preliminary exposure-response arrays. In these arrays, a significant effect (indicated by a filled circle) is based on statistical significance by the study authors. The complete list of references considered in preparation of these materials can be found on the HERO website at (http://hero.epa.gov/DINP) and (http://hero.epa.gov/phthalates-humanstudies).

# 3.2. EPIDEMIOLOGICAL STUDIES

## 3.2.1. Sexual Differentiation Measures

**Table 3-1. Evidence pertaining to DINP metabolite(s) and measures of sexual differentiation in humans**

| Reference and study design | Results |
|---|---|
| *Cryptorchidism or testicular position* | |
| Main et al. (2006) (Denmark and Finland)<br>**Population:** 62 cases, 68 controls from two pregnancy cohorts, born 1997–2001, age 3 mo<br>**Outcome:** Cryptorchidism, at birth and/or 3 mo<br>**Exposure:** Breast milk sample collected 1–3 mo of age<br>MINP in breast milk (µg/L), all samples:<br>Median (range)<br>Denmark 101 (27–469)<br>Finland 89 (28–230)<br>**Analysis:** Mann-Whitney U test for comparison of MINP concentrations in boys with and without cryptorchidism | Median MINP in breast milk (µg/L)<br>Controls: 91.75<br>Cases: 98.52<br>($p > 0.4$) |
| *Infant hormone levels* | |
| Main et al. (2006) (Denmark and Finland)<br>**Population:** 130 male infants from two pregnancy cohorts (cryptorchidism cases and controls combined for this analysis), born 1997–2001, age 3 mo<br>**Outcome:** Serum steroidal and gonadotropin hormone levels in infants, sample collected when breast milk sample delivered to hospital<br>**Exposure:** Breast milk sample collected 1–3 mo of age<br>MINP in breast milk (µg/L), all samples:<br>Median (range)<br>Denmark 101 (27–469)<br>Finland 89 (28–230)<br>**Analysis:** Cases and controls combined for analysis of association between metabolite concentration and hormone level using partial Spearman correlation coefficients adjusted for country of birth; hormone ratios evaluated using linear regression considering gestational age, weight for gestational age, parity, smoking, diabetes, and country of origin as potential covariates | Spearman correlation coefficient ($p$-value), MINP (µg/L) and serum hormone level (n = 96 boys)<br>Testosterone (nmol/L): 0.184 (0.078)<br>Free testosterone (nmol/L): 0.070 (0.51)<br>SHBG (nmol/L): 0.187 (0.076)<br>LH (IU/L): 0.243 (0.019)<br>FSH (IU/L): -0.043 (0.68)<br>Inhibin B: -0.004 (0.97)<br>Estimated percentage increase (95% CI) in LH level with 10-fold increase in MINP = 97% (23, 214%) based on regression analysis (adjusted covariates were not reported). Regression results for other hormones were not reported.<br>The magnitude of the association between LH and MINP was greater than that observed for the other metabolites evaluated (correlation coefficients ranged from 0.001 to 0.185, all $p$-values > 0.05). |

CI = confidence interval; FSH = follicle-stimulating hormone; LH = luteinizing hormone; MINP = monoisobutyl phthalate; SHBG = sex-hormone binding globulin

### 3.2.2. Pregnancy Related Outcomes

**Table 3-2. Evidence pertaining to DINP metabolite(s) and pregnancy outcomes in humans**

| Reference and study design[a] | Results |
|---|---|
| *Birth weight, birth length, head circumference, and gestational age* | |
| Philippat et al. (2012) (France)<br>**Population:** 72 cases with undescended testis or hypospadias, 215 matched controls from two birth cohorts (EDEN and PELAGIE), 2002–2006<br>**Outcome:** Standard clinical measurements at birth<br>**Exposure:** Maternal urine sample, collected between 6 and 19 (PELAGIE) or between 24 and 30 (EDEN) gestational wks<br>MCIOP in urine (µg/L):<br>Median; 95th percentile<br>Measured: 2.7; 17.2<br>Standardized*: 3.9; 25.8<br>**Analysis:** Cases and controls combined for analysis; weighted linear regression using tertiles or ln-transformed urine concentrations, adjusting for variables shown in the results column; analysis by tertiles for evaluation of possible non-monotonic relationship; analyses corrected for oversampling of malformation cases<br>*Standardized for sampling conditions and gestational age at collection | Regression coefficient (95% CI) for change in outcome by MCIOP tertile and per unit change in ln-MCIOP (standardized, ng/mL) (adjusted for gestational duration, maternal pre-pregnancy weight and height, maternal smoking, maternal education, parity, recruitment center, and urine creatinine; head circumference model also adjusted for mode of delivery)<br>MCIOP tertile (µg/L); Birth weight (g); Birth length (cm); Head circumference (cm)<br>1 (<2.4); 0 (referent); 0 (referent); 0 (referent)<br>2 (2.4–5.9); −40 (−192, 110); −0.2 (−0.9, 0.4); −0.1 (−0.7, 0.4)<br>3 (≥5.9); −27 (−200, 147); 0.4 (−0.5, 1.2); 0.0 (−0.6, 0.6)<br>(trend *p*-value); (0.87); (0.19); (0.79)<br>Ln (MCIOP); −8 (−72, 55); 0.1 (−0.2, 0.4); 0.0 (−0.2, 0.3) |
| *Preterm birth (<37 wks)*[a] | |
| Meeker et al. (2009) (Mexico)<br>**Population:** 30 cases, 30 controls (term births) from pregnancy cohort, 2001–2003<br>**Outcome:** Preterm birth (<37 wks of gestation), determined using maternal recall of last menstrual period<br>**Exposure:** Maternal urine sample, third trimester<br>MCIOP in urine, unadjusted (µg/L):<br>Median; 75th percentile<br>Term births: 0.80; 1.2<br>Preterm births: 1.2; 1.7<br>MCIOP in urine, SG-adjusted (µg/L):<br>Median; 75th percentile<br>Term births: 0.49; 1.3<br>Preterm births: 1.0; 1.5<br>MCIOP in urine, Cr-adjusted (µg/g Cr):<br>Median; 75th percentile<br>Term births: 0.68; 1.8<br>Preterm births: 0.90; 1.7<br>**Analysis:** Logistic regression, considering maternal age, | OR (95% CI) for preterm birth by MCIOP above compared with below the median (adjusted for marital status, maternal education, infant sex, and gestational age at time of urine sample)<br>Unadjusted (µg/L): 4.3 (1.2, 14.9)<br>SG-adjusted (µg/L): 1.3 (0.5, 3.9)<br>Cr-adjusted (µg/g Cr): 2.0 (0.7, 6.0)<br>The unadjusted association between MCIOP and preterm birth was similar or smaller in magnitude compared to that for DEHP metabolites (ORs from 2.8 to 7.1), MBP (OR of 10.7), MIBP (OR of 3.6), or MCPP (OR of 6.3). It was greater in magnitude compared to that for MBzP (OR of 2.5), MCNP (OR of 1.3) or MEP (OR of 2.3). |

| Reference and study design[a] | Results |
|---|---|
| prepregnancy BMI, parity, education, marital status, infant's sex, and gestational age at urine sample as potential covariates | |

DEHP = di(2-ethylhexyl)phthalate; MBP = monobutyl phthalate; MBzP = mono-benzyl phthalate; MCIOP = mono-carboxyisooctyl phthalate; MCNP = monocarboxyisononyl phthalate; MCPP = mono(3-carboxypropyl) phthalate; MEP = monoethyl phthalate; MIBP = methyl isobutyl phthalate; OR = odds ratio

### 3.2.3. Male Reproductive Effects in Humans

**Table 3-3. Evidence pertaining to DINP metabolite(s) and male reproductive effects in humans**

| Reference and study design | Results |
|---|---|
| *Reproductive hormones* | |
| Jurewicz et al. (2013) (Poland)<br>**Population:** 269 men from infertility clinic with normal sperm concentration (20–300 million/mL) or slight oligozoospermia (15–20 million/mL), mean age 32 yrs; MINP measured in 113 samples.<br>**Outcome:** Plasma testosterone, E2, FSH<br>**Exposure:** Urine sample collected at same time as plasma sample<br>MINP: unadjusted Cr-adjusted<br>geometric mean (SD) 1.4 (1.9) µg/L 1.2 (1.9) µg/g Cr<br>**Analysis:** Linear regression, adjusting for age, smoking, medical history (mumps, cryptorchidism, testes surgery, testes trauma), abstinence time, and urinary creatinine | Adjusted regression coefficient (β) for increase in hormone in relation to ln-transformed MINP (adjusted for age, smoking, medical history (mumps, cryptorchidism, testes surgery, testes trauma), abstinence time, and urinary creatinine)<br>Hormone — Beta — (*p*-value)<br>Testosterone (ng/mL) — 0.30 — (0.37)<br>$E_2$ (pg/mL) — 0.96 — (0.61)<br>FSH (IU/L) — 0.53 — (0.38) |
| Joensen et al. (2012) (Denmark)<br>**Population:** 881 men from general population, assessed at military conscript exam*, 2007–2009, median age 19.1 yrs ($5^{th}$–$95^{th}$ percentile: 18.4, 22.0 yrs)<br>**Outcome:** Serum steroidal and gonadotropin hormones<br>**Exposure:** Urine sample collected at same time as serum sample<br>Unadjusted DINP metabolites in urine (ng/mL):<br>Median — $95^{th}$ percentile<br>MINP 0.6 4.7<br>MHINP 4.5 23<br>MOINP 2.3 12<br>MCIOP 7.7 41<br>ΣDINP metabolites 21 107<br>%MINP 5% 15%<br>(%MINP calculated as percentage of total ΣDINP metabolites excreted as MINP)<br>**Analysis:** Linear regression considering age, BMI, smoking, alcohol consumption, time of blood sampling, assay type, ethnicity, BMI squared, *in utero* exposure to tobacco smoke, previous or current diseases, recent fever, and recent use of medication as potential covariates<br>*As reported by Ravnborg et al. (2011) | No association between ΣDINP metabolites and testosterone or other hormone measures (quantitative results not reported by study authors.<br><br>Additional analyses focused on %MINP as exposure measure, adjusting for age, BMI, smoking, alcohol consumption, and time of blood sampling (and assay type for inhibin-B only). Inverse associations were seen between %MINP and measures of testosterone. For example, comparing highest with lowest quartile %MINP, regression coefficient for differences in ln-transformed hormones:<br>Hormone — Beta (95% CI) — trend *p*-value<br>Total testosterone (nmol/L) — −0.05 (−0.12, 0.01) — 0.11<br>FAI — −0.15 (−0.23, −0.08) — <0.001 |

| Reference and study design | Results |
|---|---|
| *Sperm parameters* | |
| Jurewicz et al. (2013) (Poland)<br>**Population:** 269 men from infertility clinic with normal sperm concentration (20–300 million/mL) or slight oligozoospermia (15–20 million/mL), mean age 32 yrs; MINP measured in 113 samples<br>**Outcome:** Semen analysis<br>**Exposure:** Urine sample collected at same time as semen sample<br>MINP: unadjusted cr-adjusted<br>Geometric mean (SD) 1.4 (1.9) µg/L 1.2 (1.9) µg/g Cr<br>**Analysis:** Linear regression, adjusting for age, smoking, medical history (mumps, cryptorchidism, testes surgery, testes trauma), abstinence time, and urinary creatinine | Adjusted regression coefficient (β) for change in semen measure in relation to ln-transformed MINP (adjusted for age, smoking, medical history (mumps, cryptorchidism, testes surgery, testes trauma), abstinence time, and urinary creatinine)<br>Parameter / Beta / (*p*-value)<br>Concentration (million/mL) / -0.31 / (0.19)<br>Motility (%) / -9.05 / (0.033)<br>Abnormal morphology (%) / 6.21 / (0.060)<br>With additional adjustment for MEHP and 5OH-MEHP, Beta for motility = −4.00 (*p* = 0.39). |
| Joensen et al. (2012) (Denmark)<br>**Population:** 881 men from general population, assessed at military conscript exam*, 2007–2009, median age 19.1 yrs ($5^{th}$–$95^{th}$ percentile: 18.4, 22.0 yrs)<br>**Outcome:** Semen analysis<br>**Exposure:** Urine sample collected at same time as semen sample<br>Unadjusted DINP metabolites in urine (ng/mL):<br>Median / $95^{th}$ percentile<br>MINP 0.6 4.7<br>MHINP 4.5 23<br>MOINP 2.3 12<br>MCIOP 7.7 41<br>ΣDINP metabolites 21 107<br>%MINP 5% 15%<br>(%MINP calculated as percentage of total ΣDINP metabolites excreted as MINP)<br>**Analysis:** Linear regression, considering age, BMI, smoking, alcohol consumption, time of blood sampling, assay type, ethnicity, BMI squared, in utero exposure to tobacco smoke, previous or current diseases, recent fever, recent use of medication, abstinence time, and time from ejaculation to analysis as potential covariates | No association between ΣDINP metabolites and testosterone or other hormone measures (quantitative results not reported by study authors.<br><br>Additional analyses focused on %MINP as exposure measure and semen volume, sperm concentration, and sperm count (adjusted for abstinence time), motility (adjusted for time from ejaculation to analysis), and morphology (unadjusted). Associations were not observed with these variables (trend *p*-values ranged from 0.18 to 0.99), with negative Beta coefficients (indicating inverse associations) comparing highest with lowest quartile %MINP seen only with sperm concentration (Beta = −0.03, 95% CI −0.27, 0.31) and % normal morphology (Beta = −0.06, 95% CI −0.27, 0.15). |

BMI = body mass index; MEHP = mono-(2-ethylhexyl) phthalate; MHINP = mono-hydroxyisononyl phthalate; MOINP = oxo-(mono-oxoisononyl) phthalate; SD = standard deviation

### 3.2.4. Male Pubertal Development in Humans

**Table 3-4. Evidence pertaining to DINP metabolite(s) and the timing of male puberty in humans**

| Reference and study design | Results |
|---|---|
| Mieritz et al. (2012) (Denmark)<br>**Population:** 38 boys with pubertal gynecomastia and 190 age-matched controls drawn from 555 boys from population-based cohort (COPENHAGEN Puberty Study), 2006−2008; ages 6−19 yrs<br>**Outcome:** Anthropometry, pubertal stage (pubic hair and genital development), presence of gynecomastia, and serum testosterone<br>**Exposure:** Urine sample collected at clinical evaluation<br>DINP metabolites in urine (ng/mL), Group 3:<br>MINP: Median 0.65, 95th percentile 3.59<br>MHINP: Median 5.6, 95th percentile 22.92<br>MOINP: Median 3.29, 95th percentile 14.02<br>MCIOP: Median 7.66, 95th percentile 31.10<br>ΣDINP metabolites: Median 23.48, 95th percentile 90.93<br>(boys without gynecomastia, all ages)<br>**Analysis:** Two-tailed Mann-Whitney U-test for comparisons between groups; linear regression with age adjustment for association with serum testosterone; probit analysis with phthalate concentrations divided in quartiles for analysis of puberty timing | ΣDINP metabolites (ng/mL) by group<br>Group 1 = boys with palpable gynecomastia<br>Group 2 = boys without palpable gynecomastia (age-matched)<br>Group 3 = boys without palpable gynecomastia (all ages)<br>MINP — Median: Group 1 (n = 38) 23.55; Group 2 (n = 189) 20.14; Group 3 (n = 517) 23.48<br>MINP — 95th percentile: Group 1 112.6; Group 2 84.53; Group 3 90.93<br>No association between DINP metabolite concentration and timing of puberty or serum testosterone level (quantitative results not reported). |

### 3.2.5. Female Reproductive Effects in Humans

**Table 3-5. Evidence pertaining to DINP metabolite(s) and gynecological conditions or reproductive and steroidal hormones in humans**

| Reference and study design | Results |
|---|---|
| *Endometriosis* | |
| Buck Louis et al. (2013) (California and Utah, United States)<br>**Population:** 473 women undergoing laparoscopy or laparotomy and 127 population age- and residence-matched referents, 2007–2009; ages 18–44 yrs; confirmed cases of endometriosis matched to women without endometriosis within each cohort: operative cohort, 190 cases, 238 controls; population cohort: 14 cases, 127 controls<br>**Outcome:** Endometriosis confirmed by surgery (operative cohort) or MRI (population cohort)<br>**Exposure:** Urine sample, collected at time of surgery Cr-adjusted MINP in urine (ng/mL):<br>Geometric mean (95% CI)<br>Operative cohort-Controls 0.16 (0.14, 0.18)<br>Population cohort-Controls 0.16 (0.12, 0.21)<br>**Analysis:** Student's t-test or Wilcoxon test for continuous data; logistic regression, adjusting for variables shown in results column; sensitivity analyses conducted restricting cohort to endometriosis stages 3 and 4 diagnoses or visually and histologically confirmed endometriosis, and referent group consisting of women with postoperative diagnosis of normal pelvis | OR (95% CI) for endometriosis per unit increase in ln-MINP concentration, by cohort (adjusted for age, BMI, and creatinine)<br>Operative cohort 0.85 (0.68, 1.06)<br>Population cohort 0.90 (0.50, 1.63)<br>OR (95% CI) for endometriosis per unit increase in ln-MINP in operative cohort (sensitivity analysis)<br>Endometriosis stage 3 and 4 (n = 339) 0.99 (0.76–1.28)<br>Visual/histological confirmed endometriosis (n = 473) 0.93 (0.70, 1.25)<br>Comparison with women with postoperative diagnosis normal pelvis (n = 320) 0.84 (0.64, 1.11)<br>Note: Concentrations were log transformed and rescaled by their SDs for analysis. |

| Reference and study design | Results |
|---|---|
| *Polycystic ovary and hormones in adolescence* | |
| Hart et al. (2013) (Australia)<br>**Population:** 121 girls from pregnancy cohort study (Western Australian Pregnancy Cohort), born 1989–1991; follow-up at ages 14–16 yrs<br>**Outcome:** Uterine volume, ovarian volume, and antral follicle count by ultrasound, polycystic ovarian morphology defined as ≥1 ovary more than 10 $cm^3$ or ≥12 follicles between 2 and 9 mm in diameter; two definitions of polycystic ovarian syndrome (1: presence of at least two of: polycystic ovarian morphology, clinical or biochemical hyperandrogenism, or oligo-anovulation; 2) oligo-anovulatory menstrual cycles with either clinical or biochemical hyperandrogenism); reproductive and gonadotropin hormones; all measures on d 2–5 of menstrual cycle, blinded to phthalate measures<br>**Exposure:** Maternal serum samples (n = 123) collected at 18 and 34–36 wks of gestation (combined aliquot from both time periods)<br>Unadjusted DINP metabolite in serum (ng/mL):<br>Median / 90th percentile<br>MINP: <LOD* / <LOD*<br>MCIOP: 0.17 / 0.59<br>∑DINP metabolites (molar sum): 0.44 / 1.13<br>*LOD for MiNP = 0.20 ng/mL<br>Analysis: Correlation between log-transformed DINP metabolites and uterine volume, ovarian volume, and antral follicle counts; associations between DINP metabolites and PCOS were calculated using t-tests or Mann-Whitney U tests | Correlation between log-transformed ∑DINP metabolites and:<br>Uterine volume (mL): r = 0.17 ($p$ = 0.058)<br>Correlation between log-transformed MCIOP and:<br>Ovarian volume ($cm^3$): r < 0.10 ($p$ > 0.29)<br>Antral follicle count: r < 0.12 ($p$ > 0.19)<br>No association with polycystic ovarian syndrome using either definition (quantitative results not reported by authors).<br>No association with SHBG, FSH, total testosterone, free androgen index, anti-Müllerian hormone, or inhibin B (quantitative results not reported by study authors). |
| *Maternal hormones during pregnancy* | |
| Hart et al. (2013) (Australia)<br>**Population:** 123 mothers from pregnancy cohort (Western Australian Pregnancy Cohort), 1989–1991<br>**Outcome:** Serum androgens, samples collected at 18 and 34–36 wks of gestation<br>**Exposure:** Maternal serum samples collected at 18 and 34/36 wks of gestation (combined aliquot from both time periods)<br>Unadjusted DINP metabolite in serum (ng/mL):<br>Median / 90th percentile<br>MINP: <LOD* / <LOD*<br>MCIOP: 0.17 / 0.59<br>∑DINP metabolites (molar sum): 0.44 / 1.13<br>*LOD for MINP = 0.20 ng/mL<br>**Analysis:** Correlation between log-transformed ∑DINP metabolites and hormone levels | Correlation between log-transformed ∑DINP metabolites at 18 weeks gestation (n = 119) and<br>Androstenedione (nmol/L): r =–0.19 ($p$ < 0.035)*<br>DHEAS (µmol/L): r = –0.24 ($p$ < 0.008)*<br>Testosterone (pmol/L): r = –0.06 ($p$ > 0.10)<br>SHBG (nmol/L): r = 0.14 ($p$ > 0.10)<br>Free testosterone (pmol/L): r = –0.10 ($p$ > 0.10)<br>Free testosterone index: r = –0.12 ($p$ > 0.10)<br>*Text states negative correlation, but Table 4 displays positive correlation; email (May 30, 2014) from study authors confirmed negative correlation is correct. |

| | | | |
|---|---|---|---|
| | Correlation between log-transformed ∑DINP metabolites at 34−36 gestation wks (n = 114) and | | |
| | Androstenedione (nmol/L) | r = −0.09 | ($p$ > 0.10) |
| | DHEAS (µmol/L) | r = −0.12 | ($p$ > 0.10) |
| | Testosterone (pmol/L) | r = 0.02 | ($p$ > 0.10) |
| | SHBG (nmol/L) | r = 0.10 | ($p$ > 0.10) |
| | Free testosterone (pmol/L) | r = −0.04 | ($p$ > 0.10) |
| | Free testosterone index | r = −0.04 | ($p$ > 0.10) |

LOD = level of detection; PCOS = polycystic ovarian syndrome
DHEAS= Dehydroepiandrosterone

### 3.2.6. Female Pubertal Development in Humans

**Table 3-6. Evidence pertaining to DINP metabolite(s) and the timing of female puberty in humans**

| Reference and study design | Results |
|---|---|
| *Precocious puberty and premature thelarche* | |
| Frederiksen et al. (2012) (Denmark)<br>**Population:** 24 girls with precocious puberty (n = 13 with central precocious puberty, n = 6 with early normal puberty, n = 5 with premature thelarche) from outpatient clinic, 2008–2009 and 184* age-matched controls from population-based cohort (COPENHAGEN Puberty Study), recruited from high schools 2006–2008<br>**Outcome:** Precocious puberty, early normal puberty, or premature thelarche, defined based on clinical standards<br>**Exposure:** Urine sample (child's), collected at clinical evaluation<br>ΣDINP metabolites (MINP, MHINP, MOINP, and MCIOP) in urine (ng/mL), controls:<br>Median (range)<br>Unadjusted 30 (1.0–214)<br>**Analysis:** Urine concentrations in cases and controls compared with Mann-Whitney U test<br>*Study reports number of controls inconsistently; text reports 164 controls, while Table 4 reports 184 | Median (range) ΣDINP metabolites in urine (ng/mL) in cases and controls:<br>Controls: 30 (1.0–214)<br>Precocious puberty: 34 (7.9–575)<br>(*p*-value): (>0.05) |
| *Pubertal development (general population)* | |
| Hart et al. (2013) (Australia)<br>**Population:** 121 girls from pregnancy cohort study (Western Australian Pregnancy Cohort), born 1989–1991; follow-up at ages 14–16 years<br>**Outcome:** Age at menarche (questionnaire) (blinded to phthalate measures)<br>**Exposure:** Maternal serum samples (n = 123) collected at 18 and 34–36 wks of gestation (combined aliquot from both time periods)<br>Unadjusted DINP metabolite in serum (ng/mL):<br>Median; 90th percentile<br>MINP: <LOD*; <LOD*<br>MCIOP: 0.17; 0.59<br>∑DINP metabolites (molar sum): 0.44; 1.13<br>*LOD for MiNP = 0.20 ng/mL<br>**Analysis:** Correlation between log-transformed ∑DINP metabolites and age at menarche | No association between DINP metabolites and age at menarche (quantitative results not reported by study authors). |

<table>
<tr><th>Reference and study design</th><th>Results</th></tr>
<tr><td>Frederiksen et al. (2012) (Denmark)<br>**Population:** 725 healthy girls ages 5.6–19.1 yrs from COPENHAGEN Puberty Study cohort, recruited from high schools during 2006–2008<br>**Outcome:** Stage of breast or pubic hair development; Serum steroid and gonadotropin hormones<br>**Exposure:** Urine sample (child's), collected at time of pubertal stage assessment<br>Unadjusted DINP metabolite in urine (ng/mL), all 725 participants:<br><table><tr><th></th><th>Median</th><th>95th percentile</th></tr><tr><td>MINP</td><td>0.7</td><td>4.8</td></tr><tr><td>MHINP</td><td>6.1</td><td>26</td></tr><tr><td>MOINP</td><td>3.6</td><td>17</td></tr><tr><td>MCIOP</td><td>8.7</td><td>35</td></tr><tr><td>ΣDINP metabolites</td><td>not reported</td><td></td></tr></table>**Analysis:** Probit analysis, results verified using Pool-Adjacent-Violators algorithm</td><td>Mean age (95% CI) (yrs) at entry into breast stage 2 or pubic hair stage 2, by quartile of ∑DINP metabolites:<br><table><tr><th>∑DINP metabolite quartile</th><th>Breast stage 2 (n = 394)</th><th>Pubic hair stage 2 (n not reported)</th></tr><tr><td>1 (low)</td><td>9.78 (9.29, 10.26)</td><td>10.84 (10.54, 11.14)</td></tr><tr><td>2</td><td>9.94 (9.47, 10.41)</td><td>11.05 (10.76, 11.35)</td></tr><tr><td>3</td><td>10.15 (9.69, 10.63)</td><td>11.46* (11.15, 11.78)</td></tr><tr><td>4 (high)</td><td>9.87 (9.42, 10.33)</td><td>11.15 (10.86, 11.47)</td></tr></table>*Significantly different from quartile 1, $p < 0.05$<br><br>Levels of FSH, LH, estradiol, and testosterone were similar across DINP metabolite exposure groups when adjusted for age distribution (quantitative results not reported).</td></tr>
</table>

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### 3.2.7. Thyroid Effects in Humans

**Table 3-7. Evidence pertaining to DINP metabolite(s) and thyroid effects in humans**

| Reference and study design[a] | Results |
|---|---|
| Boas et al. (2010) (Denmark)<br>**Population:** 758 children who were participants in longitudinal cohort study, examined 2006–2007 at ages 4–9 yrs<br>**Outcome:** Serum thyroid hormone levels (nonfasting sample)<br>**Exposure:** Urine sample (child's) collected same day as serum sample<br>Cr-unadjusted DINP metabolites in urine (µg/L):<br>MINP Boys Median 0.6, 75th percentile 1.8<br>Girls 0.5, 1.7<br>MCIOP Boys 7.2, 12<br>Girls 6.5, 12<br>Cr-adjusted DINP metabolites in urine (µg/g Cr):<br>MINP Boys Median 1.0, 75th percentile 2.7<br>Girls 1.1, 3.3<br>MCIOP Boys 10, 18<br>Girls 12, 18<br>MHINP and MOINP also analyzed in 250 randomly selected samples.<br>**Analysis:** Linear regression, adjusting for variables shown in results column. Statistical analysis was not performed on metabolites detected in <50% of samples (included MINP) | Regression coefficient (p-value) for change in hormone level with unit change in ln-MCIOP (adjusted for sex and age) (0.0 = no effect)<br>T3 (nmol/L): Cr-unadjusted −0.07 (0.017); Cr-adjusted −0.01 (0.84)<br>Free T3 (pmol/L): Cr-unadjusted −0.18 (0.002); Cr-adjusted −0.04 (0.58)<br>T4 (nmol/L): Cr-unadjusted −0.31 (0.84); Cr-adjusted 1.14 (0.57)<br>Free T4 (pmol/L): Cr-unadjusted 0.03 (0.86); Cr-adjusted −0.01 (0.97)<br>TSH (mU/L): Cr-unadjusted −0.02 (0.25); Cr-adjusted 0.00 (0.96)<br>Similar patterns seen in analyses stratified by gender, except that Cr-adjusted MCIOP was significantly negatively associated with TSH in girls (β = −0.08, $p$ = 0.048). Inverse association with Free T3 also seen in analyses of Cr-unadjusted and MOINP (Beta = −0.17, $p$ = 0.05).<br>The association between MCIOP and T3 and the Cr-unadjusted association between MCIOP (and MOINP) and free T3 were similar in magnitude to the associations seen with the summed DEHP metabolites. |

[a] Wu et al. (2013) also contains data on thyroid effects, but the analysis focuses on DEHP (although contamination with DINP also occurred).

T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone

## 3.2.8. Immune Effects in Humans

**Table 3-8. Evidence pertaining to DINP metabolite(s) and immune effects in humans**

| Reference and study design[a] | Results |
|---|---|
| Boas et al. (2010) (Denmark)<br>**Population:** 758 children from birth cohort study, born 1997–2001; examined 2006–2007, ages 4–9 yrs<br>**Outcome:** Serum thyroid hormone levels (nonfasting sample)<br>**Exposure:** Urine sample (child's) collected same day as serum sample<br>Unadjusted DINP metabolites in urine (µg/L):<br>MINP Boys Median 0.6, 75th percentile 1.8<br>Girls 0.5, 1.7<br>MCIOP Boys 7.2, 12<br>Girls 6.5, 12<br>Cr-adjusted DINP metabolites in urine (µg/g Cr):<br>MINP Boys Median 1.0, 75th percentile 2.7<br>Girls 1.1, 3.3<br>MCIOP Boys 10, 18<br>Girls 12, 18<br>MHINP and MOINP also analyzed in 250 randomly selected samples.<br>**Analysis:** Linear regression, adjusting for variables shown in results column. Statistical analysis was not performed on metabolites detected in <50% of samples (included MINP) | Regression coefficient (*p*-value) for change in hormone level with unit change in ln-MCIOP (adjusted for sex and age) (0.0 = no difference in hormone level per unit change in ln-MCIOP exposure)<br>Unadjusted DINP / Cr-adjusted DINP<br>T3 (nmol/L): −0.07 (0.017) / −0.01 (0.84)<br>Free T3 (pmol/L): −0.18 (0.002) / −0.04 (0.58)<br>T4 (nmol/L): −0.31 (0.84) / 1.14 (0.57)<br>Free T4 (pmol/L): 0.03 (0.86) / −0.01 (0.97)<br>TSH (mU/L): −0.02 (0.25) / 0.00 (0.96)<br>Similar patterns seen in analyses stratified by gender, except that a statistical significant inverse association was detected between Cr-adjusted MCIOP with TSH among girls (β = 0.08, *p* = 0.048). Inverse association with Free T3 also seen in analyses of Cr-unadjusted and MOINP (β = −0.17, *p* = 0.05) for boys and girls.<br>The association between MCIOP and T3 and the Cr-unadjusted association between MCIOP (and MOINP) and free T3 were similar in magnitude to the associations seen with the summed DEHP metabolites. |

[a] Wu et al. (2013) also contains data on thyroid effects, but the analysis focuses on DEHP (although contamination with DINP also occurred).

## 3.2.9. Immune Effects in Humans

**Table 3-9. Evidence pertaining to DINP metabolite(s) and immune effects in humans**

| Reference and study design | Results |
|---|---|
| Hoppin et al. (2013) (United States, NHANES)<br>**Population:** 2,325 participants in population-based survey (NHANES), 2005–2006; ages ≥6 yrs<br>**Outcome:** Self-reported (self-administered questionnaire) current allergy symptoms (asthma, wheeze, hay fever, allergy, itchy rash, rhinitis) in past year; allergic sensitization as measured by serum IgE (19 allergen specific IgEs)<br>**Exposure:** Urine sample collected same day as serum sample (data reported in Ferguson et al., 2011)<br>MCOP in urine (µg/L):<br>Median; 75th percentile; 95th percentile<br>Cr-adjusted: 4.98; 10.86; 52.74<br>**Analysis:** Logistic regression, adjusting for age, race/ethnicity, gender, BMI, creatinine, and cotinine; separate analyses for children (ages 6–17 yrs) and adults (>17 yrs) | Prevalence (weighted by sampling weights) and OR per 1 unit change (log 10) in urinary MCOP level<br>Children (n = 779)<br>Asthma: 8.4%; 0.74 (0.36, 1.52)<br>Wheeze: 10.7%; 1.16 (0.65, 2.07)<br>Hay fever: 3.6%; 0.54 (0.11, 2.56)<br>Rhinitis: 27.6%; 1.40 (0.83, 2.37)<br>IgE sensitization (any): 46.1%; 0.69 (0.40, 1.18)<br>Adults (n = 1,546)<br>Asthma: 7.4%; 0.96 (0.73, 1.25)<br>Wheeze: 16.6%; 0.83 (0.58, 1.18)<br>Hay fever: 7.4%; 0.64 (0.37, 1.11)<br>Rhinitis: 35.4%; 0.97 (0.76, 1.25)<br>IgE sensitization (any): 44.0%; 1.21 (0.95, 1.54) |
| Bertelsen et al. (2013) (Norway)<br>**Population:** 623 children from birth cohort (Environment and Childhood Asthma study), 1992–1993; children with current asthma over-sampled (follow-up 2001–2004); ages 10 yrs<br>**Outcome:** Current asthma (parental report of history of asthma plus ≥1 of the following: dyspnea, chest tightness and/or wheezing in previous 12 mo; use of asthma medications in previous 12 mo; positive exercise challenge test)<br>**Exposure:** First morning urine sample, collected at study examination<br>MCOP in urine (µg/L):<br>Median; 75th percentile; 95th percentile<br>Unadjusted: 6.0; 10.2; 21.2<br>SG-adjusted: 6.2; 10.2; 21.9<br>**Analysis:** Logistic regression, potential confounders considered included: sex, BMI, allergic sensitization in the child, parental smoking at home [between the school age of the child (6–7 yrs) and the 10-yr follow-up], parental asthma (at child's birth), maternal education (at child's birth), and household income (at the 10-yr follow-up) | OR (95% CI) for current asthma by quartile of MCOP (µg/L) (adjusted for urine specific gravity, sex, parental asthma, and household income)<br>1: ≤3.5 (referent): 1 (referent)<br>2: >3.5–6.0: 1.0 (0.60, 1.9)<br>3: >6.0–10.2: 1.2 (0.67, 2.3)<br>4: >10.2: 1.9 (1.0, 3.3)<br>Increase in odds of current asthma per $\log_{10}$ interquartile range MCOP (95% CI) = 1.3 (0.98, 1.7) |

| Reference and study design | Results |
|---|---|
| Bornehag et al. (2004) (Sweden)<br>**Population:** 198 cases, 202 controls from population-based cohort (Dampness in Buildings and Health cohort) (n = 10,852), 2001–2002; ages 2–7 yrs<br>**Outcome:** Eczema, wheezing, or rhinitis (cases report at least two incidents of eczema, or wheezing or rhinitis without a cold, in the preceding year, and at follow-up 1.5 yrs later)<br>**Exposure:** Surface dust sample from children's bedrooms<br>DINP in dust (mg/g):<br>Median<br>All homes 0.041<br>**Analysis:** Mann-Whitney U-test for comparing concentrations in all homes; t-test for comparing log-transformed concentrations in homes with concentrations above detection limit | Concentration in dust (mg/g dust)<br>Median, all homes (n = 346) / Geometric mean (95% CI), homes with phthalate > detection limit (n = 175)<br>Controls: 0.047 / 0.446 (0.351, 0.566)<br>Cases (all): 0.000 / 0.453 (0.352, 0.583)<br>$p > 0.8$ in both tests |

IgE = immunoglobulin E; NHANES = National Health and Nutrition Examination Survey

### 3.2.10. Obesity Effects in Humans

**Table 3-10. Evidence pertaining to DINP metabolite(s) and obesity in humans**

| Reference and study design | Results |
|---|---|
| Hart et al. (2013) (Australia)<br>**Population:** 121 girls from pregnancy cohort study (Western Australian Pregnancy Cohort), born 1989–1991; follow-up at ages 14–16 yrs<br>**Outcome:** BMI (height and weight measured at clinic visit)<br>**Exposure:** Maternal serum samples (n = 123) collected at 18 and 3,436 wks of gestation (combined aliquot from both time periods)<br>Unadjusted DINP metabolite in serum (ng/mL):<br>Median 90th percentile<br>MINP <LOD* <LOD*<br>MCIOP 0.17 0.59<br>∑DINP metabolites (molar sum) 0.44 1.13<br>*LOD for MiNP = 0.20 ng/mL<br>**Analysis:** Correlation between metabolite measures and BMI | No association with adolescent BMI (either as absolute value or as age- and gender-adjusted z-score) for any of the phthalate metabolite measures (r = −0.10–0.04, *p* = 0.345–0.931); specific quantitative results for DINP not reported by study authors. |

# 3.3. ANIMAL STUDIES

## 3.3.1. Liver Effects

**Table 3-11. Evidence pertaining to liver effects in animals following oral exposure to DINP**

| Reference and study design[a] | Results | | | | | |
|---|---|---|---|---|---|---|
| *Liver weight change* | | | | | | |
| Bio Dynamics (1986)<br>Rat (Sprague-Dawley); 70/sex/dose<br>0, 500, 5,000, 10,000 ppm (0, 27, 271, 553 mg/kg-day in males; 0, 33, 331, 672 mg/kg-day in females)<br>Diet (Santicizer 900)<br>2 years (interim sacrifice at 1 year) | **Liver weight at terminal sacrifice** (n = 26–47/sex/dose) *(percent change compared to control)* | | | | | |
| | Doses (M) | 0 | 27 | 271 | 553 | |
| | *absolute weight* | 0% | 0% | 5% | 27*% | |
| | *liver/body weight* | 0% | 0% | 1% | 27*% | |
| | Doses (F) | 0 | 33 | 331 | 672 | |
| | *absolute weight* | 0% | −2% | 15% | 14*% | |
| | *liver/body weight* | 0% | −3% | 16*% | 26*% | |
| Lington et al. (1997)<br>Rat (F344); 110/sex/dose<br>0, 0.03, 0.3, 0.6% (0, 15, 152, 307 mg/kg-day in males; 0, 18, 184, 375 mg/kg-day in females)<br>Diet (DINP-1)<br>2 years (interim sacrifices at 6, 12, and 18 months) | **Liver weight at terminal sacrifice** (n = 48–65/sex/dose) *(percent change compared to control)* | | | | | |
| | Doses (M) | 0 | 15 | 152 | 307 | |
| | *absolute weight* | Data not reported | | | | |
| | *liver/body weight* | 0% | 6% | 19* | 31*% | |
| | Doses (F) | 0 | 18 | 184 | 375 | |
| | *absolute weight* | Data not reported | | | | |
| | *liver/body weight* | 0% | 3% | 16*% | 29*% | |
| Covance Laboratories (1998b)<br>Rat (F344); 70 or 85/sex/dose<br>0, 500, 1,500, 6,000, 12,000 ppm (0, 29, 88, 359, 733 mg/kg-day in males; 0, 36, 109, 442, 885 mg/kg-day in females)<br>Recovery group (55/sex/dose): 12,000 ppm (637 mg/kg-day in males, 774 mg/kg-day in females)<br>Diet<br>Main study: 2 years (interim sacrifices at 1, 2, 13, and 79 weeks)<br>Recovery group: 78 weeks, followed by a 26-week recovery period with basal diet alone | **Liver weight at terminal sacrifice** (n = 32–45/sex/dose) *(percent change compared to control)* | | | | | |
| | Doses (M) | 0 | 29 | 88 | 359 | 733 | Recovery |
| | *absolute weight* | 0% | −5% | −4% | 28*% | 47*% | 5% |
| | *liver/body weight* | 0% | −4% | 1% | 35*% | 61*% | 10% |
| | Doses (F) | 0 | 36 | 109 | 442 | 885 | Recovery |
| | *absolute weight* | 0% | 4% | 3% | 23*% | 57*% | 3% |
| | *liver/body weight* | 0% | 7% | 3% | 26*% | 71*% | 8% |

| Reference and study design[a] | Results | | | | | | |
|---|---|---|---|---|---|---|---|
| **Covance Laboratories (1998a)**<br>Mouse ($B6C3F_1$); 70/sex/dose<br>0, 500, 1,500, 4,000, 8,000 ppm (0, 90, 276, 742, 1,560 mg/kg-day in males; 0, 112, 336, 910, 1,888 mg/kg-day in females)<br>Recovery group (55/sex/dose): 8,000 ppm (1,377 mg/kg-day in males; 1,581 mg/kg-day in females)<br>Diet<br>Main study: 2 years (interim sacrifice at 79 weeks)<br>Recovery group: 78 weeks, followed by a 26-week recovery period with basal diet alone | **Liver weight at terminal sacrifice** (n = 32–46/sex/dose) *(percent change compared to control)* | | | | | | |
| | Doses (M) | 0 | 90 | 276 | 742 | 1,560 | Recovery |
| | *absolute weight* | 0% | 1% | 1% | 13*% | 33*% | 16% |
| | *liver/body weight* | 0% | 4% | 4% | 25*% | 60*% | 32*% |
| | Doses (F) | 0 | 112 | 336 | 910 | 1,888 | Recovery |
| | *absolute weight* | 0% | 8% | 23% | 18% | 35% | 34% |
| | *liver/body weight* | 0% | 8% | 30% | 24% | 48% | 39% |
| **Hazleton Laboratories (1991)**<br>Rat (F344); 10/sex/dose<br>0, 2,500, 5,000, 10,000, 20,000 ppm (0, 175.8, 354.6, 719.6, 1,544.7 mg/kg-day in males; 0, 218.9, 438, 823.8, 1,687.1 mg/kg-day in females)<br>Diet (DINP-2/3)<br>13 weeks | **Liver weight** *(percent change compared to control)* | | | | | | |
| | Doses (M) | 0 | 176 | 355 | 720 | 1,545 | |
| | *absolute weight* | 0% | 7% | 29*% | 47*% | 86*% | |
| | *liver/body weight* | 0% | 11*% | 27*% | 54*% | 110*% | |
| | Doses (F) | 0 | 219 | 438 | 824 | 1,687 | |
| | *absolute weight* | 0% | 12% | 20*% | 35*% | 77*% | |
| | *liver/body weight* | 0% | 7% | 18*% | 37*% | 103*% | |
| **Bio Dynamics (1982a)**<br>Rat (F344); 15/sex/dose<br>0, 0.1, 0.3, 0.6, 1.0, 2.0% (0, 67, 210, 410, 730, 1,500 mg/kg-day in males; 0, 77, 230, 480, 830, 1,600 mg/kg-day in females)[b]<br>Diet<br>13 weeks | **Liver weight***(percent change compared to control)* | | | | | | |
| | Doses (M) | 0 | 67 | 210 | 410 | 730 | 1,500 |
| | *absolute weight* | 0% | −1% | 8% | 23*% | 33*% | 58*% |
| | *liver/body weight* | 0% | 38% | 50*% | 73*% | 92*% | 158*% |
| | Doses (F) | 0 | 77 | 230 | 480 | 830 | 1,600 |
| | *absolute weight* | 0% | 2% | 5% | 21*% | 39* | 77*% |
| | *liver/body weight* | 0% | 3% | 9% | 24*% | 48*% | 103*% |

| Reference and study design[a] | Results | | | | |
|---|---|---|---|---|---|
| Hall et al. (1999) | **Liver weight** *(percent change compared to control)* | | | | |
| Marmoset; 4/sex/dose | Doses (M) | 0 | 100 | 500 | 2,500 |
| 0, 100, 500, 2,500 mg/kg-day | *absolute weight* | 0% | 58% | 25% | 19% |
| Gavage in 1% methylcellulose and 0.5% Tween | *liver/body weight* | 0% | 47% | 17% | 20% |
| | Doses (F) | 0 | 100 | 500 | 2,500 |
| 13 weeks | *absolute weight* | 0% | 18% | 30% | 3% |
| | *liver/body weight* | 0% | 8% | 18% | −1% |
| Boberg et al. (2011) | **Liver weight in males, PND 90** | | | | |
| Rat (Wistar); 1–7 litters/dose; 18–35 males/dose | Doses | 0 | 300 | 600 | 750 | 900 |
| 0, 300, 600, 750, 900 mg/kg-day | *absolute weight* | 0% | 4% | 8% | −2% | −5% |
| Gavage in corn oil (DINP-2) | Note: Study authors did not examine this endpoint in females. Relative weights not reported by study authors. | | | | | |
| GDs 7–21 | | | | | | |
| Clewell et al. (2013b) | **Liver weight in males, PNDs 49–50** | | | | |
| Rat (Sprague-Dawley); 20 dams (litters)/dose; 25 control dams (litters) | Doses | 0 | 109 | 555 | 1,513 |
| | *absolute weight* | 0% | 4% | −1% | −2% |
| 0, 760, 3,800, 11,400 ppm (0, 109, 555, 1,513 mg/kg-day) | *liver/body weight* | 0% | 3% | -0.4% | 2% |
| Diet (DINP-1) | | | | | |
| GD 12–PND 14 | | | | | |
| Clewell et al. (2013a) | **Liver weight in dams, GD 19** *(percent change compared to control)* | | | | |
| Rat (Sprague-Dawley); 4–9 dams/timepoint/dose; 8 litters/dose and 9 control litters | Doses | 0 | 50 | 250 | 750 |
| | absolute weight | 0% | −1% | 17*% | 15*% |
| 0, 50, 250, 750 mg/kg-day | *liver/body weight* | 0% | 2% | 12*% | 12*% |
| Gavage in corn oil (DINP-1) | | | | | |
| GD 12–19; dams sacrificed 0.5, 1, 2, 6, 12, and 24 hours after final dose | | | | | |

| Reference and study design[a] | Results | | | | |
|---|---|---|---|---|---|
| Hellwig et al. (1997)<br>Rat (Wistar), 8–10 dams (litters)/dose per DINP formulation<br>0, 40, 200, 1,000 mg/kg-day<br>Gavage in olive oil (DINP-1,2,3)<br>GDs 6–15; dams sacrificed on GD 20 | **Liver weight in dams** *(percent change compared to control)* | | | | |
| | Doses | 0 | 40 | 200 | 1,000 |
| | DINP-1 *absolute weight* | 0% | 0% | −2% | 6% |
| | DINP-2 *absolute weight* | 0% | −1% | 2% | 5% |
| | DINP-3 *absolute weight* | 0% | −2% | 3% | 11*% |
| | Note: Relative weight not reported by study authors. | | | | |
| **Waterman et al. (2000)**; one-generation study<br>Rat (Sprague-Dawley), 30 breeding pairs/dose<br>0, 0.5, 1, 1.5%<br>(0, 446, 889.5, 1,321 mg/kg-day in males;<br>0, 493.5, 951.5, 1,404 mg/kg-day in premating females;<br>0, 390.5, 768.5, 1,136.5 mg/kg-day during gestation in females;<br>0, 706.5, 1,384, 1,760 mg/kg-day during lactation in females)<br>Diet (DINP-1)<br>10 weeks prior to mating and through mating (M) or PND 21 (F) | **Liver weight in P0 animals** *(percent change compared to control)* | | | | |
| | Doses (M) | 0 | 446 | 889.5 | 1,321 |
| | *absolute weight* | 0% | 13*% | 27*% | 34*% |
| | *liver/body weight* | | Data not reported | | |
| | Doses (F) | 0 | 493.5 | 951.5 | 1,404 |
| | *absolute weight* | 0% | 26*% | 44*% | 52*% |
| | *liver/body weight* | | Data not reported | | |
| **Waterman et al. (2000)**; two-generation study<br>Rat (Sprague-Dawley), 30 breeding pairs/dose<br>0, 0.2, 0.4, 0.8%<br>P1 animals<br>0, 165, 331, 665 mg/kg-day in males;<br>0, 182, 356, 696 mg/kg-day in premating females;<br>0, 146, 287, 555 mg/kg-day during gestation in females;<br>0, 254, 539, 1,026 mg/kg-day during lactation in females<br>P2 (F1) animals<br>0, 189, 379, 779 mg/kg-day in males;<br>0, 197, 397, 802 mg/kg-day in premating females; | **Liver weight in P1 animals** *(percent change compared to control)* | | | | |
| | Doses (M) | 0 | 165 | 331 | 665 |
| | *absolute weight* | 0% | 1% | 6% | 16*% |
| | *liver/body weight* | | Data not reported | | |
| | Doses (F) | 0 | 182 | 356 | 696 |
| | *absolute weight* | 0% | 11% | 20*% | 22*% |
| | *liver/body weight* | | Data not reported | | |
| | **Liver weight in P2 (F1) animals** *(percent change compared to control)* | | | | |
| | Doses (M) | 0 | 189 | 379 | 779 |
| | *absolute weight* | 0% | 4% | 1% | 6% |
| | *liver/body weight* | | Data not reported | | |
| | Doses (F) | 0 | 197 | 397 | 802 |
| | *absolute weight* | 0% | 9% | 13% | 18*% |

| Reference and study design[a] | Results | | | | |
|---|---|---|---|---|---|
| 0, 143, 288, 560 mg/kg-day during gestation in females;<br>0, 285, 553, 1,229 mg/kg-day during lactation in females<br>Diet (DINP-1)<br>10 weeks prior to mating, and through mating (M) or PND 21 (F) | *liver/body weight* | Data not reported | | | |
| *Serum clinical chemistry* | | | | | |
| **Bio Dynamics (1986)**<br>Rat (Sprague-Dawley); 70/sex/dose<br>0, 500, 5,000, 10,000 ppm (0, 27, 271, and 553 mg/kg-day in males; 0, 33, 331, and 672 mg/kg-day in females)<br>Diet (Santicizer 900)<br>2 years (interim sacrifice at 1 year) | **Serum liver enzyme levels at terminal sacrifice** (n = 10/sex/dose) *(percent change compared to control)* | | | | |
| | Doses (M) | 0 | 27 | 271 | 553 |
| | *ALT* | 0% | 6% | 6% | 218% |
| | *AST* | 0% | 15% | 11% | 111% |
| | *ALP* | 0% | −25% | −10% | 33% |
| | Doses (F) | 0 | 33 | 331 | 672 |
| | *ALT* | 0% | −3% | 8% | 63% |
| | *AST* | 0% | −39% | −25% | −11% |
| | *ALP* | 0% | −36% | −41% | 38% |
| **Lington et al. (1997)**<br>Rat (F344); 110/sex/dose<br>0, 0.03, 0.3, 0.6% (0, 15, 152, or 307 mg/kg-day in males; 0, 18, 184, or 375 mg/kg-day in females)<br>Diet (DINP-1)<br>2 years (interim sacrifices at 6, 12, and 18 months) | **Serum liver enzyme levels at terminal sacrifice** (n = 20/sex/dose) *(percent change compared to control)* | | | | |
| | Doses (M) | 0 | 15 | 152 | 307 |
| | *ALT* | 0% | 7% | 112*% | 76% |
| | *AST* | 0% | 1% | 22% | 124% |
| | *ALP* | 0% | 15% | 59*% | 183*% |
| | Doses (F) | 0 | 18 | 184 | 375 |
| | *ALT* | 0% | 7% | 29% | 145% |
| | *AST* | 0% | 45% | 33% | 123% |
| | *ALP* | 0% | 38% | 55% | 66% |

| Reference and study design[a] | Results | | | | | | |
|---|---|---|---|---|---|---|---|
| **Covance Laboratories (1998b)**<br>Rat (F344); 70 or 85/sex/dose<br>0, 500, 1,500, 6,000, 12,000 ppm (0, 29, 88, 359, 733 mg/kg-day in males; 0, 36, 109, 442, 885 mg/kg-day in females)<br>Recovery group (55/sex): 12,000 ppm (637 mg/kg-day in males, 774 mg/kg-day in females)<br>Diet<br>Main study: 2 years (interim sacrifices at 1, 2, 13, and 79 weeks)<br>Recovery group: 78 weeks, followed by a 26-week recovery period with basal diet alone | **Serum liver enzyme levels at terminal sacrifice** (10/sex/dose) *(percent change compared to control)* | | | | | | |
| | Doses (M) | 0 | 29 | 88 | 359 | 733 | Recovery |
| | *ALT* | 0% | 13% | −4% | 123% | 113% | 123% |
| | *AST* | 0% | 9% | −12% | 136*% | 103% | 162*% |
| | *ALP* | Not evaluated | | | | | |
| | Doses (F) | 0 | 36 | 109 | 442 | 885 | Recovery |
| | *ALT* | 0% | −10% | −6% | 137*% | 73% | 16% |
| | *AST* | 0% | −6% | −5% | 165*% | 57% | 13% |
| | *ALP* | Not evaluated | | | | | |
| **Covance Laboratories (1998a)**<br>Mouse (B6C3F$_1$); 70/sex/dose<br>0, 500, 1,500, 4,000, 8,000 ppm (0, 90, 276, 742, 1,560 mg/kg-day in males; 0, 112, 336, 910, 1,888 mg/kg-day in females)<br>Recovery group (55/sex/dose): 8,000 ppm (1,377 mg/kg-day in males; 1,581 mg/kg-day in females)<br>Diet<br>Main study: 2 years (interim sacrifice at 79 weeks)<br>Recovery group: 78 weeks, followed by a 26-week recovery period with basal diet alone | **Serum liver enzyme levels at terminal sacrifice** (10/sex/dose) *(percent change compared to control)* | | | | | | |
| | Doses (M) | 0 | 90 | 276 | 742 | 1,560 | Recovery |
| | *ALT* | 0% | −12% | −8% | 20% | 960% | 742% |
| | *AST* | 0% | 8% | 24% | 30% | 473% | 343% |
| | *ALP* | Not evaluated | | | | | |
| | Doses (F) | 0 | 112 | 336 | 910 | 1,888 | Recovery |
| | *ALT* | 0% | −26% | 134% | 6% | −2% | 118% |
| | *AST* | 0% | −12% | 83% | 9% | 7% | 31% |
| | *ALP* | Not evaluated | | | | | |
| **Bio Dynamics (1982a)**<br>Rat (F344); 15/sex/dose<br>0, 0.1, 0.3, 0.6, 1.0, 2.0% (0, 67, 210, 410, 730, 1,500 mg/kg-day in males; 0, 77, 230, 480, 830, or 1,600 mg/kg-day in females)<br>Diet<br>13 weeks | **Serum liver enzyme levels at terminal sacrifice** (n = 10−13/dose) *(percent change compared to control)* | | | | | | |
| | Doses (M) | 0 | 67 | 210 | 410 | 730 | 1,500 |
| | *ALT* | 0% | −13% | 0% | −8% | 26% | 38*% |
| | *AST* | 0% | −17% | −9% | −21% | 14% | 14% |
| | *ALP* | 0% | 3% | 9% | 9% | 27*% | 49*% |
| | Doses (F) | 0 | 77 | 230 | 480 | 830 | 1,600 |
| | *ALT* | 0% | 17% | 3% | 0% | 11% | 11% |
| | *AST* | 0% | 5% | −2% | 0% | 0% | −8% |
| | *ALP* | 0% | −4% | 7% | 13% | 27% | 70*% |

| Reference and study design[a] | Results | | | | |
|---|---|---|---|---|---|
| Hall et al. (1999)<br>Marmoset; 4/sex/dose<br>0, 100, 500, or 2,500 mg/kg-day<br>Gavage in 1% methylcellulose and 0.5% Tween<br>13 weeks | Blood chemistry was analyzed at weeks 4 and 13. No treatment-related effects were observed (quantitative data not reported by study authors) | | | | |
| *Histopathology*[g] | | | | | |
| Bio Dynamics (1986); CPSC (2001)<br>Rat (Sprague-Dawley); 70/sex/dose<br>0, 500, 5,000, 10,000 ppm (0, 27, 271, 553 mg/kg-day in males; 0, 33, 331, 672 mg/kg-day in females)<br>Diet (Santicizer 900)<br>2 years (interim sacrifice at 1 year) | Doses (M) | 0 | 27 | 271 | 553 |
| | **Hepatic necrosis (all animals)**[c] | | | | |
| | *incidence* | 5/70 | 17/69 | 11/69 | 23/70 |
| | *percentage* | 7% | 25% | 16% | 33% |
| | **Spongiosis hepatis (all animals)**[c] | | | | |
| | *incidence* | 16/70 | 11/69 | 30/69** | 32/70** |
| | *percentage* | 23% | 16% | 43% | 46% |
| | Doses (F) | 0 | 33 | 331 | 672 |
| | **Hepatic necrosis (all animals)**[c] | | | | |
| | *incidence* | 10/70 | 15/70 | 7/70 | 10/70 |
| | *percentage* | 14% | 21% | 10% | 14% |
| | **Spongiosis hepatis (all animals)**[c] | | | | |
| | *incidence* | 4/70 | 3/70 | 6/70 | 11/70** |
| | *percentage* | 6% | 4% | 9% | 16% |
| **(EPL (1999); Lington et al. (1997))**<br>Rat (F344); 110/sex/dose<br>0, 0.03, 0.3, 0.6% (0, 15, 152, 307 mg/kg-day in males; 0, 18, 184, 375 mg/kg-day in females)<br>Diet (DINP-1)<br>2 years (interim sacrifices at 6, 12, and 18 months) | Doses (M) | 0 | 15 | 152 | 307 |
| | **Hepatocellular enlargement** | | | | |
| | *incidence* | 1/81 | 1/80 | 1/80 | 9/80** |
| | *percentage* | 1% | 1% | 1% | 11% |
| | **Hepatic necrosis** | | | | |
| | *incidence* | 10/81 | 9/80 | 16/80 | 26/80 |
| | *percentage* | 12% | 11% | 20% | 33% |
| | **Spongiosis hepatis**[d] | | | | |
| | *incidence* | 22/81 | 24/80 | 51/80** | 62/80** |
| | *percentage* | 27% | 30% | 64% | 78% |
| | Doses (F) | 0 | 18 | 184 | 375 |
| | **Hepatocellular enlargement** | | | | |
| | *incidence* | 1/81 | 0/81 | 0/80 | 11/80** |
| | *percentage* | 1% | 0% | 0% | 14% |

| Reference and study design[a] | Results | | | | | |
|---|---|---|---|---|---|---|
| | **Hepatic necrosis** | | | | | |
| | *incidence* | 13/81 | 11/81 | 19/80 | 21/80 | |
| | *percentage* | 16% | 14% | 24% | 26% | |
| | **Spongiosis hepatis**[d] | | | | | |
| | *incidence* | 4/81 | 1/81 | 3/80 | 4/80 | |
| | *Percentage* | 5% | 1% | 4% | 5% | |
| [Covance Laboratories (1998b)](); [EPL (1999)]() | Doses (M) | 0 | 29 | 88 | 359 | 733 | Recovery |
| Rat (F344); 70 or 85/sex/dose<br>0, 500, 1,500, 6,000, 12,000 ppm (0, 29, 88, 359, 733 mg/kg-day in males; 0, 36, 109, 442, 885 mg/kg-day in females)<br>Recovery group (55/sex): 12,000 ppm (637 mg/kg-day in males, 774 mg/kg-day in females<br>Diet<br>Main study: 2 years (interim sacrifices at 1, 2, 13, and 79 weeks)<br>Recovery group: 78 weeks, followed by a 26-week recovery period with basal diet alone | **Hepatocellular enlargement** | | | | | | |
| | *incidence* | 0/55 | 0/55 | 0/55 | 0/55 | 17/55[e] | 0/55 |
| | *percentage* | 0% | 0% | 0% | 0% | 31% | 0% |
| | **Hepatic necrosis** | | | | | | |
| | *incidence* | 0/55 | 0/55 | 0/55 | 1/55 | 5/55[e] | 0/55 |
| | *percentage* | 0% | 0% | 0% | 2% | 9% | 0% |
| | **Spongiosis hepatis**[d] | | | | | | |
| | *incidence* | 6/55 | 6/50 | 3/50 | 18/55** | 26/55** | 10/55 |
| | *percentage* | 11% | 12% | 6% | 33% | 47% | 20% |
| | **Increased cytoplasmic eosinophilic hypertrophy of hepatocytes** | | | | | | |
| | *incidence* | 0/55 | 0/55 | 0/55 | 0/55 | 31/55[e] | 0/55 |
| | *percentage* | 0% | 0% | 0% | 0% | 56% | 0% |
| | Doses (F) | 0 | 36 | 109 | 442 | 885 | Recovery |
| | **Hepatocellular enlargement** | | | | | | |
| | *incidence* | 0/55 | 0/55 | 0/55 | 0/55 | 27/55[e] | 0/55 |
| | *percentage* | 0% | 0% | 0% | 0% | 49% | 0% |
| | **Hepatic necrosis** | | | | | | |
| | Evaluated but data not reported | | | | | | |
| | **Spongiosis hepatis**[d] | | | | | | |
| | *incidence* | 0/55 | 0/50 | 0/50 | 1/55 | 2/55 | 0/50 |
| | *percentage* | 0% | 0% | 0% | 2% | 4% | 0% |
| | **Increased cytoplasmic eosinophilic hypertrophy of hepatocytes** | | | | | | |
| | *incidence* | 0/55 | 0/55 | 0/55 | 0/55 | 35/55[e] | 0/55 |
| | *percentage* | 0% | 0% | 0% | 0% | 64% | 0% |

| Reference and study design[a] | Results | | | | | | |
|---|---|---|---|---|---|---|---|
| Covance Laboratories (1998a) | Doses (M) | 0 | 90 | 276 | 742 | 1,560 | Recovery |
| Mouse ($B6C3F_1$); 70/sex/dose | **Hepatocellular enlargement** | | | | | | |
| 0, 500, 1,500, 4,000, 8,000 ppm (0, 90, 276, 742, 1,560 mg/kg-day in males; 0, 112, 336, 910, 1,888 mg/kg-day in females) | *incidence* | 0/46 | 1/41 | 0/36 | 1/35 | 32/32 | 0/38 |
| Recovery group (55/sex/dose): 8,000 ppm (1,377 mg/kg-day in males; 1,581 mg/kg-day in females) | *percentage* | 0% | 2% | 0% | 3% | 100% | 0% |
| | **Spongiosis hepatis** | | | | | | |
| | Evaluated but data not reported | | | | | | |
| | **Increased cytoplasmic eosinophilic hypertrophy of hepatocytes** | | | | | | |
| Diet | *incidence* | 0/46 | 0/41 | 0/36 | 0/35 | 32/32 | 0/38 |
| | *percentage* | 0% | 0% | 0% | 0% | 100% | 0% |
| Main study: 2 years (interim sacrifice at 79 weeks) | Doses (F) | 0 | 112 | 336 | 910 | 1,888 | Recovery |
| Recovery group: 78 weeks, followed by a 26-week recovery period with basal diet alone | **Hepatocellular enlargement** | | | | | | |
| | *incidence* | 0/42 | 0/36 | 0/37 | 0/29 | 40/40 | 0/35 |
| | *percentage* | 0% | 0% | 0% | 0% | 100% | 0% |
| | **Spongiosis hepatis** | | | | | | |
| | Evaluated but data not reported | | | | | | |
| | **Increased cytoplasmic eosinophilic hypertrophy of hepatocytes** | | | | | | |
| | *incidence* | 0/42 | 0/36 | 0/37 | 0/29 | 40/40 | 0/35 |
| | *percentage* | 0% | 0% | 0% | 0% | 100% | 0% |
| Hazleton Laboratories (1991) | Doses (M) | | 0 | 176 | 355 | 720 | 1,545 |
| Rat (F344); 10/sex/dose | **Hepatocellular enlargement** | | | | | | |
| 0, 2,500, 5,000, 10,000, 20,000 ppm (0, 175.8, 354.6, 719.6, 1,544.7 mg/kg-day in males; 0, 218.9, 438, 823.8, 1,687.1 mg/kg-day in females) | *incidence minimal* | | 0/10 | 0/10 | 0/10 | 0/10 | 3/10 |
| | *percentage* | | 0% | 0% | 0% | 0% | 30% |
| | *incidence slight* | | 0/10 | 0/10 | 0/10 | 0/10 | 7/10 |
| | *percentage* | | 0% | 0% | 0% | 0% | 70% |
| Diet (DINP-2/3) | **Hepatic necrosis** | | | | | | |
| 13 weeks | *incidence minimal* | | 0/10 | 0/10 | 1/10 | 0/10 | 0/10 |
| Note: Study authors did not perform statistical analysis on histopathological findings. | *percentage* | | 0% | 0% | 10% | 0% | 0% |
| | *incidence slight* | | 0/10 | 1/10 | 1/10 | 0/10 | 0/10 |
| | *percentage* | | 0% | 10% | 10% | 0% | 0% |
| | Doses (F) | | 0 | 2,199 | 438 | 824 | 1,687 |
| | **Hepatocellular enlargement** | | | | | | |
| | *incidence minimal* | | 0/10 | 0/10 | 0/10 | 1/10 | 0/10 |
| | *percentage* | | 0% | 0% | 0% | 10% | 0% |
| | *incidence slight* | | 0/10 | 0/10 | 0/10 | 0/10 | 10/10 |
| | *percentage* | | 0% | 0% | 0% | 0% | 100% |

| Reference and study design[a] | Results |
|---|---|
| | **Hepatic necrosis** No incidence of necrosis<br>**Increased cytoplasmic eosinophilic hypertrophy of hepatocytes**<br>Evaluated but data not reported for males or females |
| **Bio Dynamics (1982a)**<br>Rat (F344); 15/sex/dose<br>0, 0.1, 0.3, 0.6, 1.0, 2.0% (0, 67, 210, 410, 730, 1,500 mg/kg-day in males; 0, 77, 230, 480, 830, 1,600 mg/kg-day in females)[b]<br>Diet<br>13 weeks<br>Note: Study authors did not perform statistical analysis on histopathological findings. | **Increased cytoplasmic eosinophilic hypertrophy of hepatocytes**<br>Doses (M) 0 67 210 410 730 1,500<br>*incidence* 0/13 12/12 13/13 12/12 13/13 13/13<br>Doses (F) 0 77 230 480 830 1,600<br>*incidence* 0/13 13/13 12/12 13/13 13/13 13/13 |
| **Waterman et al. (2000)**<br>One-generation study<br>Rat (Sprague-Dawley), 30 breeding pairs/dose<br>0, 0.5, 1, 1.5%<br>(0, 446, 889.5, 1,321 mg/kg-day in males;<br>0, 493.5, 951.5, 1,404 mg/kg-day in premating females;<br>0, 390.5, 768.5, 1,136.5 mg/kg-day during gestation in females;<br>0, 706.5, 1,384, 1,760 mg/kg-day during lactation in females)[b]<br>Diet (DINP-1)<br>10 weeks prior to mating, and through mating (M) or PND 21 (F) | **Increased cytoplasmic eosinophilic hypertrophy of hepatocytes**<br>Minimal to moderately increased cytoplasmic eosinophilia in males and females from all treatment groups (quantitative data not reported by study authors) |

| Reference and study design[a] | Results | | | | |
|---|---|---|---|---|---|
| Waterman et al. (2000); two-generation study<br>Rat (Sprague-Dawley), 30 breeding pairs/dose<br>0, 0.2, 0.4, 0.8%<br>P1 (or F1) animals[b]<br>0, 165, 331, 665 mg/kg-day in males<br>0, 182, 356, 696 mg/kg-day in premating females<br>0, 146, 287, 555 mg/kg-day during gestation in females<br>0, 254, 539, 1,026 mg/kg-day during lactation in females<br>P2 (or F2) animals[b]<br>0, 189, 379, 779 mg/kg-day in males<br>0, 197, 397, 802 mg/kg-day in premating females<br>0, 143, 288, 560 mg/kg-day during gestation in females<br>0, 285, 553, 1,229 mg/kg-day during lactation in females<br>Diet (DINP-1)<br>10 weeks prior to mating, and through mating (M) or PND 21 (F) | **Increased cytoplasmic eosinophilic hypertrophy of hepatocytes**<br>Minimal to moderately increased cytoplasmic eosinophilia in males and females from all treatment groups (quantitative data not reported by study authors) | | | | |
| *Hepatocellular adenoma and carcinoma* | | | | | |
| Bio Dynamics (1986); CPSC (2001)<br>Rat (Sprague-Dawley); 70/sex/dose<br>0, 500, 5,000, 10,000 ppm (0, 27, 271, 553 mg/kg-day in males; 0, 33, 331, 672 mg/kg-day in females)<br>Diet (Santicizer 900)<br>2 years (interim sacrifice at 1 year) | Doses (M) | 0 | 27 | 271 | 553 |
| | **Neoplastic nodules (all animals)[c]** | | | | |
| | *incidence* | 2/70 | 5/69 | 6/69 | 5/70 |
| | *percentage* | 3% | 7% | 9% | 7% |
| | **Carcinomas (all animals)[c]** | | | | |
| | *incidence* | 2/70 | 2/69 | 6/69** | 4/70 |
| | *percentage* | 3% | 3% | 9% | 6% |
| | Doses (F) | 0 | 33 | 331 | 672 |
| | **Neoplastic nodules (all animals)[c]** | | | | |
| | *incidence* | 1/70 | 1/70 | 5/70 | 2/70 |
| | *percentage* | 1% | 1% | 7% | 3% |
| | **Carcinomas (all animals)[c]** | | | | |
| | *incidence* | 0/70 | 0/70 | 5/70** | 7/70** |
| | *percentage* | 0% | 0% | 7% | 10% |

| Reference and study design[a] | Results | | | | | |
|---|---|---|---|---|---|---|
| **(EPL (1999); Lington et al. (1997))** | Doses (M) | 0 | 15 | 152 | 307 | |
| Rat (F344); 110/sex/dose | **Ademonas at terminal sacrifice[d]** | | | | | |
| 0, 0.03, 0.3, 0.6% (0, 15, 152, 307 mg/kg-day in males; 0, 18, 184, 375 mg/kg-day in females) | *incidence* | 3/81 | 1/80 | 2/80 | 1/80 | |
| | *percentage* | 4% | 1% | 3% | 1% | |
| | **Carcinomas at terminal sacrifice[d]** | | | | | |
| Diet (DINP-1) | *incidence* | 0/81 | 1/80 | 0/80 | 3/80 | |
| 2 years (interim sacrifices at 6, 12, and 18 months) | *percentage* | 0% | 1% | 0% | 4% | |
| | **Combined[d]** | | | | | |
| | *incidence* | 3/81 | 2/80 | 2/80 | 4/80 | |
| | *percentage* | 4% | 3% | 3% | 5% | |
| | Doses (F) | 0 | 18 | 184 | 375 | |
| | **Adenomas at terminal sacrifice[d]** | | | | | |
| | *incidence* | 0/81 | 4/81 | 0/80 | 2/80 | |
| | *percentage* | 0% | 5% | 0% | 3% | |
| | **Carcinomas at terminal sacrifice[d]** | | | | | |
| | *incidence* | 1/81 | 0/81 | 0/80 | 1/80 | |
| | *percentage* | 1% | 0% | 0% | 1% | |
| | **Combined[d]** | | | | | |
| | *incidence* | 1/81 | 4/81 | 0/80 | 2/80 | |
| | *percentage* | 1% | 5% | 0% | 2.5% | |
| **Covance Laboratories (1998b); EPL (1999)** | Doses (M) | 0 | 29 | 88 | 359 | 733 | Recovery |
| Rat (F344); 70 or 85/sex/dose | **Adenomas at terminal sacrifice[d]** | | | | | | |
| 0, 500, 1,500, 6,000, 12,000 ppm (0, 29, 88, 359, 733 mg/kg-day in males; 0, 36, 109, 442, 885 mg/kg-day in females) Recovery group (55/sex/dose): 12,000 ppm (637 mg/kg-day in males, 774 mg/kg-day in females) | *incidence* | 2/55 | 4/50 | 1/50 | 4/55 | 7/55 | 6/50 |
| | *percentage* | 4% | 8% | 2% | 7% | 13% | 12% |
| | **Carcinomas at terminal sacrifice[d]** | | | | | | |
| | *incidence* | 1/55 | 0/50 | 0/50 | 3/55 | 11/55 | 3/50 |
| | *percentage* | 2% | 0% | 0% | 5% | 20% | 6% |
| Diet | **Combined[d]** | | | | | | |
| Main study: 2 years (interim sacrifices at 1, 2, 13, and 79 weeks) Recovery group: 78 weeks, followed by a 26-week recovery period with basal diet alone | *incidence* | 3/55 | 4/50 | 1/50 | 7/55 | 17/55 | 9/50 |
| | *percentage* | 5% | 8% | 2% | 13% | 31% | 18% |
| | Doses (F) | 0 | 36 | 109 | 442 | 885 | Recovery |
| | **Adenomas at terminal sacrifice[d]** | | | | | | |

| Reference and study design[a] | Results | | | | | | |
|---|---|---|---|---|---|---|---|
| Note: PWG did not perform statistical analysis on histopathological findings. | *incidence* | 1/55 | 1/50 | 0/50 | 1/55 | 1/55 | 1/50 |
| | *percentage* | 2% | 2% | 0% | 2% | 2% | 2% |
| | **Carcinomas at terminal sacrifice[d]** | | | | | | |
| | *incidence* | 0/55 | 0/50 | 0/50 | 1/55 | 7/55 | 2/50 |
| | *percentage* | 0% | 0% | 0% | 2% | 11% | 4% |
| | **Combined[d]** | | | | | | |
| | *incidence* | 1/55 | 1/50 | 0/50 | 2/55 | 8/55 | 2/50 |
| | *percentage* | 2% | 2% | 0% | 4% | 14.5% | 4% |
| Covance Laboratories (1998a); CPSC (2001) | Doses (M) | 0 | 90 | 276 | 742 | 1,560 | Recovery[e] |
| Mouse ($B6C3F_1$); 70/sex/dose | **Adenomas (all animals)[f]** | | | | | | |
| 0, 500, 1,500, 4,000, 8,000 ppm (0, 90, 276, 742, 1,560 mg/kg-day in males; 0, 112, 336, 910, 1,888 mg/kg-day in females) Recovery group (55/sex/dose): 8,000 ppm (1,377 mg/kg-day in males; 1,581 mg/kg-day in females) | *incidence* | 10/70 | 7/60 | 8/60 | 15/60 | 13/70 | 8/50 |
| | *percentage* | 14% | 10% | 12% | 23% | 19% | 16% |
| | **Carcinomas (all animals)[c]** | | | | | | |
| | *incidence* | 10/70 | 8/67 | 10/66 | 17/65** | 20/70** | 12/50 |
| | *percentage* | 14% | 12% | 15% | 26% | 29% | 24% |
| Diet | **Combined (all animals)[c]** | | | | | | |
| Main study: 2 years (interim sacrifice at 79 weeks) Recovery group: 78 weeks, followed by a 26-week recovery period with basal diet alone | *incidence* | 16/70 | 13/67 | 18/66 | 28/65** | 31/70** | |
| | *percentage* | 23% | 19% | 27% | 43% | 44% | |
| | Doses (F) | 0 | 112 | 336 | 910 | 1,888 | Recovery[e] |
| | **Adenomas (all animals)[f]** | | | | | | |
| | *incidence* | 2/70 | 4/61 | 5/60 | 4/60 | 18/70* | 8/50* |
| | *percentage* | 3% | 6% | 7% | 6% | 26% | 16% |
| | **Carcinomas (all animals)[c]** | | | | | | |
| | *incidence* | 1/70 | 2/68 | 5/68 | 7/67** | 19/70** | 13/50* |
| | *percentage* | 1% | 3% | 7% | 10% | 27% | 26% |
| | **Combined (all animals)[c]** | | | | | | |
| | *incidence* | 3/70 | 5/68 | 10/68** | 11/67** | 33/70** | |
| | *percentage* | 4% | 7% | 15% | 16% | 47% | |

[a]DINP formulation referenced when the study authors provided the specific formulation.
[b]Calculated as follows: [% in diet × intake food/water (mg)] ÷ body weight (kg) = mg/kg-day.
[c]Incidence data as reported by Chronic Hazard Advisory Panel (CPSC, 2001).
[d]Incidence data as reported by Pathology Working Group reanalysis (EPL, 1999).
[e]Recovery group incidence data from study authors; Chronic Hazard Advisory Panel (CPSC, 2001) did not evaluate these data.
[f]Incidence data from study authors; Chronic Hazard Advisory Panel (CPSC, 2001) did not evaluate these data.

[g]Results shown are at terminal sacrifice unless otherwise stated.
*Statistically significant from control group, as reported by study authors.
**Statistically significant, as reported by Chronic Hazard Advisory Panel (CPSC, 2001).
Percent change compared to control = ([treated value − control value] ÷ control value) x 100

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GD = gestational day; PND = postnatal day

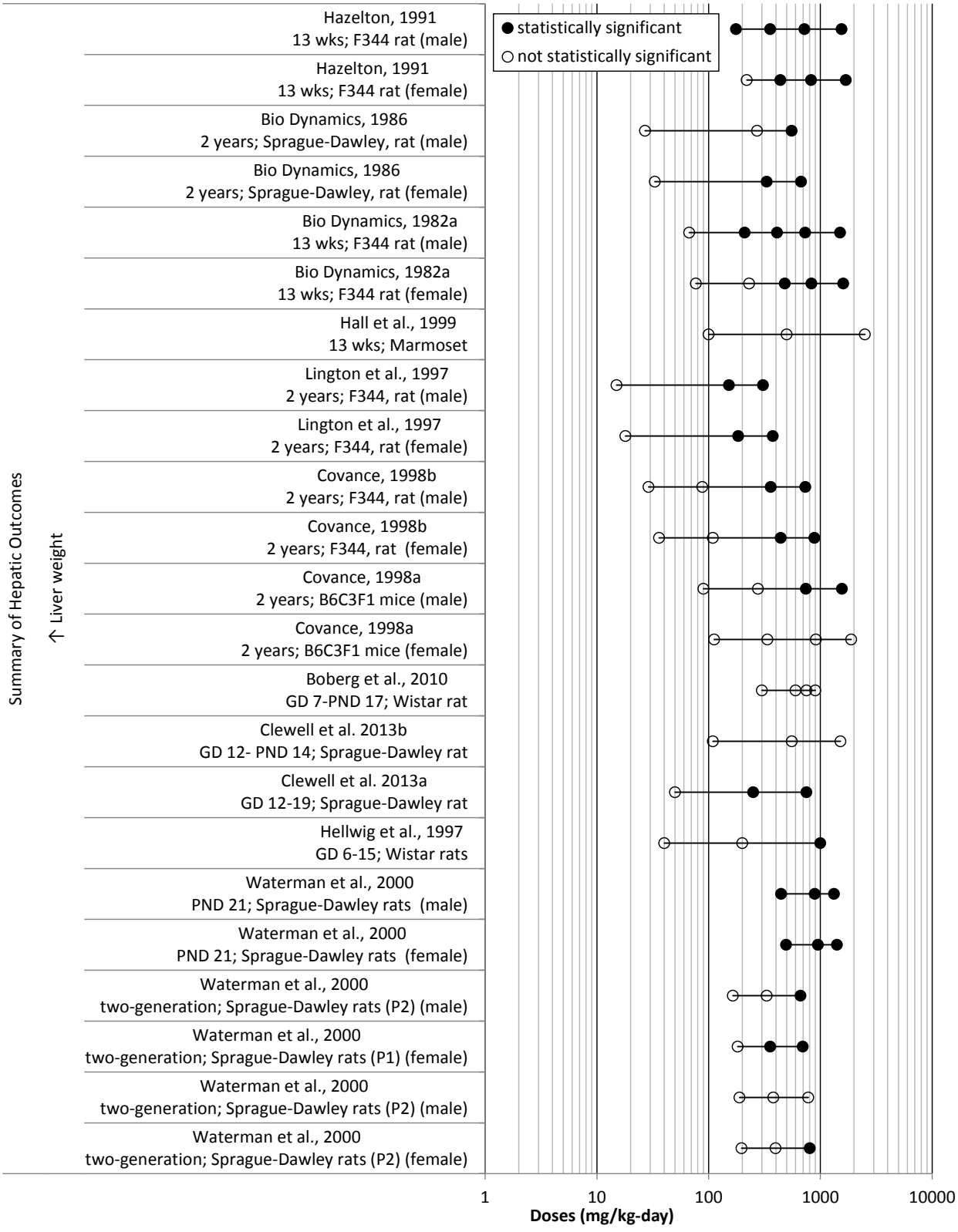


**Figure 3-1. Exposure-response array of liver weight effects following oral exposure to DINP.**

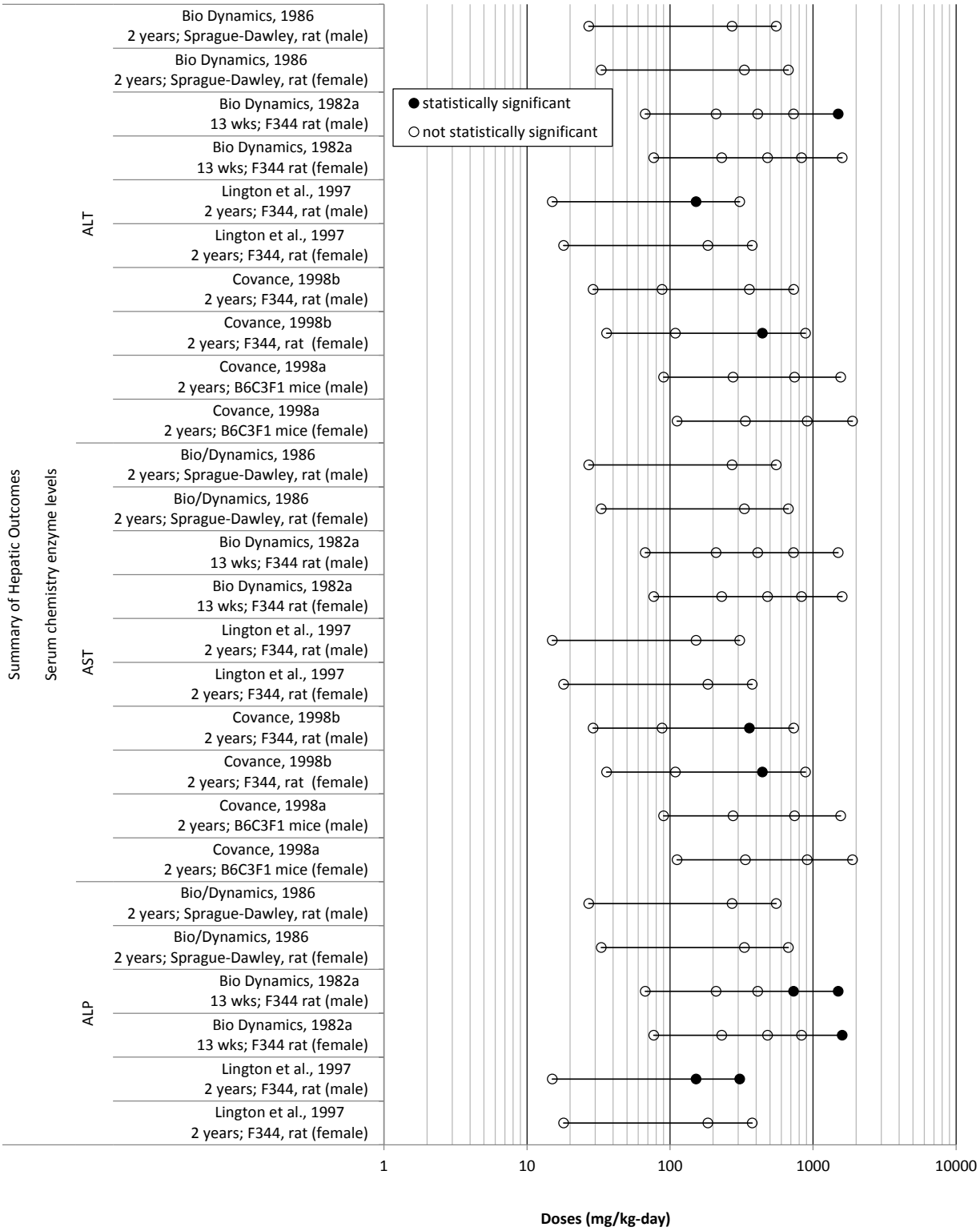


**Figure 3-2. Exposure-response array of liver serum chemistry enzyme levels following oral exposure to DINP.**

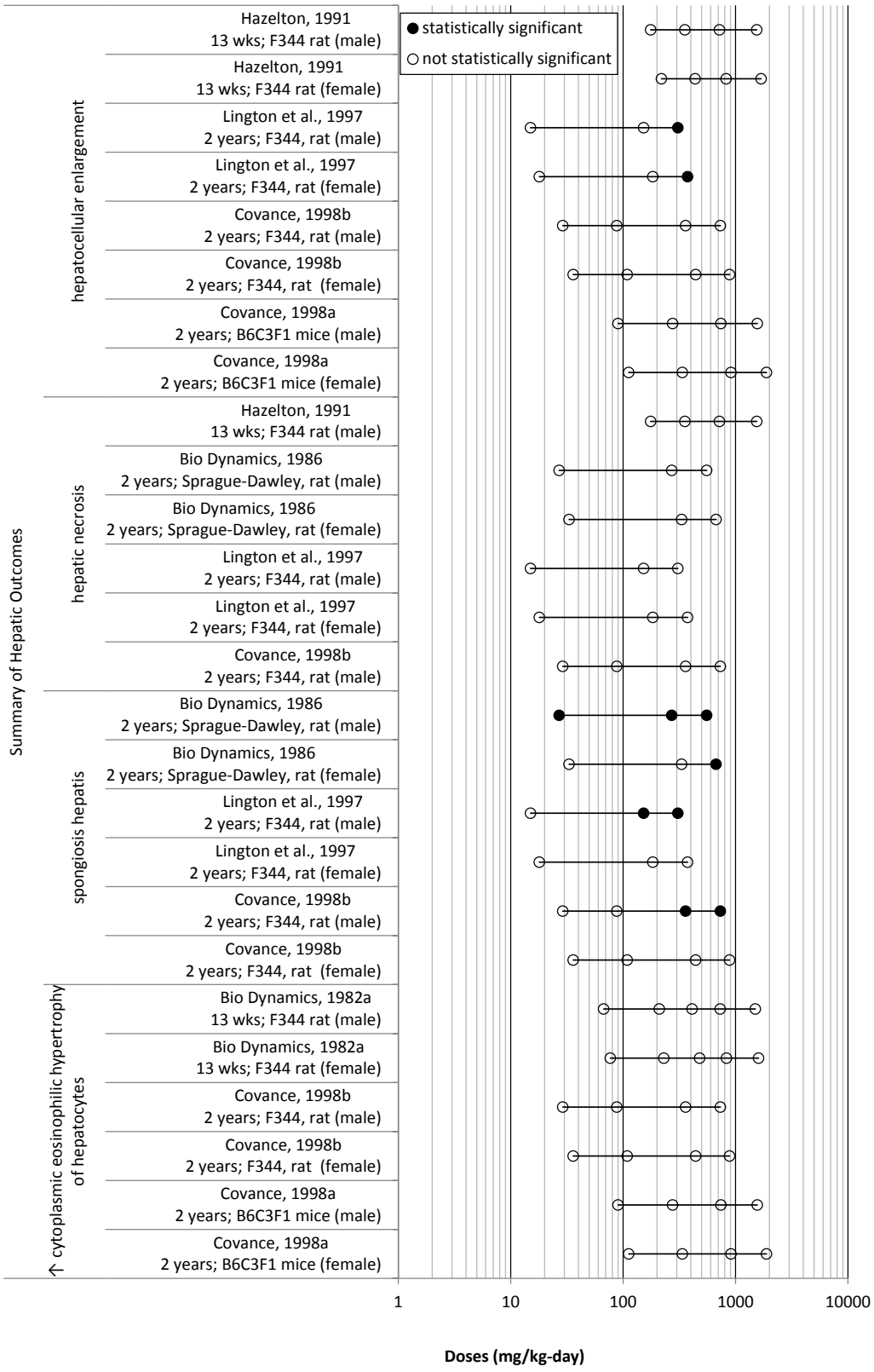


**Figure 3-3. Exposure-response array of liver histopathological effects following oral exposure to DINP.**

## 3.3.2. Kidney Effects

**Table 3-12. Evidence pertaining to kidney effects in animals following oral exposure to DINP**

| Reference and study design[a] | Results | | | | | |
|---|---|---|---|---|---|---|
| *Kidney weight change* | | | | | | |
| Bio Dynamics (1986)<br><br>Rat (Sprague-Dawley); 70/sex/dose;<br><br>0, 500, 5,000, 10,000 ppm (0, 27, 271, 553 mg/kg-day in males; 0, 33, 331, 672 mg/kg-day in females)<br><br>Diet (SANTICIZER 900)<br><br>2 years (interim sacrifice at 1 year) | **Kidney weight at terminal sacrifice** (n = 25–47/sex/dose) *(percent change compared to control)* | | | | | |
| | Doses (M) | 0 | 27 | 271 | 553 | |
| | *absolute weight* | 0% | 5% | −2% | 13*% | |
| | *kidney/body weight* | 0% | 4% | −6% | 12*% | |
| | Doses (F) | 0 | 33 | 331 | 672 | |
| | *absolute weight* | 0% | −3% | 9*% | 3 % | |
| | *kidney/body weight* | 0% | −5% | 10% | 14*% | |
| Lington et al. (1997)<br><br>Rat (F344); 110/sex/dose;0, 0.03.<br><br>0.3. 0.6% (0, 15, 152, 307 mg/kg-day in males; 0, 18, 184, 375 mg/kg-day in females)<br><br>Diet (DINP-1)<br><br>2 years (interim sacrifices at 6, 12, and 18 months) | **Kidney weight at terminal sacrifice** (n = 48–65/sex/dose) *(percent change compared to control)* | | | | | |
| | Doses (M) | 0 | 15 | 152 | 307 | |
| | *absolute weight* | | Data not reported | | | |
| | *kidney/body weight* | 0% | 7% | 10* | 20*% | |
| | Doses (F) | 0 | 18 | 184 | 375 | |
| | *absolute weight* | | Data not reported | | | |
| | *kidney/body weight* | 0% | −1% | 7*% | 10*% | |
| Covance Laboratories (1998b)<br><br>Rat (F344); 70 or 85/sex/dose<br><br>0, 500, 1,500, 6,000, 12,000 ppm (0, 29, 88, 359, 733 mg/kg-day in males; 0, 36, 109, 442, 885 mg/kg-day in females)<br>Recovery group (55/sex/dose): 12,000 ppm (637 mg/kg-day in males; 733 mg/kg-day in females)<br><br>Diet<br><br>Main study: 2 years (interim sacrifices at 1, 2, 13, and 79 weeks)<br>Recovery group: 78 weeks, followed by a 26-week recovery period with basal diet alone | **Kidney weight at terminal sacrifice** (n = 27–40/sex/group) *(percent change compared to control)* | | | | | | |
| | Doses (M) | 0 | 29 | 88 | 359 | 733 | Recovery |
| | *absolute weight* | 0% | 0% | 3% | 6% | 15*% | 3% |
| | *kidney/body weight* | 0% | 0% | 7% | 8% | 25*% | 8% |
| | Doses (F) | 0 | 36 | 109 | 442 | 885 | Recovery |
| | *absolute weight* | 0% | 1% | 2% | 10*% | 10*% | 2% |
| | *kidney/body weight* | 0% | 5% | 6% | 14* | 22*% | 4% |

| Reference and study design[a] | Results | | | | | | |
|---|---|---|---|---|---|---|---|
| Covance Laboratories (1998a)<br><br>Mouse (B6C3F$_1$); 70/sex/dose<br>0, 500, 1,500, 4,000, 8,000 ppm (0, 90, 276, 742, 1,560 mg/kg-day in males; 0, 112, 336, 910, 1,888 mg/kg-day in females)<br>Recovery group (55/sex/group): 8,000 ppm (1,377 mg/kg-day in males; 1,581 mg/kg-day in females)<br>Diet<br>Main study: 2 years (interim sacrifice at 79 weeks)<br>Recovery group: 78 weeks, followed by a 26-week recovery period with basal diet alone | **Kidney weight at terminal sacrifice** (n = 24-42/sex/dose) *(percent change compared to control)* | | | | | | |
| | Doses (M) | 0 | 90 | 276 | 742 | 1,560 | Recovery |
| | *absolute weight* | 0% | −4% | −11*% | −24*% | −27*% | −17*% |
| | *kidney/body weight* | 0% | −1% | −7% | −13*% | −9% | −8% |
| | Doses (F) | 0 | 112 | 336 | 910 | 1,888 | Recovery |
| | *absolute weight* | Study authors did not observe a change compared to controls (quantitative data not reported by study authors) | | | | | |
| | *kidney/body weight* | Study authors did not observe a change compared to controls (quantitative data not reported by study authors) | | | | | |
| Hazleton Laboratories (1991)<br><br>Rat (F344); 10/sex/dose<br>0, 2,500, 5,000, 10,000, 20,000 ppm (0, 175.8, 354.6, 719.6, 1,544.7 mg/kg-day in males; 0, 218.9, 438, 823.8, 1,687.1 mg/kg-day in females)<br>Diet (DINP-2/3)<br>13 weeks | **Kidney weight** *(percent change compared to control)* | | | | | | |
| | Doses (M) | 0 | 176 | 355 | 720 | 1,545 | |
| | *absolute weight* | 0% | 2% | 11*% | 16*% | 15*% | |
| | *kidney/ body weight* | 0% | 5*% | 9*% | 21*% | 29*% | |
| | Doses (F) | 0 | 220 | 438 | 824 | 1,687 | |
| | *absolute weight* | 0% | 8*% | 10*% | 11*% | 8*% | |
| | *kidney/ body weight* | 0% | 3% | 7*% | 13*% | 24*% | |
| Bio Dynamics (1982a)<br><br>Rat (F344); 15/sex/dose<br>0, 0.1 0.3, 0.6, 1.0, 2.0% (0, 67, 210, 410, 730, 1,500 mg/kg-day in males;<br>0, 77, 230, 480, 830, 1,600 mg/kg-day in females)[b]<br>Diet<br>13 weeks | **Kidney weight** *(percent change compared to control)* | | | | | | |
| | Doses (M) | 0 | 67 | 210 | 410 | 730 | 1,500 |
| | *absolute weight* | 0% | −4% | −3% | 5% | 9*% | 7% |
| | *kidney/body weight* | 0% | 0% | 3% | 7% | 13*% | 25*% |
| | Doses (F) | 0 | 77 | 230 | 480 | 830 | 1,600 |
| | *absolute weight* | 0% | 2% | 7*% | 12*% | 15*% | 7*% |
| | *kidney/body weight* | 0% | 4% | 10*% | 14*% | 19*% | 17*% |
| Waterman et al. (2000); one-generation study<br><br>Rat (Sprague-Dawley), 30 breeding pairs/dose<br>0, 0.5, 1, 1.5% (0, 446, 889.5, 1,321 mg/kg-day in males | **Kidney weight in P0 animals** *(percent change compared to control)* | | | | | | |
| | Doses (M) | 0 | | 446 | 889.5 | | 1,321 |
| | *absolute weight* | 0% | | 25*% | 28*% | | 28*% |
| | *liver/body weight* | Data not reported | | | | | |
| | Doses (F) | 0 | | 493.5 | 951.5 | | 1,404 |

| Reference and study design[a] | Results | | | | |
|---|---|---|---|---|---|
| 0, 493.5, 951.5, 1,404 mg/kg-day in premating females<br>0, 390.5, 768.5, 1,136.5 mg/kg-day during gestation in females<br>0, 706.5, 1,384, 1,760 mg/kg-day during lactation in females) [d]<br>Diet (DINP-1)<br>10 weeks prior to mating, and through mating (M) or PND 21 (F) | *absolute weight* | 0% | 13*% | 8*% | 0.4% |
| | *liver/body weight* | Data not reported | | | |
| Waterman et al. (2000); two-generation study<br>Rat (Sprague-Dawley), 30 breeding pairs/dose<br>0, 0.2, 0.4, 0.8%<br>P1 (or F1) animals[b]<br>0, 165, 331, 665 mg/kg-day in males<br>0, 182, 356, 696 mg/kg-day in premating females<br>0, 146, 287, 555 mg/kg-day during gestation in females<br>0, 254, 539, 1,026 mg/kg-day during lactation in females<br>P2 (or F2) animals[b]<br>0, 189, 379, 779 mg/kg-day in males<br>0, 197, 397, 802 mg/kg-day in premating females<br>0, 143, 288, 560 mg/kg-day during gestation in females<br>0, 285, 553, 1,229 mg/kg-day during lactation in females<br>Diet (DINP-1)<br>10 weeks prior to mating, and through mating (M) or PND 21 (F) | **Kidney weight in P1 animals** *(percent change compared to control)* | | | | |
| | Doses (M) | 0 | 165 | 331 | 665 |
| | *absolute weight* | 0% | 8% | 14*% | 20*% |
| | *liver/body weight* | Data not reported | | | |
| | Doses (F) | 0 | 182 | 356 | 696 |
| | *absolute weight* | 0% | 8*% | 10*% | 8*% |
| | *liver/body weight* | Data not reported | | | |
| | **Kidney weight in P2 (F2) animals** *(percent change compared to control)* | | | | |
| | Doses (M) | 0 | 165 | 331 | 665 |
| | *absolute weight* | 0% | 6% | 7% | 14*% |
| | *liver/body weight* | Data not reported | | | |
| | Doses (F) | 0 | 182 | 356 | 696 |
| | *absolute weight* | 0% | 5% | 4% | 3% |
| | *liver/body weight* | Data not reported | | | |
| Boberg et al. (2011)<br>Rat (Wistar); 1–7 litters/dose; 18–35 males/dose<br>0, 300, 600, 750, 900 mg/kg-day<br>Gavage in corn oil (DINP-2)<br>GDs 7–21 | **Kidney weight in males at PND 90** *(percent change compared to control)* | | | | |
| | Doses | 0 | 300 | 600 | 750 | 900 |
| | *absolute weight* | 0% | −1% | −2% | −1% | −3% |
| | Note: Study authors did not examine this endpoint in females. Relative weights not reported by study authors. | | | | | |

| Reference and study design[a] | Results | | | | | | |
|---|---|---|---|---|---|---|---|
| **Hellwig et al. (1997)**<br>Rat (Wistar), 8–10 dams (litters)/dose per DINP formulation<br>0, 40, 200, 1,000 mg/kg-day<br>Gavage in olive oil (DINP-1,2,3)<br>GDs 6–15; dams sacrificed on GD 20 | **Kidney weight in dams** *(percent change compared to control)* | | | | | | |
| | Doses | 0 | 40 | 200 | 1,000 | | |
| | DINP-1 *absolute weight* | 0% | 5% | 8% | 13*% | | |
| | DINP-2 *absolute weight* | 0% | 10*% | 4% | 7% | | |
| | DINP-3 *absolute weight* | 0% | 6% | 7% | 9% | | |
| | Note: Relative weight not reported by study authors. | | | | | | |
| *Serum clinical chemistry; kidney function* | | | | | | | |
| **Covance Laboratories (1998b)**<br>Rat (F344); 70 or 85/sex/dose<br>0, 500, 1,500, 6,000, 12,000 ppm (0, 29, 88, 359, 733 mg/kg-day in males; 0, 36, 109, 442, 885 mg/kg-day in females)<br>Recovery group (55/sex/dose): 12,000 ppm (637 mg/kg-day in males; 733 mg/kg-day in females)<br>Diet<br>Main study: 2 years (interim sacrifices at 1, 2, 13, and 79 weeks)<br>Recovery group: 78 weeks, followed by a 26-week recovery period with basal diet alone | **BUN levels at terminal sacrifice (n = 10/sex/dose)** *(percent change compared to control)* | | | | | | |
| | Doses (M) | 0 | 29 | 88 | 359 | 733 | Recovery |
| | *BUN* | 0% | −7% | 0% | −13% | 40*% | 57% |
| | Doses (F) | 0 | 36 | 109 | 442 | 885 | Recovery |
| | *BUN* | 0% | 0% | 0% | 31% | 25% | -6% |
| *Renal histopathology* | | | | | | | |
| **Bio Dynamics (1986)**<br>Rat (Sprague-Dawley); 70/sex/dose<br>0, 500, 5,000, 10,000 ppm (0, 27, 271, 553 mg/kg-day in males; 0, 33, 331, 672 mg/kg-day in females)<br>Diet (SANTICIZER 900)<br>2 years (interim sacrifice at 1 year, 10/sex/group)<br>Note: Study authors did not perform statistical analysis on | **Papillary mineralization** | | | | | | |
| | Doses (M) | 0 | 27 | 271 | 553 | | |
| | *incidence (unilateral)* | 3/70 | NE | NE | 9/70 | | |
| | *percentage* | 4% | NE | NE | 13% | | |
| | *incidence (bilateral)* | 0/70 | NE | NE | 16/70 | | |
| | *percentage* | 0% | NE | NE | 23% | | |
| | Doses (F) | 0 | 33 | 331 | 672 | | |
| | *incidence (unilateral)* | 6/70 | NE | NE | 4/70 | | |
| | *percentage* | 9% | NE | NE | 6% | | |

| Reference and study design[a] | Results | | | | | | |
|---|---|---|---|---|---|---|---|
| histopathological findings. | *incidence (bilateral)* | 8/70 | NE | NE | 11/70 | | |
| | *percentage* | 11% | NE | NE | 16% | | |
| Lington et al. (1997)<br>Rat (F344); 110/sex/dose<br>0, 0.03. 0.3. 0.6% (0, 15, 152, 307 mg/kg-day in males; 0, 18, 184, 375 mg/kg-day in females)<br>Diet (DINP-1)<br>2 years (interim sacrifices at 6, 12, and 18 months; 10/sex/dose) | **Renal tubule pigmentation**<br>Increase noted in high dose males at the 18-month interim sacrifice (quantitative data not reported by study authors) | | | | | | |
| Covance Laboratories (1998b)<br>Rat (F344); 70 or 85/sex/dose 0,<br>500, 1,500, 6,000, 12,000 ppm (0, 29, 88, 359, 733 mg/kg-day in males; 0, 36, 109, 442, 885 mg/kg-day in females)<br>Recovery group (55/sex/dose): 12,000 ppm (637 mg/kg-day in males; 733 mg/kg-day in females)<br>Diet<br>Main study: 2 years (interim sacrifices at 1, 2, 13, and 79 weeks)<br>Recovery group: 78 weeks, followed by a 26-week recovery period with basal diet alone<br>Note: Study authors did not perform statistical analysis on histopathological findings. | **Histopathological lesions at terminal sacrifice** | | | | | | |
| | Doses (M) | 0 | 29 | 88 | 359 | 733 | Recovery |
| | **Renal tubule pigmentation** | | | | | | |
| | *incidence* | 34/36 | 35/35 | 39/39 | 31/31 | 27/27 | 29/29 |
| | *percentage* | 94% | 100% | 100% | 100% | 100% | 100% |
| | *severity* | 1.2 | 1.5 | 1.5 | 2.3 | 2.9 | 2.1 |
| | **Tubule dilation** | | | | | | |
| | *incidence* | 0/36 | 0/35 | 0/39 | 0/31 | 1/27 | 1/29 |
| | *percentage* | 0% | 0% | 0% | 0% | 4% | 3% |
| | **Papillary mineralization** | | | | | | |
| | *incidence* | 6/36 | 11/35 | 9/39 | 30/31 | 25/27 | 29/29 |
| | *percentage* | 17% | 31% | 23% | 97% | 93% | 100% |
| | *severity* | 0.2 | 0.3 | 0.2 | 1.7 | 2.6 | 2.9 |
| | Doses (F) | 0 | 36 | 109 | 442 | 885 | Recovery |
| | **Renal tubule pigmentation** | | | | | | |
| | *incidence* | 36/37 | 38/38 | 40/40 | 33/33 | 32/32 | 34/34 |
| | *percentage* | 97% | 100% | 100% | 100% | 100% | 100% |
| | *severity* | 1.4 | 1.3 | 1.2 | 2.0 | 2.4 | 2.0 |
| | **Tubule dilation** | | | | | | |
| | *incidence* | 0/37 | 0/38 | 0/40 | 1/33 | 0/32 | 0/34 |
| | *percentage* | 0% | 0% | 0% | 3% | 0% | 0% |
| | **Papillary mineralization** | | | | | | |
| | *incidence* | 7/37 | 7/38 | 1/40 | 8/33 | 8/32 | 5/34 |
| | *percentage* | 19% | 18% | 3% | 24% | 25% | 15% |
| | *severity* | 0.2 | 0.2 | 0 | 0.2 | 0.3 | 0.1 |

| Reference and study design[a] | Results | | | | | |
|---|---|---|---|---|---|---|
| Hazleton Laboratories (1991) | Doses (M) | 0 | 176 | 355 | 720 | 1,545 |
| Rat (F344); 10/sex/dose | **Granular casts/dilation** | | | | | |
| 0, 2,500, 5,000, 10,000, 20,000 ppm (0, 175.8, 354.6, 719.6, 1,544.7 mg/kg-day in males; 0, 218.9, 438, 823.8, 1,687.1 mg/kg-day in females) | *incidence minimal* | 0/10 | 0/10 | 6/10 | 0/10 | 0/10 |
| | *percentage* | 0% | 0% | 60% | 0% | 0% |
| | *incidence slight* | 0/10 | 0/10 | 0/10 | 10/10 | 10/10 |
| | *percentage* | 0% | 0% | 0% | 100% | 100% |
| Diet (DINP-2/3) | **Tubular regeneration** | | | | | |
| 13 weeks | *incidence minimal* | 10/10 | 7/10 | 0/10 | 0/10 | 0/10 |
| Note: Study authors did not perform statistical analysis on histopathological findings. | *percentage* | 100% | 70% | 0% | 0% | 0% |
| | *incidence slight* | 0/10 | 3/10 | 9/10 | 9/10 | 2/10 |
| | *percentage* | 0% | 30% | 90% | 90% | 20% |
| | *incidence moderate* | 0/10 | 0/10 | 1/10 | 1/10 | 8/10 |
| | *percentage* | 0% | 0% | 10% | 10% | 80% |
| | Doses (F) | 0 | 220 | 438 | 824 | 1,687 |
| | **Granular casts/dilation:** no incidence | | | | | |
| | **Tubular regeneration** | | | | | |
| | *incidence minimal* | 1/10 | 0/10 | 0/10 | 0/10 | 2/10 |
| | *percentage* | 10% | 0% | 0% | 0% | 20% |
| Bio Dynamics (1982a) | Doses (M) | 0 | 67 | 210 | 410 | 730 | 1,500 |
| Rat (F344); 15/sex/dose; kidneys examined microscopically in 12–13/sex/dose | **Nephrosis** (incidence) | | | | | | |
| 0, 0.1 0.3, 0.6, 1.0, 2.0% (0, 67, 210, 410, 730, 1,500 mg/kg-day in males; 0, 77, 230, 480, 830, 1,600 mg/kg-day in females)[b] | *incidence minimal* | 0/13 | 0/12 | 4/13 | 3/12 | 0/13 | 3/13 |
| | *percentage* | 0% | 0% | 31% | 25% | 0% | 23% |
| | *incidence slight* | 0/13 | 0/12 | 0/13 | 6/12 | 7/13 | 5/13 |
| | *percentage* | 0% | 0% | 0% | 50% | 54% | 38% |
| Diet | *incidence moderate* | 0/13 | 0/12 | 0/13 | 3/12 | 5/13 | 1/13 |
| 13 weeks | *percentage* | 0% | 0% | 0% | 25% | 38% | 8% |
| Note: Study authors did not perform statistical analysis on histopathological findings. | **Granular casts** (incidence) | | | | | | |
| | *incidence minimal* | 0/13 | 0/12 | 0/13 | 4/12 | 2/13 | 1/13 |
| | *percentage* | 0% | 0% | 0% | 33% | 15% | 8% |
| | *incidence slight* | 0/13 | 0/12 | 0/13 | 2/12 | 9/13 | 4/13 |
| | *percentage* | 0% | 0% | 0% | 17% | 69% | 31% |
| | *incidence moderate* | 0/13 | 0/12 | 0/13 | 0/12 | 2/13 | 4/13 |
| | *percentage* | 0% | 0% | 0% | 0% | 15% | 31% |

| Reference and study design[a] | Results | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Tubular regeneration** | | | | | | |
| | *incidence minimal* | 4/13 | 6/12 | 0/13 | 0/12 | 1/13 | 3/13 |
| | *percentage* | 31% | 50% | 0% | 0% | 8% | 23% |
| | *incidence slight* | 7/13 | 6/12 | 13/13 | 4/12 | 9/13 | 7/13 |
| | *percentage* | 54% | 50% | 100% | 33% | 69% | 54% |
| | *incidence moderate* | 0/13 | 0/12 | 0/13 | 8/12 | 3/13 | 3/13 |
| | *percentage* | 0% | 0% | 0% | 67% | 23% | 23% |
| | Doses (F) | 0 | 77 | 230 | 480 | 830 | 1,600 |
| | **Nephrosis:** no incidence<br>**Granular casts:** no incidence<br>**Tubular regeneration:** no incidence | | | | | | |
| | *incidence minimal* | 2/13 | 0/13 | 1/12 | 0/13 | 1/13 | 0/13 |
| | *percentage* | 15% | 0% | 8% | 0% | 8% | 0% |
| *Chronic progressive nephropathy* | | | | | | | |
| **Covance Laboratories (1998a)**<br>Mouse (B6C3F1); 70/sex/dose<br>0, 500, 1,500, 4,000, 8,000 ppm (0, 90, 276, 742, 1,560 mg/kg-day in males; 0, 112, 336, 910, 1,888 mg/kg-day in females)<br>Recovery group (55/sex/group): 8,000 ppm (1,377 mg/kg-day in males; 1,581 mg/kg-day in females)<br>Diet<br>2 years (18-month interim sacrifice; 15/sex/group)<br>Recovery group: 78 weeks, followed by a 26-week recovery period with basal diet alone<br>Note: Study authors did not perform statistical analysis on histopathological findings. | Doses (M) | 0 | 90 | 276 | 742 | 1,560 | Recovery |
| | Not observed | | | | | | |
| | Doses (F) | 0 | 112 | 336 | 910 | 1,888 | Recovery |
| | *incidence* | 40/60 | 36/61 | 39/60 | 39/60 | 61/62 | 39/50 |
| | *percentage* | 67% | 59% | 65% | 65% | 98% | 78% |
| | *severity* | 0.8 | 0.7 | 0.8 | 0.8 | 1.8 | 0.9 |
| *Renal carcinoma* | | | | | | | |
| **Lington et al. (1997)**<br>Rat (F344); 110/sex/dose<br>0, 0.03. 0.3. 0.6 % (0, 15, 152, 307 mg/kg-day in males; 0, 18, 184, 375 mg/kg-day in females)<br>Diet (DINP-1) | Doses (M) | 0 | | 15 | 152 | | 307 |
| | **Renal tubular cell carcinoma at terminal sacrifice** | | | | | | |
| | *incidence* | 0/81 | | 1/80 | 0/80 | | 2/80 |
| | *percentage* | 0% | | 1% | 0% | | 3% |
| | **Renal transitional cell carcinoma at terminal sacrifice** | | | | | | |

| Reference and study design[a] | Results | | | | | | |
|---|---|---|---|---|---|---|---|
| 2 years (interim sacrifices at 6, 12, and 18 months; 10/sex/dose) | *incidence* | 0/81 | 0/80 | 3/80 | 0/80 | | |
| | *percentage* | 0% | 0% | 4% | 0% | | |
| | Doses (F) | 0 | 18 | 184 | 375 | | |
| | **Renal tubular cell carcinoma:** no incidence<br>**Renal transitional cell carcinoma:** no incidence | | | | | | |
| Covance Laboratories (1998b); CPSC (2001)<br><br>Rat (F344); 70 or 85/sex/dose<br><br>0, 500, 1,500, 6,000, 12,000 ppm (0, 29, 88, 359, 733 mg/kg-day in males; 0, 36, 109, 442, 885 mg/kg-day in females)<br>Recovery group (55/sex/dose): 12,000 ppm (637 mg/kg-day in males; 733 mg/kg-day in females)<br><br>Diet<br><br>Main study: 2 years (interim sacrifices at 1, 2, 13, and 79 weeks)<br>Recovery group: 78 weeks, followed by a 26-week recovery period with basal diet alone | Doses (M) | 0 | 29 | 88 | 359 | 733 | Recovery |
| | Renal tubular cell carcinoma at terminal sacrifice[c] | | | | | | |
| | *incidence* | 0/65 | 0/55 | 0/55 | 0/65 | 2/65** | 4/50** |
| | *percentage* | 0% | 0% | 0% | 0% | 3% | 8% |
| | Doses (F) | 0 | 36 | 109 | 442 | 885 | Recovery |
| | **Renal tubular cell carcinoma**<br>No incidence | | | | | | |

*Statistically significant ($p < 0.05$) based on analysis of data conducted by study authors.
**Statistically significant difference from control group ($p < 0.05$), as reported by Chronic Hazard Advisory Panel (CPSC, 2001).
[a]DINP formulation referenced when the study authors provided the specific formulation.
[b]Calculated as follows: [% in diet × intake food (mg)] ÷ body weight (kg) = mg/kg-day
[c]Incidence data as reported by Chronic Hazard Advisory Panel (CPSC, 2001).Percent change compared to control = ([treated value − control value] ÷ control value) x 100

BUN = blood urea nitrogen; NE = not examined

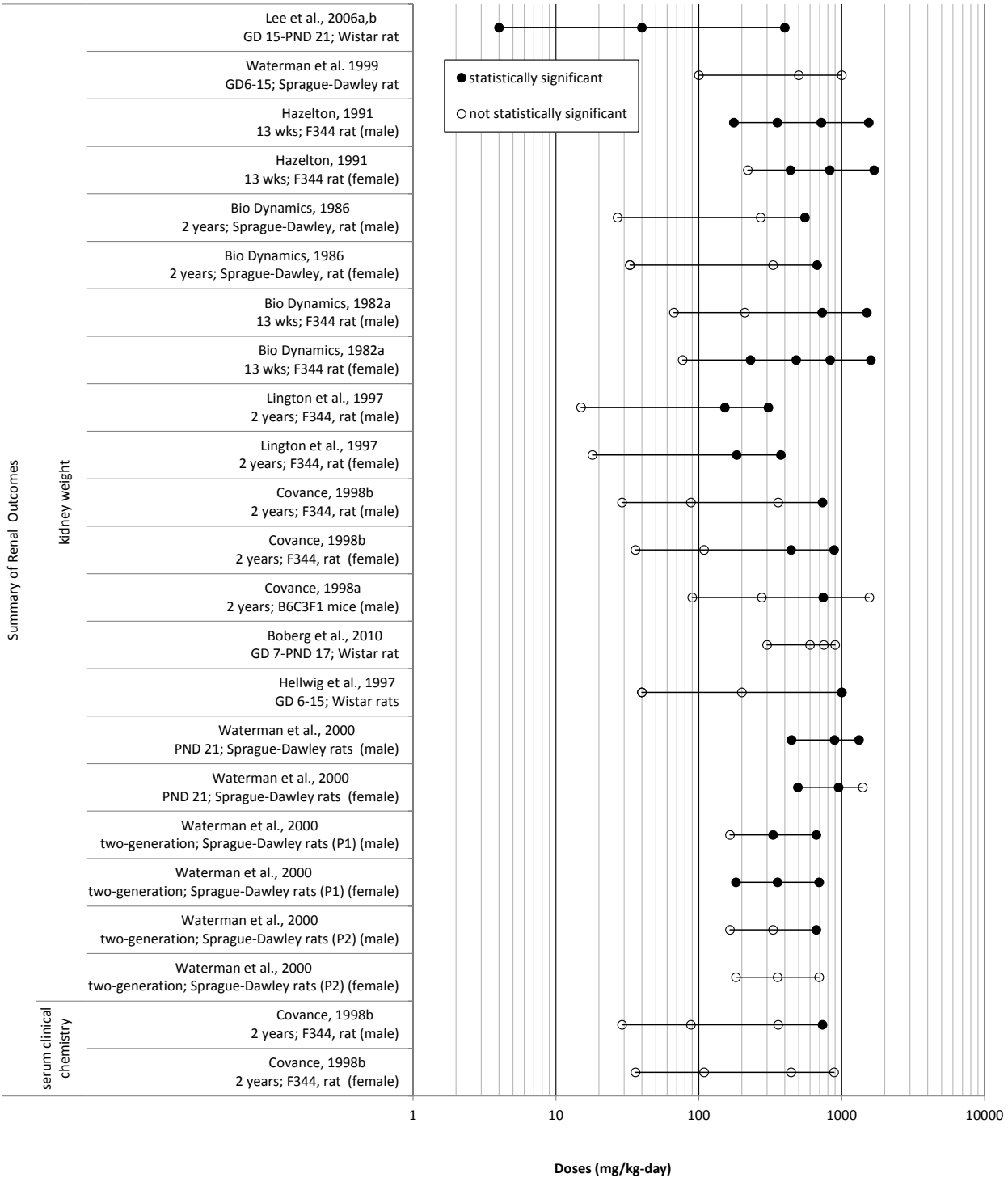


**Figure 3-4. Exposure-response array of kidney weight effects following oral exposure to DINP.**

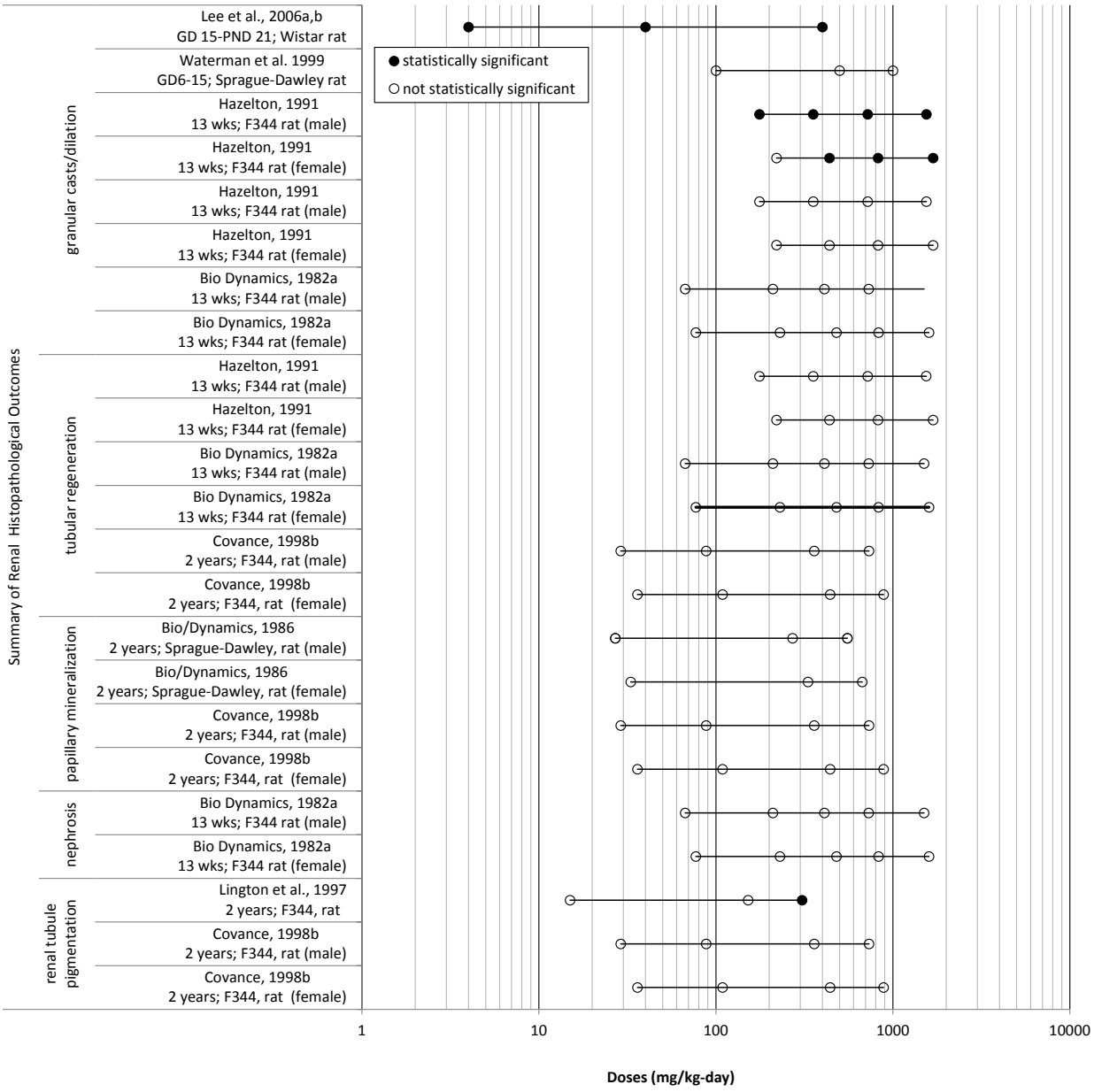


**Figure 3-5. Exposure-response array of kidney histopathological effects following oral exposure to DINP.**

## 3.3.3. Male Reproductive Effects

**Table 3-13. Evidence pertaining to male reproductive effects in animals following oral exposure to DINP**

| Reference and study design | Results | | | | | |
|---|---|---|---|---|---|---|
| *Anogenital distance (AGD)*[b] | | | | | | |
| Boberg et al. (2011)<br>Rat (Wistar); AGD assessed in 9–10 litters/dose<br>0, 300, 600, 750, 900 mg/kg-day<br>Gavage in corn oil (DINP-2)<br>GD 7–PND 17 | **AGD/BW$^{1/3}$** *(percent change compared to control)* | | | | | |
| | Doses | 0 | 300 | 600 | 750 | 900 |
| | *PND 1* | 0% | −1% | −2% | −3% | −5*% |
| | Note: When more than one pup per litter was examined, statistical analysis was adjusted using litter as an independent, random and nested factor. Author sent original data for this endpoint. | | | | | |
| Clewell et al. (2013b)<br>Rat (Sprague-Dawley); 20 dams (litters)/dose; 25 control dams (litters)<br>0, 760, 3,800, 11,400 ppm (0, 109, 555, 1,513 mg/kg-day)<br>Diet (DINP-1)<br>GD 12–PND 14 | **AGD/BW$^{1/3}$** *(percent change compared to control)* | | | | | |
| | Doses | 0 | 109 | 555 | 1,513 | |
| | *PND 2* | 0% | 2% | 2% | −1% | |
| | *PND 14* | 0% | −1% | −2% | −7*% | |
| | Note: The litter was the statistical unit of comparison. | | | | | |
| Clewell et al. (2013a)<br>Rat (Sprague-Dawley); 4–9 dams/timepoint/dose; AGD assessed in 8 litters/dose and 9 control litters<br>0, 50, 250, 750 mg/kg-day<br>Gavage in corn oil (DINP-1)<br>GDs 12–19; dams sacrificed 0.5, 1, 2, 6, 12, and 24 hours after final dose | **AGD/BW$^{1/3}$** *(percent change compared to control)* | | | | | |
| | Doses | 0 | 109 | 555 | 1,513 | |
| | *GD 20* | 0% | −3% | −2% | 0.7% | |
| | Note: The litter was the statistical unit of comparison. | | | | | |
| Lee et al. (2006b)[c]<br>Rat (Wistar-Imamichi); number of dams/dose not reported; 16–47 pups/sex/dose<br>0, 40, 400, 4,000, 20,000 ppm (0, 4, 40, 400, 2,000 mg/kg-day)[c]<br>Diet (DINP-2)<br>GD 15 to PND 21 | **AGD/BW$^{1/3}$** *(percent change compared to control)* | | | | | |
| | Doses | 0 | 4 | 40 | 400 | 2,000 |
| | *PND 1* | 0% | 4*% | 5*% | 6*% | 9*% |
| | Note: The individual was the statistical unit of comparison. | | | | | |

| Reference and study design | Results | | | | |
|---|---|---|---|---|---|
| Masutomi et al. (2003) | **Absolute AGD** *(percent change compared to control)* | | | | |
| Rats (Sprague-Dawley); 5 dams/dose; AGD was assessed in 5 litters/dose<br>0, 400, 4,000, 20,000 ppm<br>Gestation: 0, 30.7, 306.7, 1,164.5 mg/kg-day<br>Lactation: 0, 66.2, 656.7, 2,656.7 mg/kg-day<br>Diet (DINP-2)<br>GD 15–PND 10 | Doses | 0 | 66.2 | 656.7 | 2,656.7 |
| | *PND 2* | 0% | −3% | −9% | −9% |
| | Note: The litter was the statistical unit of comparison. | | | | |
| *Nipple retention* | | | | | |
| **Boberg et al. (2011)**<br>Rat (Wistar); nipple retention assessed in 9–10 litters/dose<br>0, 300, 600, 750, 900 mg/kg-day<br>Gavage in corn oil (DINP-2)<br>GD 7–PND 17 | **Nipple retention** *(percent change compared to control in litters)* | | | | |
| | Doses | 0 | 300 | 600 | 750 | 900 |
| | *PND 13* | 0% | 1% | 47% | 59*% | 60*% |
| | Note: When more than one pup per litter was examined, statistical analysis was adjusted using litter as an independent, random and nested factor. Author sent original data for this endpoint. | | | | | |
| **Clewell et al. (2013b)** | **Nipple retention** *(percent change compared to control in litters)* | | | | |
| Rat (Sprague-Dawley); 20 dams (litters)/dose; 24 control dams (litters)<br>0, 760, 3,800, 11,400 ppm (0, 109, 555, 1,513 mg/kg-day)<br>Diet (DINP-1)<br>GD 12–PND 14 | Doses | 0 | 109 | 555 | 1,513 |
| | *PND 14* | 0% | −6% | 6% | 17% |
| | Note: The litter was the statistical unit of comparison. | | | | |
| *Fetal testicular testosterone production* | | | | | |
| **Adamsson et al. (2009)**[c]<br>Rat (Sprague-Dawley); 7–8 dams/dose; fetal testosterone production assessed in 5–8 litters/dose<br>0, 250, 750 mg/kg-day<br>Gavage in corn oil<br>EDs 13.5–17.5 | **Intratesticular testosterone content** *(percent change compared to control in litters)* | | | | |
| | Doses | 0 | 250 | 750 | |
| | *ED 19.5* | 0% | 3% | −16% | |
| | Note: The litter was the statistical unit of comparison. | | | | |

| Reference and study design | Results | | | | |
|---|---|---|---|---|---|
| **Boberg et al. (2011)**<br>Rat (Wistar); fetal testosterone production assessed in 3–4 litters/dose (1–2 testes/litter)<br>0, 300, 600, 750, 900 mg/kg-day<br>Gavage in corn oil (DINP-2)<br>GDs 7–21 | **Fetal testicular testosterone production** *(percent change compared to control in litters)* | | | | |
| | Doses | 0 | 300 | 600 | 750 | 900 |
| | *GD 21* | 0% | −51% | −75% | −69% | −76% |
| | Note: When more than one pup per litter was examined, statistical analysis was adjusted using litter as an independent, random and nested factor. | | | | |
| **Borch et al. (2004)**[c]<br>Rat (Wistar); 8 dams/dose; fetal testosterone production assessed in 7–8 litters/dose (2 testes/litter)<br>0, 750 mg/kg-day<br>Gavage in peanut oil (DINP-2)<br>GDs 7–21 | **Fetal testicular testosterone production** *(percent change compared to control in litters)* | | | | |
| | Doses | 0 | 750 | | |
| | *GD 21* | 0% | −73*% | | |
| | Note: The litter was the statistical unit of comparison. | | | | |
| **Clewell et al. (2013a)**<br>Rat (Sprague-Dawley); 4–9 dams/timepoint/dose; Assessed in 8 litters/dose and 9 control litters<br>0, 50, 250, 750 mg/kg-day<br>Gavage in corn oil (DINP-1)<br>GDs 12–19; dams sacrificed 0.5, 1, 2, 6, 12, and 24 hours after final dose | **Fetal testicular testosterone production** *(percent change compared to control in litters)* | | | | |
| | Doses | 0 | 109 | 555 | 1,513 |
| | *2 hours following final dose* | 0% | 4% | −50*% | −65*% |
| | *24 hours following final dose* | 0% | −16% | 61% | 22% |
| | Note: The litter was the statistical unit of comparison. | | | | |
| **Hannas et al. (2011)**<br>Rat (Sprague-Dawley); 3–6 dams/group, 3–6 litters DINP1, 3 dams/group, 1–3 litters DINP 2<br>0, 500, 750, 1,000, 1,500 mg/kg-day<br>Gavage in corn oil (DINP-1 and DINP-2)<br>GDs 14–18 | **Fetal testicular testosterone production** *(percent change compared to control in litters)* | | | | |
| | Doses | 0 | 500 | 750 | 1,000 | 1,500 |
| | *GD 18* | 0% | −30*% | −45*% | −57*% | −69*% |
| | Note: The litter was the statistical unit of comparison. Litter means from DINP-1- and DINP-2-treated rats were combined for statistical analysis. | | | | | |

| Reference and study design | Results | | | | |
|---|---|---|---|---|---|
| Adamsson et al. (2009)[c]<br>Rat (Sprague-Dawley); 7–8 dams/dose; fetal testosterone production assessed in 5–8 litters/dose<br>0, 250, 750 mg/kg-day<br>Gavage in corn oil<br>EDs 13.5–17.5 | **Intratesticular testosterone content** *(percent change compared to control in litters)*<br>Doses: 0 / 250 / 750<br>*ED 19.5*: 0% / 3% / −16%<br>Note: The litter was the statistical unit of comparison. | | | | |
| *Sperm motility* | | | | | |
| Boberg et al. (2011)[c]<br>Rat (Wistar); semen quality analysis in 1–3 males/litter (6–10 males/dose)<br>0, 300, 600, 750, 900 mg/kg-day<br>Gavage in corn oil (DINP-2)<br>GD 7–PND 17 | **Sperm motility at PND 90** *(percent change compared to control in litters)*<br>Doses: 0 / 300 / 600 / 750 / 900<br>*PND 90*: 0% / −4% / −13*% / −19*% / −20*%<br>Note: When more than one pup per litter was examined, statistical analysis was adjusted using litter as an independent, random and nested factor. Author sent original data for this endpoint. | | | | |
| *Malformations* | | | | | |
| Clewell et al. (2013b)<br>Rat (Sprague-Dawley); 20 dams (litters)/dose; 24 control dams (litters)<br>0, 760, 3,800, 11,400 ppm (0, 109, 555, 1,513 mg/kg-day)<br>Diet (DINP-1)<br>GD 12–PND 14 | **Hypospadias, PNDs 49–50** *(incidence/total pups)*<br>*Doses*: 0 / 109 / 555 / 1,513<br>*incidence*: 1/111 / 0/87 / 0/83 / 2/84<br>*percent*: 0.9% / 0% / 0% / 2%<br>Note: Study authors listed positive effect as very slight/borderline hypospadias. Other effects were evaluated (epididymal agenesis, incomplete epididymis, flaccid epididymis, undescended testes, unilateral enlarged testis, atrophic testis, absent seminal vesicles) but no effects were observed by study authors (quantitative data reported but not presented in evidence tables). | | | | |
| Gray et al. (2000)<br>Rat (Sprague-Dawley); 14 exposed dams, 19 control dams<br>0, 750 mg/kg-day<br>Gavage in corn oil (DINP-1)<br>GD 14–PND 3 | **Epididymal agenesis**<br>Doses: 0 / 750<br>*incidence*: 0/80 / 4/52*<br>*percent*: 0* / 8% | | | | |

| Reference and study design | Results | | | | |
|---|---|---|---|---|---|
| *Histopathological changes* | | | | | |
| **Bio Dynamics (1986)**<br>Rat (Sprague-Dawley); 70/sex/dose<br>0, 760, 3,800, 11,400 ppm (0, 109, 555, 1,513 mg/kg-day)<br>0, 500, 5,000, 10,000 ppm (0, 27, 271, 553 mg/kg-day in males; 0, 33, 331, 672 mg/kg-day in females)<br>Diet (DINP-1)<br>Diet (Santicizer 900)<br>2 years (interim sacrifice at 1 year) | No hyperplasia at interim sacrifice | | | | |
| | Doses | 0 | | 553 | |
| | **Unilateral interstitial cell hyperplasia** | | | | |
| | *incidence* | 3/69 | | 9/70 | |
| | *percent* | 4% | | 13% | |
| | **Bilateral interstitial cell hyperplasia** | | | | |
| | *incidence* | 1/69 | | 13/70 | |
| **Boberg et al. (2011)**<br>Rat (Wistar); 3–4 litters/dose; one testis section evaluated from 1–4 males/litter<br>0, 300, 600, 750, 900 mg/kg-day<br>Gavage in corn oil (DINP-2)<br>GDs 7–21 | **Multinucleated gonocytes** *(affected litters/total number of litters)* | | | | |
| | Doses | 0 | 300 | 600 | 750 | 900 |
| | *incidence* | 0/3 | 2/4 | 3/3 | 3/3 | 3/3 |
| | *percent* | 0% | 50% | 100*% | 100*% | 100*% |
| **Clewell et al. (2013b)**<br>Rat (Sprague-Dawley); 20 dams (litters)/dose; 24 control dams (litters)<br>0, 760, 3,800, 11,400 ppm (0, 109, 555, 1,513 mg/kg-day)<br>Diet (DINP-1)<br>GD 12–PND 14 | **Multinucleated germ cells *(affected animals/total number of animals PND 2)*** | | | | |
| | Doses | 0 | 109 | 555 | 1,513 |
| | *incidence* | 1/24 | 2/20 | 7/20* | 18/19* |
| | *percent* | 4% | 10% | 35*% | 95*% |
| | **Leydig cell aggregates** | | | | |
| | *incidence* | 4/24 | 4/20 | 8/20 | 19/19* |
| | *percent* | 17% | 20% | 40% | 100%* |
| **Clewell et al. (2013a)**<br>Rat (Sprague-Dawley); 4–9 dams/timepoint/dose; Assessed in 8 litters/dose and 9 control litters<br>0, 50, 250, 750 mg/kg-day<br>Gavage in corn oil (DINP-1)<br>GDs 12–19; dams sacrificed 0.5, 1, 2, 6, 12, and 24 hours after final dose | **Multinucleated gonocytes (24 hours following final dose)** *(affected animals/total number of litters)* | | | | |
| | Doses | 0 | 50 | 250 | 750 |
| | *incidence* | 0/25 | 0/8 | 2/8 | 6/7* |
| | **Leydig cell aggregates (24 hours following final dose)** *(affected animals/total number of litters)* | | | | |
| | *incidence* | 2/25 | 3/8 | 1/8 | 7/7* |

| Reference and study design | Results |
|---|---|
| *Testes weight change* | |
| **Boberg et al. (2011)**<br>Rat (Wistar); testes weighed in 6–10 litters/group (1–7 males/litter, 18–35 males/group)<br>0, 300, 600, 750, 900 mg/kg-day<br>Gavage in corn oil (DINP-2)<br>GD 7–PND 17 | ***Testes weight at PND 90*** *(percent change compared to control)*<br>Doses: 0 / 300 / 600 / 750 / 900<br>*absolute weight (right)*: 0% / −1% / 4% / −4% / 0%<br>*absolute weight (left)*: 0% / −1% / 2% / −3% / 3%<br>Note: When more than one pup per litter was examined, statistical analysis was adjusted using litter as an independent, random and nested factor. |
| **Clewell et al. (2013b)**<br>Rat (Sprague-Dawley); 20 dams(litters)/dose; 24 control dams (litters); testes weighed in 1 pup/litter<br>0, 760, 3,800, 11,400 ppm (0, 109, 555, 1,513 mg/kg-day)<br>Diet (DINP-1)<br>GD 12–PND 14 | ***Testes weight at PND 2*** *(percent change compared to control)*<br>Doses: 0 / 109 / 555 / 1,513<br>*absolute weight (right)*: 0% / 2% / 2% / −2%<br>*absolute weight (left)*: 0% / 0% / 3% / −2% |
| **Masutomi et al. (2003)**<br>Rats (Sprague-Dawley); 5 dams/dose; testes weighed in 5 male pups/dose<br>0, 400, 4,000, 20,000 ppm<br>Gestation: 0, 30.7, 306.7, 1,164.5 mg/kg-day<br>Lactation: 0, 66.2, 656.7, 2,656.7 mg/kg-day<br>Diet (DINP-2)<br>GD 15–PND 10 | ***Testes weight at PND 27*** *(percent change compared to control)*<br>Doses: 0 / 30.7 / 306.7 / 1,164.5<br>*absolute weight*: 0% / 4% / −21% / −54*%<br>Note: There was no significant treatment-related effect on testes weight at PNW 11. |

| Reference and study design | Results | | | | | | |
|---|---|---|---|---|---|---|---|
| Covance Laboratories (1998a)<br>Mouse (B6C3F$_1$); 70/sex/dose (35–40/dose used for this endpoint)<br>0, 500, 1,500, 4,000, 8,000 ppm (0, 90, 276, 742, 1,560 mg/kg-day in males; 0, 112, 336, 910, 1,888 mg/kg-day in females)<br>Recovery group (55/sex/group): 8,000 ppm (1,377 mg/kg-day in males; 1,581 mg/kg-day in females<br>Diet<br>Main study: 2 years (interim sacrifice at 79 weeks)<br>Recovery group: 78 weeks, followed by a 26-week recovery period with basal diet alone | ***Testes weight at terminal sacrifice*** *(percent change compared to control)* | | | | | | |
| | Doses | 0 | 90 | 276 | 742 | 1,560 | Recovery |
| | *absolute weight* | 0% | 0% | −3% | −10*% | −21*% | −10*% |
| Waterman et al. (2000); one-generation study<br>Rat (Sprague-Dawley), 30 breeding pairs/dose<br>0, 0.5, 1, 1.5% (0, 446, 889.5, 1.321 mg/kg-day in males<br>0, 493.5, 951.5, 1.404 mg/kg-day in premating females<br>0, 390.5, 768.5, 1.136.5 mg/kg-day during gestation in females<br>0, 706.5, 1.384, 1.760 mg/kg-day during lactation in females)[d]<br>Diet (DINP-1)<br>10 weeks prior to mating, and through mating (M) or PND 21 (F) | ***Testes weight in P1 males*** *(percent change compared to control)* | | | | | | |
| | Doses | | 0 | 446 | 889.5 | | 1,321 |
| | *absolute weight (left)* | | 0% | 3% | 5% | | 11*% |
| | *absolute weight (right)* | | 0% | 1% | 4% | | 9*% |

| Reference and study design | Results | | | | |
|---|---|---|---|---|---|
| Waterman et al. (2000); two-generation study<br>Rat (Sprague-Dawley), 30 breeding pairs/dose/generation<br>0, 0.2, 0.4, 0.8%<br>P1 animals[d]<br>0, 165, 331, 665 mg/kg-day in males<br>0, 182, 356, 696 mg/kg-day in premating females<br>0, 146, 287, 555 mg/kg-day during gestation in females<br>0, 254, 539, 1,026 mg/kg-day during lactation in females<br>P2 (F1) animals[d]<br>0, 189, 379, 779 mg/kg-day in males<br>0, 197, 397, 802 mg/kg-day in premating females<br>0, 143, 288, 560 mg/kg-day during gestation in females<br>0, 285, 553, 1,229 mg/kg-day during lactation in females<br>Diet (DINP-1)<br>10 weeks prior to mating, and through mating (M) or PND 21 (F) | ***Testes weight in P1 males*** *(percent change compared to control)* | | | | |
| | Doses | 0 | 165 | 331 | 665 |
| | *absolute weight (left)* | 0% | 1% | 2% | 2% |
| | *absolute weight (right)* | 0% | 2% | 3% | 2%% |
| | **P2 (F1) males** | | | | |
| | Doses | 0 | 189 | 379 | 779 |
| | *absolute weight (left)* | 0% | 0% | −1.5% | 3% |
| | *absolute weight (right)* | 0% | 3% | 1% | 4% |
| *Prostate weight* | | | | | |
| Boberg et al. (2011)<br>Rat (Wistar); 6−10 litters/group (1−7 males/litter, 18−35 males/dose)<br>0, 300, 600, 750, 900 mg/kg-day<br>Gavage in corn oil (DINP-2)<br>GD 7−PND 17 | **Prostate weight at PND 90** *(percent change compared to control)* | | | | |
| | Doses | 0 | 300 | 600 | 750 | 900 |
| | *absolute weight* | 0% | 0% | 2% | −4% | −12% |
| | Note: When more than one pup per litter was examined, statistical analysis was adjusted using litter as an independent, random and nested factor | | | | | |
| Clewell et al. (2013b)<br>Rat (Sprague-Dawley); 20 dams (litters)/dose; 24 control dams (litters); testes weighed in 1 pup/litter<br>0, 760, 3,800, 11,400 ppm (0, 109, 555, 1,513 mg/kg-day)<br>Diet (DINP-1) | ***Ventral prostate at PNDs 49−50*** *(percent change compared to control)* | | | | |
| | Doses | 0 | 109 | 555 | 1,513 |
| | *absolute weight* | 0% | 8% | 0% | −8% |

| Reference and study design | Results | | | | |
|---|---|---|---|---|---|
| GD 12–PND 14 | | | | | |
| Waterman et al. (2000); one-generation study<br>Rat (Sprague-Dawley), 30 breeding pairs/dose<br>0, 0.5, 1, 1.5% (0, 446, 889.5, 1,321 mg/kg-day in males<br>0, 493.5, 951.5, 1,404 mg/kg-day in premating females<br>0, 390.5, 768.5, 1,136.5 mg/kg-day during gestation in females<br>0, 706.5, 1,384, 1,760 mg/kg-day during lactation in females)[d]<br>Diet (DINP-1)<br>10 weeks prior to mating, and through mating (M) or PND 21 (F) | ***Prostate weight*** *(percent change compared to control)* | | | | |
| | Doses | 0 | 446 | 889.5 | 1,321 |
| | *absolute weight* | 0% | 5% | 5% | −7% |
| Waterman et al. (2000); two-generation study<br>Rat (Sprague-Dawley), 30 breeding pairs/dose/generation<br>0, 0.2, 0.4, 0.8%<br>P1 animals[d]<br>0, 165, 331, 665 mg/kg-day in males<br>0, 182, 356, 696 mg/kg-day in premating females<br>0, 146, 287, 555 mg/kg-day during gestation in females<br>0, 254, 539, 1,026 mg/kg-day during lactation in females<br>P2 (F1) animals[d]<br>0, 189, 379, 779 mg/kg-day in males<br>0, 197, 397, 802 mg/kg-day in premating females<br>0, 143, 288, 560 mg/kg-day during gestation in females<br>0, 285, 553, 1,229 mg/kg-day during lactation in females<br>Diet (DINP-1)<br>10 weeks prior to mating, and through mating (M) or PND 21 (F) | ***Prostate weight in P1 males*** *(percent change compared to control)* | | | | |
| | Doses | 0 | 165 | 331 | 665 |
| | *absolute weight* | 0% | 2% | −8% | 0% |
| | **P2 (F1) males** | | | | |
| | *absolute weight* | 0% | −2% | −2% | −4% |

| Reference and study design | Results | | | | |
|---|---|---|---|---|---|
| *Epididymis weight* | | | | | |
| **Boberg et al. (2011)**<br>Rat (Wistar); 6–10 litters/group (1–7 males/litter, 18–35 males/dose)<br>0, 300, 600, 750, 900 mg/kg-day<br>Gavage in corn oil (DINP-2)<br>GD 7–PND 17 | **Left epididymis weight at PND 90** *(percent change compared to control)* | | | | |
| | Doses | 0 | 300 | 600 | 750 | 900 |
| | *absolute weight* | 0% | −3.4% | 0% | −5.2% | 0% |
| | Note: When more than one pup per litter was examined, statistical analysis was adjusted using litter as an independent, random and nested factor. | | | | | |
| **Clewell et al. (2013b)**<br>Rat (Sprague-Dawley); 20 dams(litters)/dose; 24 control dams (litters); testes weighed in 1 pup/litter<br>0, 760, 3,800, 11,400 ppm (0, 109, 555, 1,513 mg/kg-day)<br>Diet (DINP-1)<br>GD 12–PND 14 | ***Epididymis weight at PNDs 49–50*** *(percent change compared to control)* | | | | |
| | Doses | 0 | 109 | 555 | 1,513 |
| | *absolute weight (right)* | 0% | 10% | 5% | 0% |
| | *absolute weight (left)* | 0% | 5% | 0% | −5% |
| **Waterman et al. (2000)**; one-generation study<br>Rat (Sprague-Dawley), 30 breeding pairs/dose<br>0, 0.5, 1, 1.5% (0, 446, 889.5, 1,321 mg/kg-day in males<br>0, 493.5, 951.5, 1,404 mg/kg-day in premating females<br>0, 390.5, 768.5, 1,136.5 mg/kg-day during gestation in females<br>0, 706.5, 1,384, 1,760 mg/kg-day during lactation in females)[d]<br>Diet (DINP-1)<br>10 weeks prior to mating, and through mating (M) or PND 21 (F) | ***Epididymis weight in P1 males*** *(percent change compared to control)* | | | | |
| | Doses | 0 | 446 | 889.5 | 1,321 |
| | *absolute weight (right)* | 0% | -1% | 3% | 7% |
| | *absolute weight (left)* | 0% | 3% | 4% | 7% |

| Reference and study design | Results | | | | |
|---|---|---|---|---|---|
| Waterman et al. (2000); two-generation study<br><br>Rat (Sprague-Dawley), 30 breeding pairs/dose/ generation<br><br>0, 0.2, 0.4, 0.8%<br>P1 animals[d]<br>0, 165, 331, 665 mg/kg-day in males<br>0, 182, 356, 696 mg/kg-day in premating females<br>0, 146, 287, 555 mg/kg-day during gestation in females<br>0, 254, 539, 1,026 mg/kg-day during lactation in females<br>P2 (F1) animals[d]<br>0, 189, 379, 779 mg/kg-day in males<br>0, 197, 397, 802 mg/kg-day in premating females<br>0, 143, 288, 560 mg/kg-day during gestation in females<br>0, 285, 553, 1,229 mg/kg-day during lactation in females<br><br>Diet (DINP-1)<br><br>10 weeks prior to mating, and through mating (M) or PND 21 (F) | **Epididymis weight in P1 males** *(percent change compared to control)* | | | | |
| | Doses | 0 | 165 | 331 | 665 |
| | *absolute weight (right)* | 0% | −2% | 0% | 1% |
| | *absolute weight (left)* | 0% | 2% | 1% | 4% |
| | **P2 (F1) males** | | | | |
| | Doses | 0 | 189 | 379 | 779 |
| | *absolute weight (right)* | 0% | 2% | 1% | 7% |
| | *absolute weight (left)* | 0% | 2% | 0% | 6% |

*Statistically significant ($p < 0.05$) based on analysis of data conducted by study authors.
[a]DINP formulation referenced when the study authors provided the specific formulation.
[b]Normalized to the cube root of body weight
[c]Values reported by the study authors were estimated from published graphs using "Grab It!", a Microsoft Excel based free software application used to digitizes data from image files. Publisher: www.datatrendsoftware.com.
[d]Calculated as follows: [% in diet × intake food/water (mg)] ÷ body weight (kg) = mg/kg-day
Percent change compared to control = ([treated value − control value] ÷ control value) x 100

ED = estrous day; PNW = postnatal week

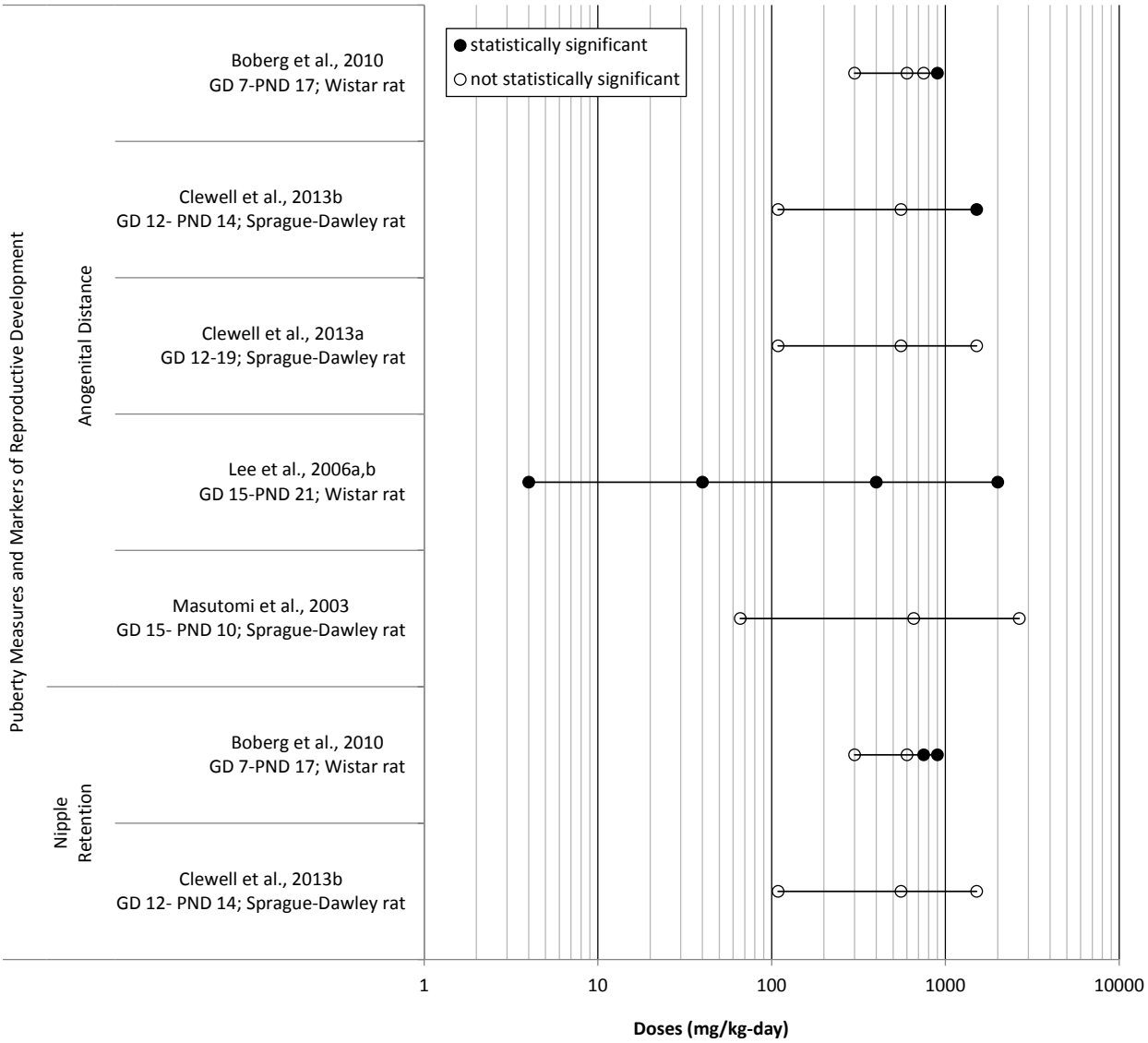


**Figure 3-6. Exposure-response array of male reproductive puberty effects following oral exposure to DINP.**

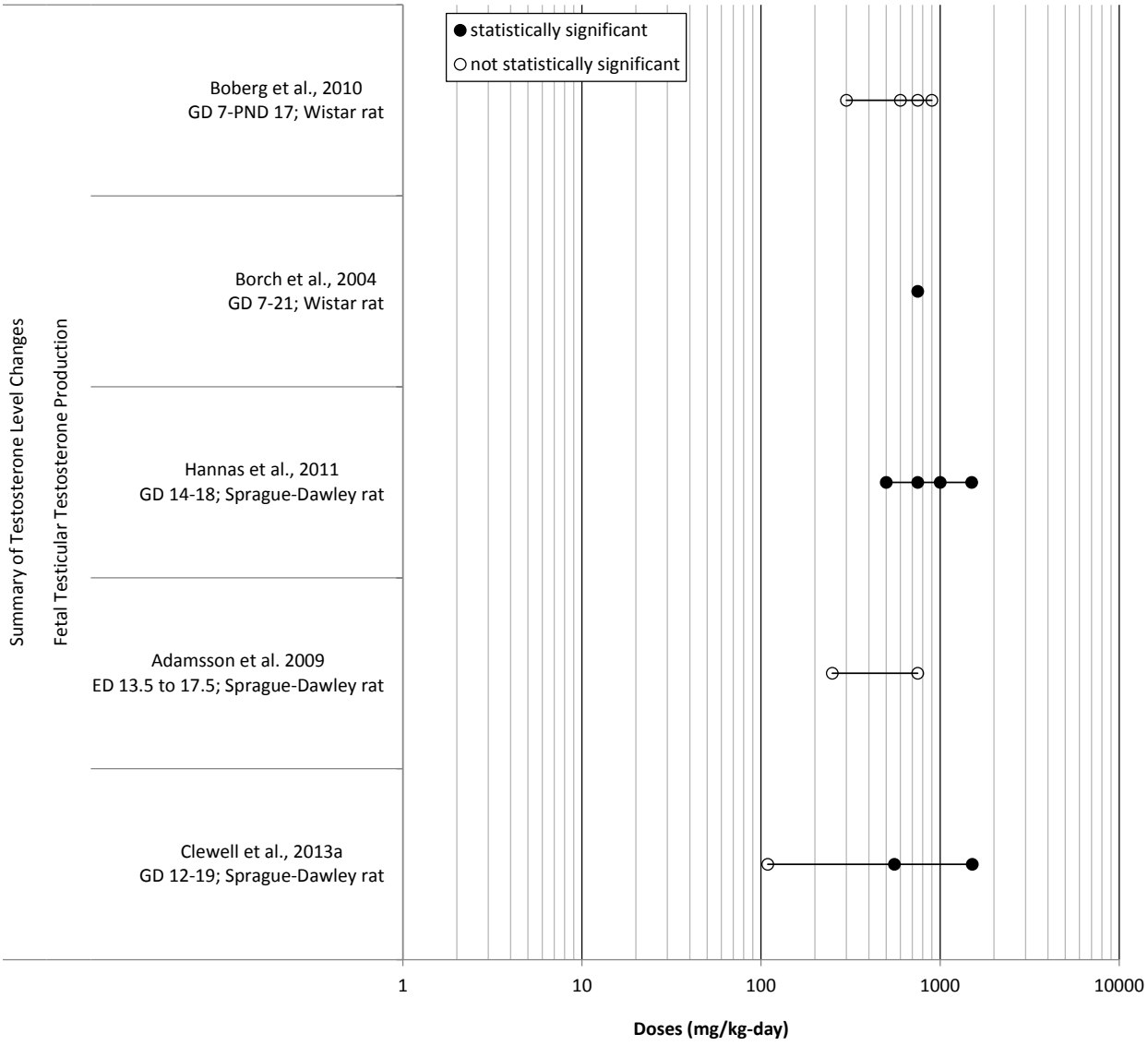


**Figure 3-7. Exposure-response array of male reproductive testosterone effects following oral exposure to DINP.**

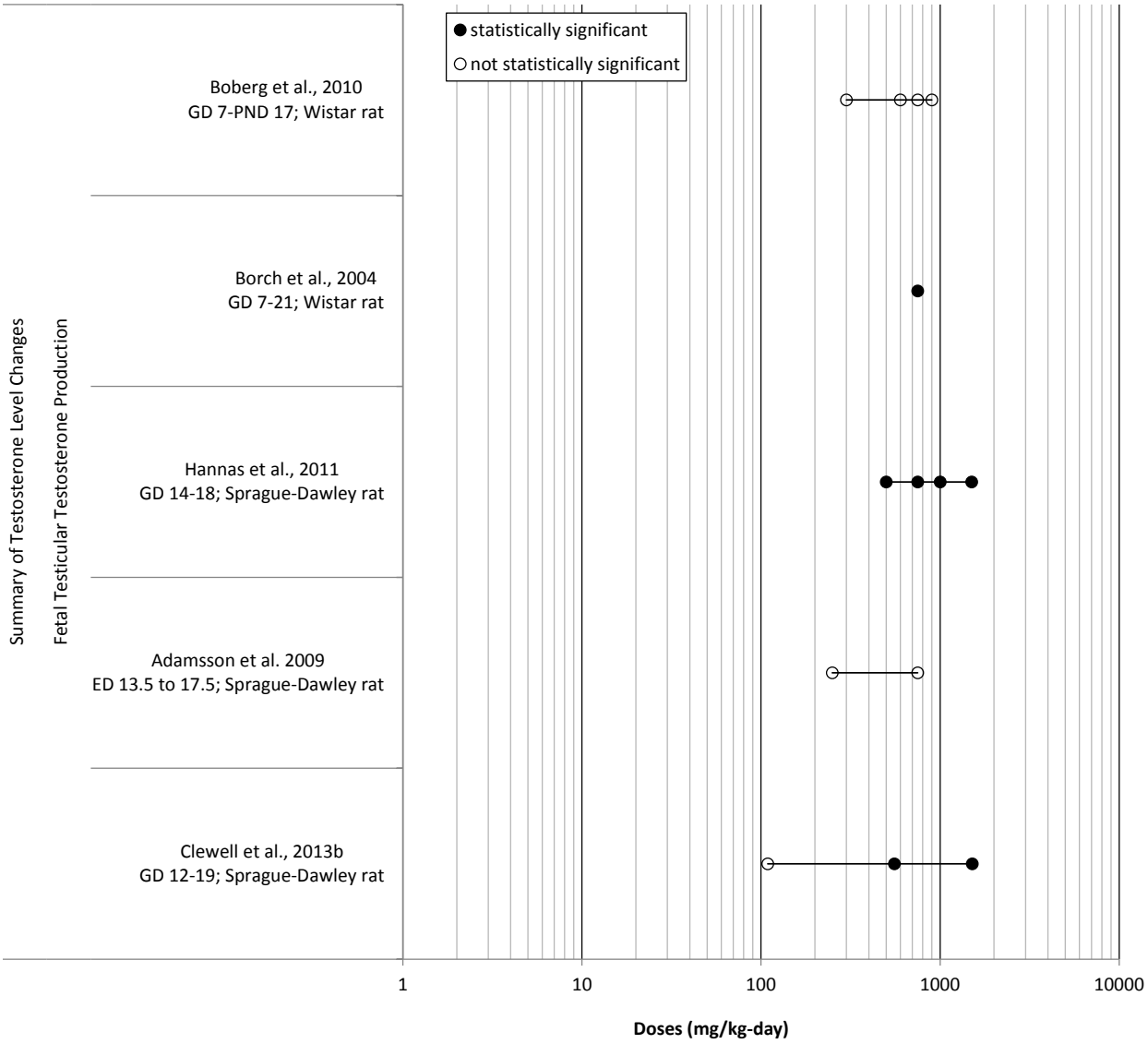


**Figure 3-8. Exposure-response array of male reproductive histopathological effects following oral exposure to DINP.**

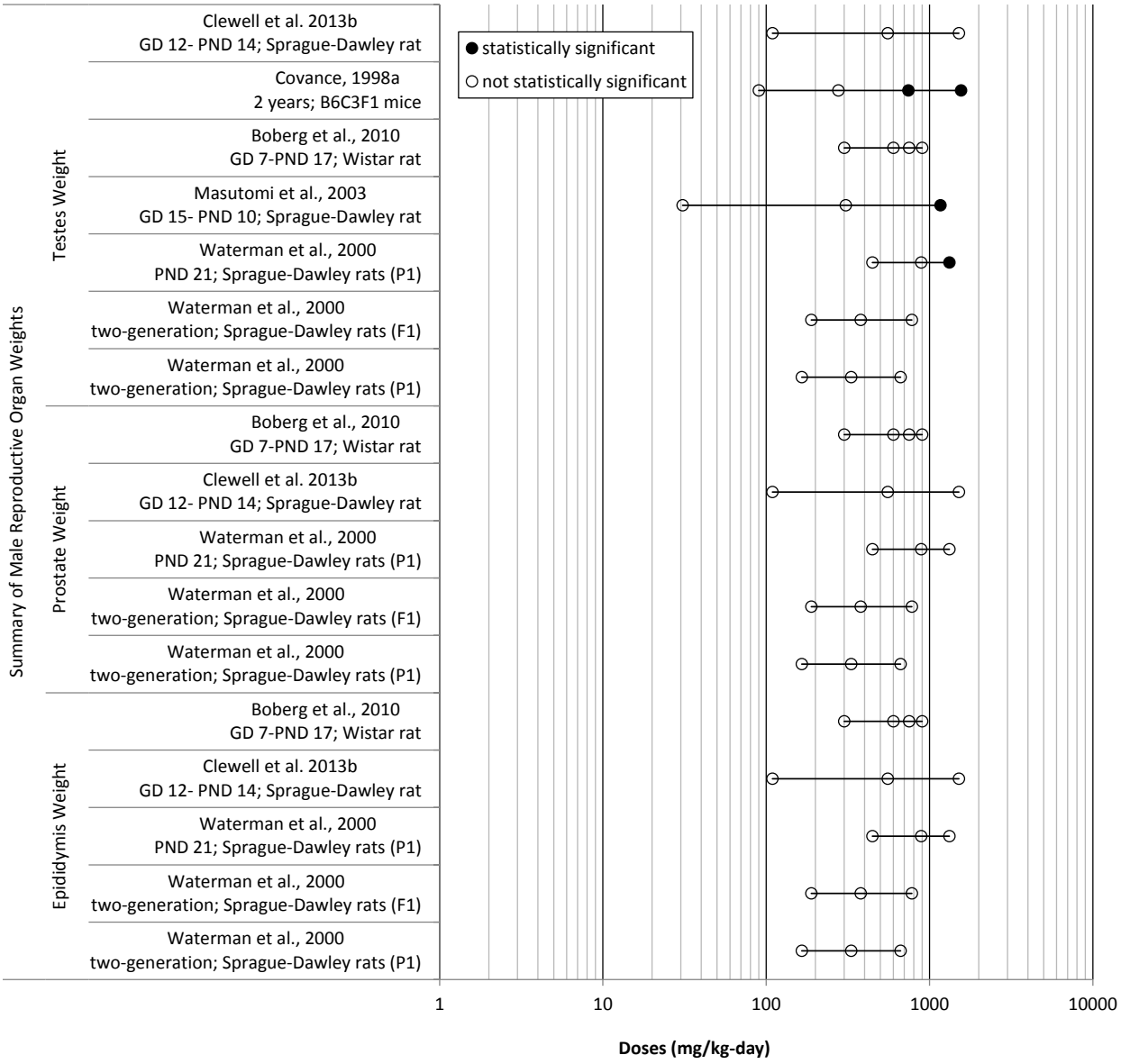


**Figure 3-9. Exposure-response array of male reproductive organ weight effects following oral exposure to DINP.**

### 3.3.4. Female Reproductive Effects

**Table 3-14. Evidence pertaining to female reproductive effects in animals following oral exposure to DINP**

| Reference and study design[a] | Results | | | | | |
|---|---|---|---|---|---|---|
| *Fertility* | | | | | | |
| Boberg et al. (2011)<br>Rat (Wistar); 12 dams/dose<br>0, 300, 600, 750, 900 mg/kg-day<br>Gavage in corn oil (DINP-2)<br>GD 7–PND 17<br>Note: 16 dams/dose were used overall, however 4 dams/dose were only exposed GDs 7–21 and sacrificed at GD 21 for fetal testosterone assessment. | **Post implantation loss (resorptions plus dead fetuses, mean %)** | | | | | |
| | Doses | 0 | 300 | 600 | 750 | 900 |
| | *percent* | 23% | 15% | 14% | 10% | 19% |
| Hellwig et al. (1997)<br>Rat (Wistar), 8–10 dams/dose per DINP formulation<br>0, 40, 200, 1,000 mg/kg-day<br>Gavage in olive oil (DINP-1,2,3)<br>GDs 6–15; dams sacrificed on GD 20 | *(Percent change compared to control)* | | | | | |
| | Doses | | 0 | 40 | 200 | 1,000 |
| | **Implantations (mean/dam)** | | | | | |
| | *DINP-1* | | 0% | −16% | −3% | −13% |
| | *DINP-2* | | 0% | −13%* | −7% | −3% |
| | *DINP-3* | | 0% | −6% | 0% | −9% |
| | **Resorptions (mean)** | | | | | |
| | *DINP-1* | | 0% | −57% | 100% | −14% |
| | *DINP-2* | | 0% | 0% | 57% | 71% |
| | *DINP-3* | | 0% | 29% | 0% | 43% |
| | **Post implantation loss (resorptions plus dead fetuses, mean %)** | | | | | |
| | *DINP-1* | | 4.1% | 2.0% | 9.0% | 4.1% |
| | *DINP-2* | | 4.1% | 4.5% | 7.5% | 7.8% |
| | *DINP-3* | | 4.1% | 6.1% | 4.3% | 6.2% |
| (Lee et al. (2006b); Lee et al. (2006a))<br>Rat (Wistar-Imamichi); 6–12 females/dose, four litters per group<br>0, 40, 400, 4,000, 20,000 ppm (0, 4, 40, 400, 2,000 mg/kg-day)[c]<br>Diet (DINP-2)<br>GD 15–PND 21 | **Lordosis quotient at PNW 20** | | | | | |
| | Doses | 0 | 4 | 40 | 400 | 2,000 |
| | *percent* | 75% | −50*% | −45*% | −25*% | Not reported |

| Reference and study design[a] | Results | | | | |
|---|---|---|---|---|---|
| Waterman et al. (1999)<br>Rat (Sprague-Dawley); 23–25 dams/dose<br>0, 100, 500, 1,000 mg/kg-day<br>Gavage in corn oil (DINP-1)<br>GDs 6–15; dams sacrificed at GD 21 | *(percent change compared to control)* | | | | |
| | Doses | 0 | 100 | 500 | 1,000 |
| | **Implantations** *(mean/dam)* | 0% | −5% | 1% | −3% |
| | **Resorptions** *(mean/dam)* | 0% | 25% | −25% | 50% |
| | **Post implantation loss (resorptions plus dead fetuses),** *mean (%)* | 3.6% | 5.0% | 3.4% | 5.5% |
| Waterman et al. (2000); one-generation study<br>Rat (Sprague-Dawley), 30 breeding pairs/dose<br>0, 0.5, 1, 1.5%<br>(0, 446, 889.5, 1,321 mg/kg-day in males<br>0, 493.5, 951.5, 1,404 mg/kg-day in premating females<br>0, 390.5, 768.5, 1,136.5 mg/kg-day during gestation in females<br>0, 706.5, 1,384, 1,760 mg/kg-day during lactation in females)[b]<br>Diet (DINP-1)<br>10 weeks prior to mating, and through mating (M) or PND 21 (F) | **Fertility** | | | | |
| | Doses | 0 | 493.5 | 951.5 | 1,404 |
| | *percent* | 96.7% | 90% | 100% | 93.3% |
| | **Fecundity** | | | | |
| | *percent* | 89.7% | 81.5% | 90% | 89.3% |
| Waterman et al. (2000); two-generation study<br>Rat (Sprague-Dawley), 30 breeding pairs/dose/ generation<br>0, 0.2, 0.4, 0.8%<br>P1 animals[b]<br>0, 165, 331, 665 mg/kg-day in males<br>0, 182, 356, 696 mg/kg-day in premating females<br>0, 146, 287, 555 mg/kg-day during gestation in females<br>0, 254, 539, 1,026 mg/kg-day during lactation in females<br>P2 (F1) animals[b]<br>0, 189, 379, 779 mg/kg-day in males<br>0, 197, 397, 802 mg/kg-day in premating females | **Fertility, P1 animals** | | | | |
| | Doses | 0 | 182 | 356 | 696 |
| | *Percent* | 93.3% | 93.1% | 90% | 93.3% |
| | **Fecundity, P1 animals** | | | | |
| | *Percent* | 92.9% | 88.9% | 88.9% | 85.7% |
| | **Fertility, P2 animals** | | | | |
| | Doses | *0* | *197* | *397* | *802* |
| | *Percent* | 90% | 93.3% | 83.3% | 80% |
| | **Fecundity, P2 animals** | | | | |
| | *Percent* | 77.8% | 75% | 80% | 70.8% |

| Reference and study design[a] | Results | | | | |
|---|---|---|---|---|---|
| 0, 143, 288, 560 mg/kg-day during gestation in females<br>0, 285, 553, 1,229 mg/kg-day during lactation in females<br><br>Diet (DINP-1)<br><br>10 weeks prior to mating, and through mating (M) or PND 21 (F) | | | | | |
| *Ovary effects* | | | | | |
| **Boberg et al. (2011)**<br><br>Rat (Wistar); 12 dams/dose<br><br>0, 300, 600, 750, 900 mg/kg-day<br><br>Gavage in corn oil (DINP-2)<br><br>GD 7–PND 17<br><br>Note: 16 dams/dose were used overall, however 4 dams/dose were only exposed GDs 7–21 and sacrificed at GD 21 for fetal testosterone assessment. | **Ovarian weight** *(percent change compared to control)* | | | | |
| | Doses | 0 | 300 | 600 | 750 | 900 |
| | | 0% | 10% | 9% | 1% | 17% |
| **Hellwig et al. (1997)**<br><br>Rat (Wistar), 8–10 dams/dose per DINP formulation<br><br>0, 40, 200, 1,000 mg/kg-day<br><br>Gavage in olive oil (DINP-1,2,3) GDs 6–15; dams sacrificed on<br><br>GD 20 | **Number of corpora lutea,** *mean/dam (percent change compared to control)* | | | | |
| | Doses | 0 | 40 | 200 | 1,000 |
| | *DINP-1* | 0% | −6% | 0% | −8% |
| | *DINP-2* | 0% | −7% | −7% | −4% |
| | *DINP-3* | 0% | −6% | 0% | −4% |
| **Masutomi et al. (2003)**<br><br>Rats (Sprague-Dawley); 5 dams/dose; ovaries examined microscopically in 5 female offspring/dose<br><br>0, 400, 4,000, 20,000 ppm (Gestation: 0, 30.7, 306.7, 1,164.5 mg/kg-day Lactation: 0, 66.2, 656.7, 2,656.7 mg/kg-day)<br><br>Diet (DINP-2)<br><br>GD 15–PND 10 | **Number of corpora lutea (in offspring at PNW 11)** | | | | |
| | Doses | 0 | 30.7 | 306.7 | 1,164.5 |
| | *percent change compared to control* | 0% | −16% | −16% | −27*% |
| | **Ovarian weight, PND 27 female pups** | | | | |
| | *absolute weight (percent change compared to control)* | 0% | -13% | −10% | −30*% |

| Reference and study design[a] | Results | | | | |
|---|---|---|---|---|---|
| Waterman et al. (1999)<br>Rat (Sprague-Dawley); 23–25 dams/dose<br>0, 100, 500, 1,000 mg/kg-day<br>Gavage in corn oil (DINP-1)<br>GDs 6–15; dams sacrificed at GD 21 | ***Number of corpora lutea:*** *mean/dam (percent change compared to control)* | | | | |
| | Doses | 0 | 100 | 500 | 1,000 |
| | *Mean/dam* | 0% | −5% | 0% | −2% |
| Waterman et al. (2000); one-generation study<br>Rat (Sprague-Dawley), 30 breeding pairs/dose<br>0, 0.5, 1, 1.5%<br>(0, 446, 889.5, 1,321 mg/kg-day in males<br>0, 493.5, 951.5, 1,404 mg/kg-day in premating females<br>0, 390.5, 768.5, 1,136.5 mg/kg-day during gestation in females<br>0, 706.5, 1,384, 1,760 mg/kg-day during lactation in females)[b]<br>Diet (DINP-1)<br>10 weeks prior to mating, and through mating (M) or PND 21 (F) | ***Ovarian weight*** *(percent change compared to control)* | | | | |
| | Doses | 0 | 493.5 | 951.5 | 1,404 |
| | *Left* | 0% | 8% | −11% | −27*% |
| | *Right* | 0% | 4% | −14% | −36*% |
| Waterman et al. (2000); two-generation study<br>Rat (Sprague-Dawley), 30 breeding pairs/dose/generation<br>0, 0.2, 0.4, 0.8%<br>P1 animals[b]<br>0, 165, 331, 665 mg/kg-day in males<br>0, 182, 356, 696 mg/kg-day in premating females | ***Ovarian weight*** *(percent change compared to control)*<br>**P1 animals** | | | | |
| | Doses | 0 | 182 | 356 | 696 |
| | *Left* | 0% | 0% | 6% | −17*% |
| | *Right* | 0% | 5% | 6% | −6% |
| | **P2 (F1) animals** | | | | |
| | Doses | 0 | 146 | 287 | 555 |
| | *Left* | 0% | −3% | 12% | −5% |
| | *Right* | 0% | −5% | 10% | −10% |

| Reference and study design[a] | Results | | | | | |
|---|---|---|---|---|---|---|
| 0, 146, 287, 555 mg/kg-day during gestation in females<br>0, 254, 539, 1,026 mg/kg-day during lactation in females<br>P2 (F1) animals[b]<br>0, 189, 379, 779 mg/kg-day in males<br>0, 197, 397, 802 mg/kg-day in premating females<br>0, 143, 288, 560 mg/kg-day during gestation in females<br>0, 285, 553, 1,229 mg/kg-day during lactation in females<br>Diet (DINP-1)<br>10 weeks prior to mating, and through mating (M) or PND 21 (F) | | | | | | |
| *Uterine weight* | | | | | | |
| **Boberg et al. (2011)**<br>Rat (Wistar); 12 dams/dose<br>0, 300, 600, 750, 900 mg/kg-day<br>Gavage in corn oil (DINP-2)<br>GD 7–PND 17<br>Note: 16 dams/dose were used overall, however 4 dams/dose were only exposed GDs 7–21 and sacrificed at GD 21 for fetal testosterone assessment. | *(Percent change compared to control)* | | | | | |
| | Doses | 0 | 300 | 600 | 750 | 900 |
| | | 0% | 8% | 5% | 8% | 4% |
| **Hellwig et al. (1997)**<br>Rat (Wistar), 8–10 dams/dose per DINP formulation<br>0, 40, 200, 1,000 mg/kg-day<br>Gavage in olive oil (DINP-1,2,3)<br>GDs 6–15; dams sacrificed on GD 20 | *(Percent change compared to control)* | | | | | |
| | Doses | 0 | 40 | 200 | 1,000 | |
| | *DINP-1* | 0% | −14% | −7% | −8% | |
| | *DINP-2* | 0% | −12% | −10% | −6% | |
| | *DINP-3* | 0% | −7% | 2% | −11% | |

| Reference and study design[a] | Results | | | | |
|---|---|---|---|---|---|
| **Masutomi et al. (2003)**<br>Rats (Sprague-Dawley); 5 dams/dose; uterus weighed in 5 female pups/dose<br>0, 400, 4,000, 20,000 ppm (Gestation: 0, 30.7, 306.7, 1,164.5 mg/kg-day Lactation: 0, 66.2, 656.7, 2,656.7 mg/kg-day)<br>Diet (DINP-2)<br>GD 15–PND 10 | **Female pups, PND 27** *(percent change compared to control)* | | | | |
| | Doses | 0 | 30.7 | 306.7 | 1,164.5 |
| | *absolute weight* | 0% | 7% | −1% | −48*% |
| | *PNW 11* | | | | |
| | *absolute weight* | 0% | −9% | 2% | 2% |
| *Maternal weight gain* | | | | | |
| **Boberg et al. (2011)**<br>Rat (Wistar); 12 dams/dose<br>0, 300, 600, 750, 900 mg/kg-day<br>Gavage in corn oil (DINP-2)<br>GD 7–PND 17<br>Note: 16 dams/dose were used overall; however, four dams/dose were only exposed GDs 7–21 and sacrificed at GD 21 for fetal testosterone assessment. | ***Maternal body weight gain, GDs 7–21*** *(percent change compared to control)* | | | | |
| | Doses | 0 | 300 | 600 | 750 | 900 |
| | | 0% | 15% | 9% | 11% | 12% |
| **Clewell et al. (2013b)**<br>Rat (Sprague-Dawley); 20 dams (litters)/dose; 25 control dams (litters)<br>0, 760, 3,800, 11,400 ppm (0, 109, 555, 1,513 mg/kg-day)<br>Diet (DINP-1)<br>GD 12–PND 14 | ***Maternal body weight gain*** *(percent change compared to control)* | | | | |
| | Doses | 0 | 109 | 555 | 1,513 |
| | *GDs 10–20* | 0% | −4% | −6% | −30*% |
| | *PNDs 2–14* | 0% | 23% | 15% | -35% |

| Reference and study design[a] | Results | | | | |
|---|---|---|---|---|---|
| Clewell et al. (2013a)<br>Rat (Sprague-Dawley); 4–9 dams/timepoint/dose; 8 litters/dose and 9 control litters<br>0, 50, 250, 750 mg/kg-day<br>Gavage in corn oil (DINP-1)<br>GD 12–19; dams sacrificed 0.5, 1, 2, 6, 12, and 24 hours after final dose | ***Maternal body weight gain, GDs 12–19*** *(percent change compared to control)* | | | | |
| | Doses | 0 | 50 | 250 | 750 |
| | | 0% | 11% | 11% | 2% |
| Gray et al. (2000)<br>Rat (Sprague-Dawley); 14 exposed dams, 19 control dams<br>0, 750 mg/kg-day<br>Gavage in corn oil (DINP-1)<br>GD 14–PND 3 | ***Maternal body weight gain*** *(percent change compared to control)* | | | | |
| | Doses | | 0 | | 750 |
| | *Maternal weight gain to GD 21*<br>Note: 9 controls, 6 treated | | 0% | | −14*% |
| | *Maternal weight gain to PND 3*<br>Note: 10 controls, 8 treated | | 0% | | −32% |
| Masutomi et al. (2003)<br>Rats (Sprague-Dawley); 5 dams/dose; uterus weighed in 5 female pups/dose<br>0, 400, 4,000, 20,000 ppm (Gestation: 0, 30.7, 306.7, 1,164.5 mg/kg-day Lactation: 0, 66.2, 656.7, 2,656.7 mg/kg-day)<br>Diet (DINP-2)<br>GD 15–PND 10 | ***Maternal body weight gain*** *(percent change compared to control)* | | | | |
| | Doses | 0 | 30.7 | 306.7 | 1,164.5 |
| | *GDs 15–20* | 0% | 8% | 21% | −55*% |
| | *PNDs 2–PND 10* | 0% | 8% | 13% | −85*% |
| Waterman et al. (1999)<br>Rat (Sprague-Dawley); 23–25 dams/dose<br>0, 100, 500, 1,000 mg/kg-day<br>Gavage in corn oil (DINP-1)<br>GDs 6–15; dams sacrificed at GD 21 | No significant treatment-related changes were observed in maternal body weight gain during the overall gestation period (GDs 0–21). Compared with controls, a significant reduction in maternal body weight was observed in the 1,000 mg/kg-day group during treatment (GDs 6–15). (Data reported graphically). | | | | |

*Statistically significant ($p < 0.05$) based on analysis of data conducted by study authors.
**Statistically significant difference from control group ($p < 0.05$), as reported by Chronic Hazard Advisory Panel (CPSC, 2001).
[a]DINP formulation referenced when the study authors provided the specific formulation.
[b]Calculated as follows: [% in diet × intake food (mg)] ÷ body weight (kg) = mg/kg-day

[c]Values reported by the study authors were estimated from published graphs using "Grab It!", a Microsoft Excel based free software application used to digitizes data from image files. Publisher: www.datatrendsoftware.com.
Percent change compared to control = ([treated value − control value] ÷ control value) x 100

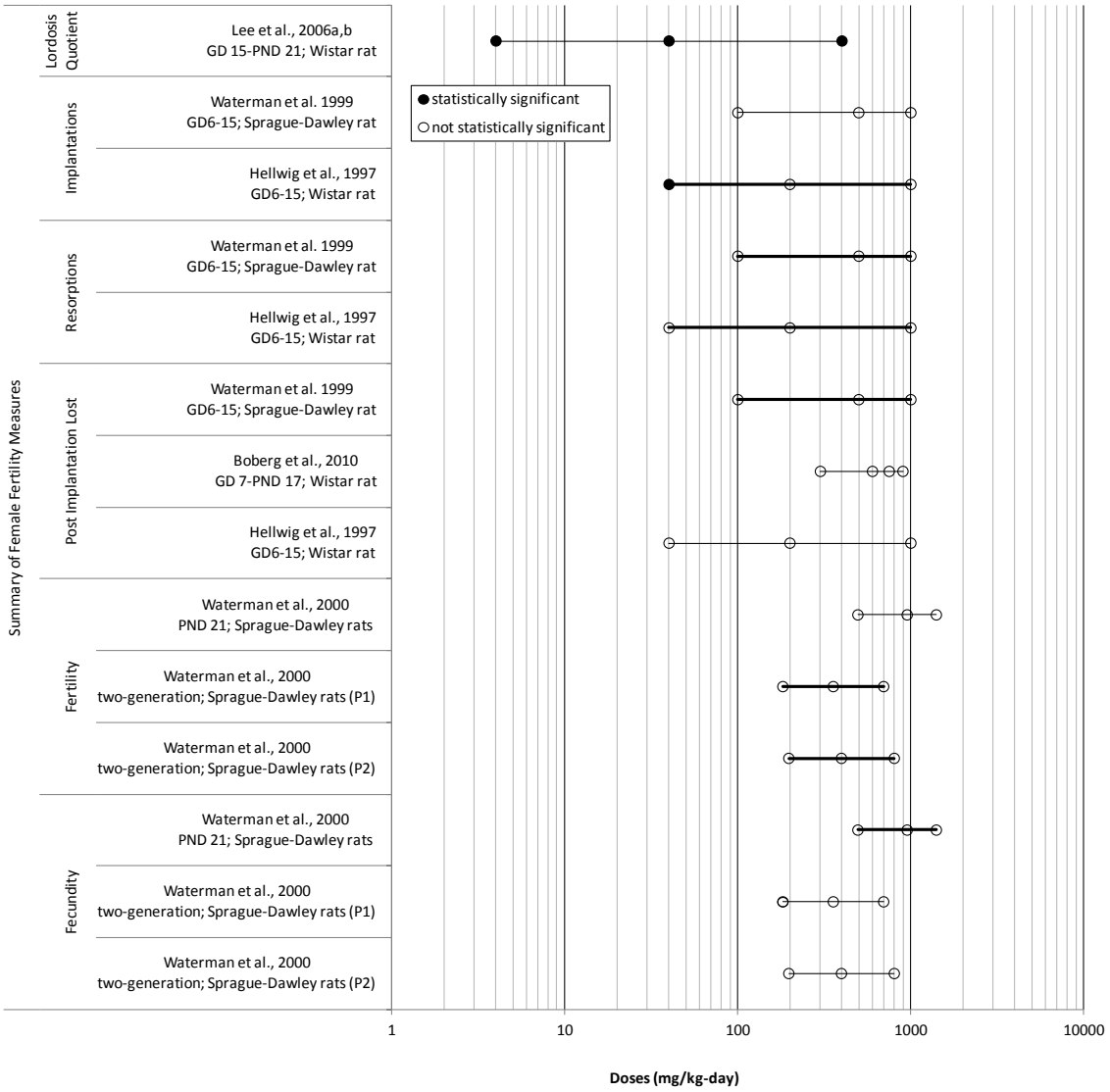


**Figure 3-10. Exposure-response array of female reproductive fertility measures following oral exposure to DINP.**

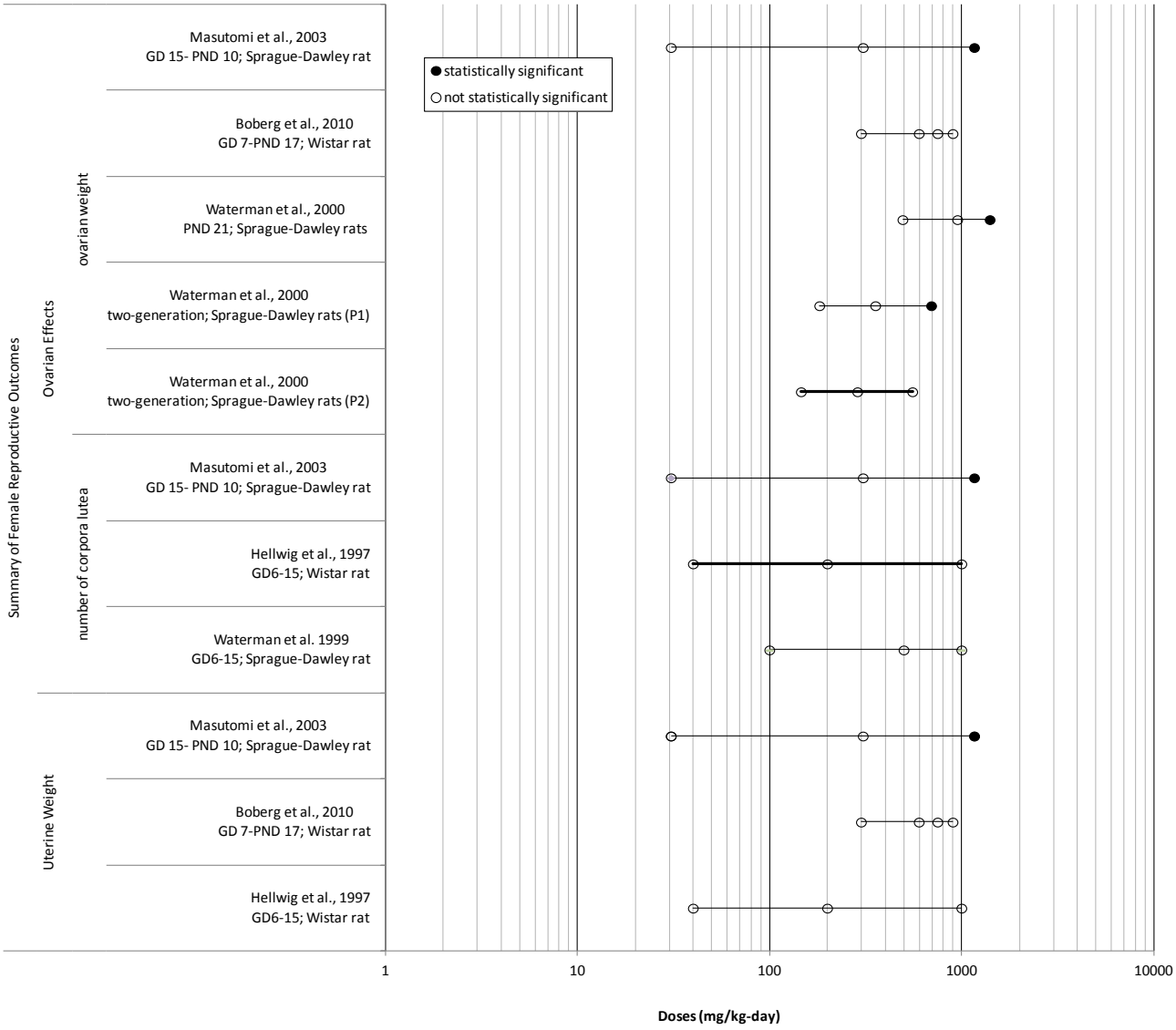


**Figure 3-11. Exposure-response array of other female reproductive effects following oral exposure to DINP.**

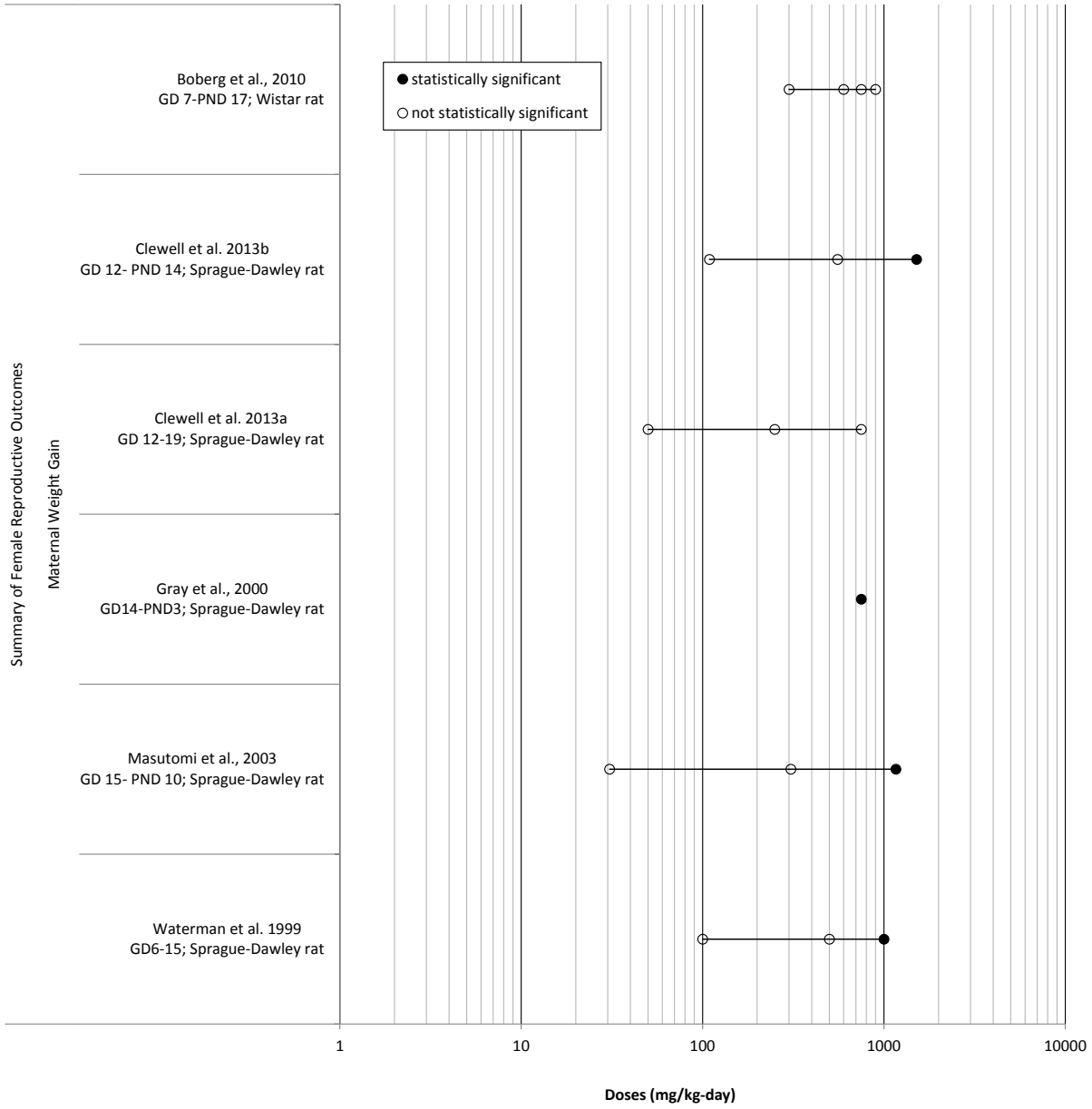


**Figure 3-12. Exposure-response array of maternal weight gain effects following oral exposure to DINP.**

## 3.3.5. Developmental Effects

**Table 3-15. Evidence pertaining to developmental effects in animals following oral exposure to DINP**

| Reference and study design | Results | | | | |
|---|---|---|---|---|---|
| *Skeletal and soft tissue variations* | | | | | |
| Hellwig et al. (1997) | **DINP-1: variations** | | | | |
| Rat (Wistar), 8–10 dams (litters)/dose per DINP formulation | Doses | 0 | 40 | 200 | 1,000 |
| | % fetuses/litter | 35.3%% | 41.5% | 29.5% | 58.4*% |
| 0, 40, 200, 1,000 mg/kg-day | *percent change compared to control* | 0% | 18% | −16% | 65% |
| Gavage in olive oil (DINP-1,2,3) | **DINP-2: variations** | | | | |
| GDs 6–15; dams sacrificed on GD 20 | *% fetuses/litter* | 35.3% | 37.5% | 40.3% | 36.6% |
| | *percent change compared to control* | 0% | 6% | 14% | 4% |
| | **DINP-3: variations** | | | | |
| | *% fetuses/litter* | 35.3% | 29.6% | 39.5% | 60.7*% |
| | *percent change compared to control* | 0% | 16% | 12% | 72% |
| (NTP-CERHR (2003); Waterman et al. (1999))[b] | **Skeletal variations** | | | | |
| | Doses | 0 | 100 | 500 | 1,000 |
| Rat (Sprague-Dawley), 23–25 dams (litters)/dose | *% fetuses/litter* | 16.4% | 15% | 28.3**% | 43.4**% |
| 0, 100, 500, 1,000 mg/kg-day | *percent change compared to control* | 0% | −9% | 73% | 165% |
| Gavage in corn oil (DINP-1) | **Visceral variations** | | | | |
| GDs 6–15; dams sacrificed at GD 21 | *% fetuses/litter* | 0.5% | 3.3**% | 3.7**% | 5.8**% |
| | *percent change compared to control* | 0% | 560% | 640% | 1,060% |
| *Pup weight* | | | | | |
| Adamsson et al. (2009) | ***Pup weight, ED 19.5*** *(percent compared to control)* | | | | |
| Rat (Sprague-Dawley); 7–8 dams/dose | Doses | 0 | 250 | | 750 |
| 0, 250, 750 mg/kg-day | M | 0% | 6*% | | 3% |
| Gavage in corn oil | F | 0% | 6% | | 1% |
| EDs 13.5–17.5; dams sacrificed on ED 19.5 | | | | | |

| Reference and study design | Results | | | | | |
|---|---|---|---|---|---|---|
| **Boberg et al. (2011)** | ***Pup weight, PND 13*** *(percent change compared to control)* | | | | | |
| Rat (Wistar); 12 dams/dose | Doses | 0 | 300 | 600 | 750 | 900 |
| 0, 300, 600, 750, 900 mg/kg-day | *M* | 0% | −0.1% | −4% | −8% | −11*% |
| Gavage in corn oil (DINP-2) | *F* | 0% | −5% | −10% | −17*% | −16% |
| GD 7−PND 17 | | | | | | |
| Note: 16 dams/dose were used overall, however 4 dams/dose were only exposed GDs 7−21 and sacrificed at GD 21 for fetal testosterone assessment. | | | | | | |
| **Clewell et al. (2013b)** | ***Male pup weight*** *(percent change compared to control)* | | | | | |
| Rat (Sprague-Dawley); 20 dams (litters)/dose; 25 control dams (litters) | Doses | 0 | 109 | 555 | 1,513 | |
| 0, 760, 3,800, 11,400 ppm (0, 109, 555, 1,513 mg/kg-day) | *PND 2* | 0% | -1% | −6% | −12*% | |
| Diet (DINP-1) | *PND 14* | 0% | -2% | −5*% | −16*% | |
| GD 12−PND 14 | Note: The litter was the statistical unit of comparison. | | | | | |
| **Clewell et al. (2013a)** | ***Fetal body weight*** *(percent change compared to control)* | | | | | |
| Rat (Sprague-Dawley); 4−9 dams/timepoint/dose; 8 litters/dose and 9 control litters | Doses | 0 | 50 | 250 | 750 | |
| 0, 50, 250, 750 mg/kg-day | *GD 19* | 0% | −2.5% | −1.5% | 0.7% | |
| Gavage in corn oil (DINP-1) | *GD 20* | 0% | −2.5% | −1.5% | 0.7% | |
| GDs 12−19; dams sacrificed 0.5, 1, 2, 6, 12, and 24 hours after final dose | Note: The litter was the statistical unit of comparison. | | | | | |
| **Hellwig et al. (1997)** | ***Fetal body weight*** *(percent change compared to control)* | | | | | |
| Rat (Wistar), 8−10 dams (litters)/ dose per DINP formulation | Doses | 0 | 40 | 200 | 1,000 | |
| 0, 40, 200, 1,000 mg/kg-day | *DINP-1* | 0% | 3% | 3% | 5% | |
| Gavage in olive oil (DINP-1,2,3) | *DINP-2* | 0% | 5% | 3% | 0% | |
| GDs 6−15; dams sacrificed on GD 20 | *DINP-3* | 0% | 3% | 5% | −3% | |

| Reference and study design | Results | | | | |
|---|---|---|---|---|---|
| Lee et al. (2006b)<br>Rat (Wistar-Imamichi); number of dams/dose not reported; 16–47 pups/sex/dose<br>0, 40, 400, 4,000, 20,000 ppm (0, 4, 40, 400, 2,000 mg/kg-day)[c]<br>Diet (DINP-2)<br>GD 15–PND 21 | ***Pup weight, PND 1*** *(percent change compared to control)* | | | | |
| | Doses | 0 | 4 | 40 | 400 | 2,000 |
| | *M* | 0% | −4*% | −5*% | −8*% | −16*% |
| | *F* | 0% | −2*% | −1% | −5*% | −18*% |
| Masutomi et al. (2003)<br>Rats (Sprague-Dawley); 5 dams (litters)/dose<br>0, 400, 4,000, 20,000 ppm (Gestation: 0, 30.7, 306.7, 1,164.5 mg/kg-day Lactation: 0, 66.2, 656.7, 2,656.7 mg/kg-day)<br>Diet (DINP-2)<br>GD 15–PND 10 | ***Pup weight gain, PNDs 2–10*** *(percent change compared to control)* | | | | |
| | Doses | 0 | 30.7 | 306.7 | 1,164.5 |
| | *M* | 0% | −11% | −22% | −56*% |
| | *F* | 0% | −11% | −22% | −56*% |
| | **Pup weight**, **PND 2** *(percent change compared to control)* | | | | |
| | *M* | 0% | 1% | −9% | −16% |
| | *F* | 0% | 6% | −7% | −11% |
| | **Pup weight**, **PND 27** (n = 5/sex/dose) *(percent change compared to control)* | | | | |
| | *M* | 0% | −5% | −18*% | −43*% |
| | *F* | 0% | 4% | −2% | −39*% |
| Waterman et al. (1999)<br>Rat (Sprague-Dawley), 23–25 dams (litters)/dose<br>0, 100, 500, 1,000 mg/kg-day<br>Gavage in corn oil (DINP-1)<br>GDs 6–15; dams sacrificed at GD 21 | **Fetal body weight, litter data** *(percent change compared to control)* | | | | |
| | Doses | 0 | 100 | 500 | 1,000 |
| | *M* | 0% | 4*% | 2% | 4*% |
| | *F* | 0% | 5*% | 2% | 3% |
| Waterman et al. (2000); one-generation study<br>Rat (Sprague-Dawley), 30 breeding pairs/dose<br>0, 0.5, 1, 1.5% (0, 446, 889.5, 1,321 mg/kg-day in males 0, 493.5, 951.5, 1,404 mg/kg-day in premating females 0, 390.5, 768.5, 1,136.5 mg/kg-day during gestation in females 0, 706.5, 1,384, 1,760 mg/kg-day during lactation in females)[c] | **Pup weight, PND 21** *(percent change compared to control)* | | | | |
| | Doses | 0 | 390.5 | 768.5 | 1,136.5 |
| | *M* | 0% | −10* | −26* | −46*% |
| | *F* | 0% | −8.5* | −27* | −47*% |
| | Note: Statistical analysis included a mixed model of covariance with pups nested within dams, dams nested within dose, and total litter size as the covariate. | | | | |

| Reference and study design | Results | | | | |
|---|---|---|---|---|---|
| Diet (DINP-1)<br>10 weeks prior to mating, and through mating (M) or PND 21 (F) | | | | | |
| Waterman et al. (2000); two-generation study<br>Rat (Sprague-Dawley), 30 breeding pairs/dose/ generation<br>0, 0.2, 0.4, 0.8%<br>P1 (or F1) animals[c]<br>0, 165, 331, 665 mg/kg-day in males<br>0, 182, 356, 696 mg/kg-day in premating females<br>0, 146, 287, 555 mg/kg-day during gestation in females<br>0, 254, 539, 1,026 mg/kg-day during lactation in females<br>P2 (F2) animals[c]<br>0, 189, 379, 779 mg/kg-day in males<br>0, 197, 397, 802 mg/kg-day in premating females<br>0, 143, 288, 560 mg/kg-day during gestation in females<br>0, 285, 553, 1,229 mg/kg-day during lactation in females<br>Diet (DINP-1)<br>10 weeks prior to mating, and through mating (M) or PND 21 (F) | **Pup weight,F1 offspring; PND 21** *(percent change compared to control)* | | | | |
| | Doses | 0 | 146 | 287 | 555 |
| | M | 0% | −10* | −16* | −19*% |
| | F | 0% | −9* | −15* | −17*% |
| | **Pup weight, F2 offspring; PND 21** *(percent change compared to control)* | | | | |
| | Doses | 0 | 143 | 288 | 560 |
| | M | 0% | −7 | −12* | −21*% |
| | F | 0% | −7 | −12* | −22*% |

*Statistically significant ($p < 0.05$) based on analysis of data conducted by study authors.
**Statistically significant difference from control group ($p < 0.05$), as reported by the National Toxicology Program (NTP)-Center for the Evaluation of Risks to Human Reproduction (CERHR) to account for within-litter correlation (NTP-CERHR, 2003).
[a]DINP formulation referenced only when the study authors provided the specific formulation.
[b]Presented data from the reanalysis conducted by NTP-CERHR to account for within-litter correlation (NTP-CERHR, 2003).
[c]Calculated as follows: [% or ppm in diet × intake food/water (mg)] ÷ body weight (kg) = mg/kg-day
Percentage change compared to control = (treated value − control value) ÷ control value × 100.

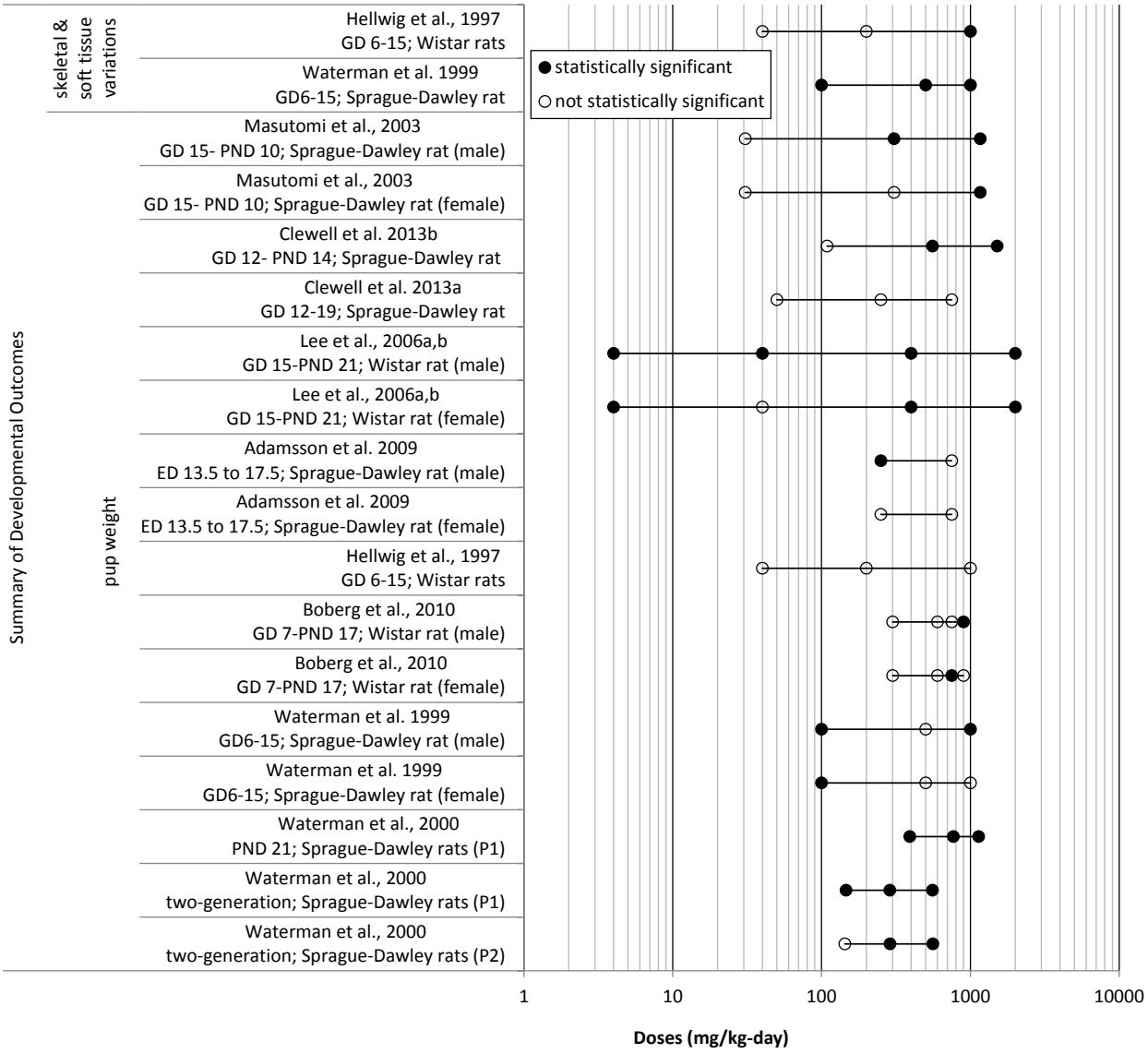


**Figure 3-13. Exposure-response array of developmental effects following oral exposure to DINP.**

## 3.3.6. Hematopoietic Effects

**Table 3-16. Evidence pertaining to hematopoietic effects in animals following oral exposure to DINP**

| Study design and reference[a] | Results | | | | | |
|---|---|---|---|---|---|---|
| *Hematology* | | | | | | |
| Bio Dynamics (1986)<br>Rat (Sprague-Dawley); 70/sex/dose<br>0, 500, 5,000, 10,000 ppm (0, 27, 271, 553 mg/kg-day in males; 0, 33, 331, 672 mg/kg-day in females)<br>Diet (SANTICIZER 900)<br>2 years (interim sacrifice at 1 year) | **Hematology at 2 years (n = 10/sex/dose)** (*percent change compared to control*) | | | | | |
| | Doses (M) | 0 | 27 | 271 | 553 | |
| | *RBCs* | 0% | −8% | 4% | −17*% | |
| | *Hgb* | 0% | −13% | 0% | −18*% | |
| | *Hct* | 0% | −14% | 0% | −19*% | |
| | Doses (F) | 0 | 33 | 331 | 672 | |
| | *RBCs* | 0% | −20% | −10% | −15% | |
| | *Hgb* | 0% | 0% | 7% | 1% | |
| | *Hct* | 0% | 0% | 11% | 3% | |
| Lington et al. (1997)<br>Rat (F344); 110/sex/dose<br>0, 0.03. 0.3. 0.6% (0, 15, 152, 307 mg/kg-day in males; 0, 18, 184, 375 mg/kg-day in females)<br>Diet (DINP-1)<br>2 years (interim sacrifices at 6, 12, and 18 months) | **Hematology at 2 years (n = 19–20/sex/dose)** (*percent change compared to control*) | | | | | |
| | Doses (M) | 0 | 15 | 152 | 307 | |
| | *RBCs* | 0% | 0% | −3% | −14*% | |
| | *Hgb* | 0% | −6% | −8% | −19*% | |
| | *Hct* | 0% | −5% | −8% | −19*% | |
| | Doses (F) | 0 | 18 | 184 | 375 | |
| | *RBCs* | 0% | −4% | −14% | −14% | |
| | *Hgb* | 0% | −5% | −15% | −13% | |
| | *Hct* | 0% | −5% | −14% | −13% | |
| Covance Laboratories (1998b)<br>Rat (F344); 70 or 85/sex/dose<br>0, 500, 1,500, 6,000, 12,000 ppm (0, 29, 88, 359, 733 mg/kg-day in males; 0, 36, 109, 442, 885 mg/kg-day in females)<br>Recovery group (55/sex/dose): 12,000 ppm (637 mg/kg-day in males; 733 mg/kg-day in females)<br>Diet<br>Main study: 2 years (interim sacrifices at 1, 2, 13, and 79 weeks) | **Hematology at 104 weeks (n = 9–10/sex/dose)** *(percent change compared to control)* | | | | | | |
| | Doses (M) | 0 | 29 | 88 | 359 | 733 | Recovery |
| | *RBCs* | 0% | 4% | −3% | −16% | −21% | −17% |
| | *Hgb* | 0% | 5% | −2% | −15% | −20*% | −15% |
| | *Hct* | 0% | 4% | −3% | −15*% | −19*% | −12% |
| | Doses (F) | 0 | 36 | 109 | 442 | 885 | Recovery |
| | *RBCs* | 0% | −4% | −3% | −18*% | −26*% | −3% |
| | *Hgb* | 0% | −4% | −3% | −16% | −25*% | −1% |
| | *Hct* | 0% | −4% | −2% | −14% | −24*% | −1% |

| Study design and reference[a] | Results | | | | | |
|---|---|---|---|---|---|---|
| Recovery group: 78 weeks, followed by a 26-week recovery period with basal diet alone | | | | | | |
| *Spleen weight*[c] | | | | | | |
| Lington et al. (1997)<br>Rat (F344); 110/sex/dose<br>0, 0.03. 0.3. 0.6 wt% (0, 15, 152, or 307 mg/kg-day in males; 0, 18, 184, or 375 mg/kg-day in females)<br>Diet (DINP-1)<br>2 years | **Spleen weight at terminal sacrifice (n = 48–65/sex/dose)** *(percent change compared to control)* | | | | | |
| | Doses (M) | 0 | 15 | 152 | 307 | |
| | *spleen/body weight* | 0% | 17% | 61*% | 61*% | |
| | Doses (F) | 0 | 18 | 184 | 375 | |
| | *spleen/body weight* | 0% | 29% | 5% | 57*% | |
| Covance Laboratories (1998b)<br>Rat (F344); 70 or 85/sex/dose<br>0, 500, 1,500, 6,000, 12,000 ppm (0, 29, 88, 359, or 733 mg/kg-day (M); 0, 36, 109, 442, or 885 mg/kg-day (F)<br>Recovery group (55/sex/dose): 12,000 ppm (637 mg/kg-day in males; 733 mg/kg-day in females)<br>Diet<br>Main study: 2 years (interim sacrifices at 1, 2, 13, and 79 weeks)<br>Recovery group: 78 weeks, followed by a 26-week recovery period with basal diet alone | **Spleen weight at terminal sacrifice (n = 27–42/sex/dose)** *(percent change compared to control)* | | | | | |
| | Doses (M) | 0 | 29 | 88 | 359 | 733 | Recovery |
| | *absolute weight* | 0% | −15% | −31% | 33% | 33% | 38% |
| | *spleen/body weight* | 0% | −14% | −30% | 38% | 53% | 45% |
| | Doses (F) | 0 | 36 | 109 | 442 | 885 | Recovery |
| | *absolute weight* | 0% | 64% | 3% | 16*% | 121*% | 51% |
| | *spleen/body weight* | 0% | 81% | 18% | 23% | 150*% | 61*% |
| *Mononuclear cell leukemia (MNCL)* | | | | | | |
| Bio Dynamics (1986)<br>Rat (Sprague-Dawley); 70/sex/dose<br>0, 500, 5,000, 10,000 ppm (0, 27, 271, 553 mg/kg-day in males; 0, 33, 331, 672 mg/kg-day in females)<br>Diet (SANTICIZER 900)<br>2 years (interim sacrifice at 1 year) | Evaluated, but incidences were not reported by study authors | | | | | |
| **(EPL (1999); Lington et al. (1997))**<br>Rat (F344); 110/sex/dose<br>0, 0.03. 0.3. 0.6% (0, 15, 152, 307 mg/kg-day in males; 0, 18, 184, 375 mg/kg-day in females)<br>Diet (DINP-1) | 104-week terminal sacrifice | | | | | |
| | Doses (M) | 0 | 15 | 152 | 307 | |
| | *incidence*[b] | 32/81 | 27/80 | 48/80** | 49/80** | |
| | *percentage* | 40% | 34% | 60% | 61% | |
| | Doses (F) | 0 | 18 | 184 | 375 | |

| Study design and reference[a] | Results | | | | | | |
|---|---|---|---|---|---|---|---|
| 2 years (interim sacrifices at 6, 12, and 18 months) | *incidence*[b] | 22/81 | | 21/81 | 29/80 | | 41/80** |
| **Covance Laboratories (1998b); EPL (1999)**<br>Rat (F344); 70 or 85/sex/dose<br>0, 500, 1,500, 6,000, 12,000 ppm (0, 29, 88, 359, 733 mg/kg-day in males; 0, 36, 109, 442, 885 mg/kg-day in females)<br>Recovery group (55/sex/dose): 12,000 ppm (637 mg/kg-day in males; 733 mg/kg-day in females)<br>Diet<br>Main study: 2 years (interim sacrifices at 1, 2, 13, and 79 weeks)<br>Recovery group: 78 weeks, followed by a 26-week recovery period with basal diet alone | 104-week terminal sacrifice | | | | | | |
| | Doses (M) | 0 | 29 | 88 | 359 | 733 | Recovery |
| | *incidence*[b] | 21/55 | 23/50 | 21/50 | 32/55** | 28/55** | 30/50 |
| | *percentage* | 38% | 46% | 42% | 58% | 51% | 60% |
| | Doses (F) | 0 | 36 | 109 | 442 | 885 | Recovery |
| | *incidence*[b] | 17/55 | 16/50 | 9/50 | 28/55** | 28/55** | 24/50 |
| | *percentage* | 31% | 32% | 18% | 51% | 51% | 48% |
| **Covance Laboratories (1998a)**<br>Mouse (B6C3F$_1$); 70/sex/dose<br>0, 500, 1,500, 4,000, 8,000 ppm (0, 90, 276, 742, 1,560 mg/kg-day in males; 0, 112, 336, 910, 1,888 mg/kg-day in females)<br>Recovery group (55/sex/group): 1,560 mg/kg-day<br>Diet<br>Main study: 2 years (interim sacrifice at 79 weeks)<br>Recovery group: 78 weeks, followed by a 26-week recovery period with basal diet alone | Evaluated, but incidences were not reported by study authors | | | | | | |

*Statistically significant from control group ($p < 0.05$), as reported by study authors.
**Statistically significant from control ($p < 0.05$), as reported by Chronic Hazard Advisory Panel (CPSC, 2001).
[a]DINP formulation referenced when the study authors provided the specific formulation.
[b]Incidence data as reported by Pathology Working Group reanalysis (EPL, 1999)
[c]Spleen weight measured but no difference observed among exposed group (Kwack et al., 2009)
[d]Calculated as follows: [% in diet × intake food/water (mg)] ÷ body weight (kg) = mg/kg-day.
Percent change compared to control = ([treated value − control value] ÷ control value) x 100

Hgb = hemoglobin; Hct = hematocrit; RBC = red blood cell

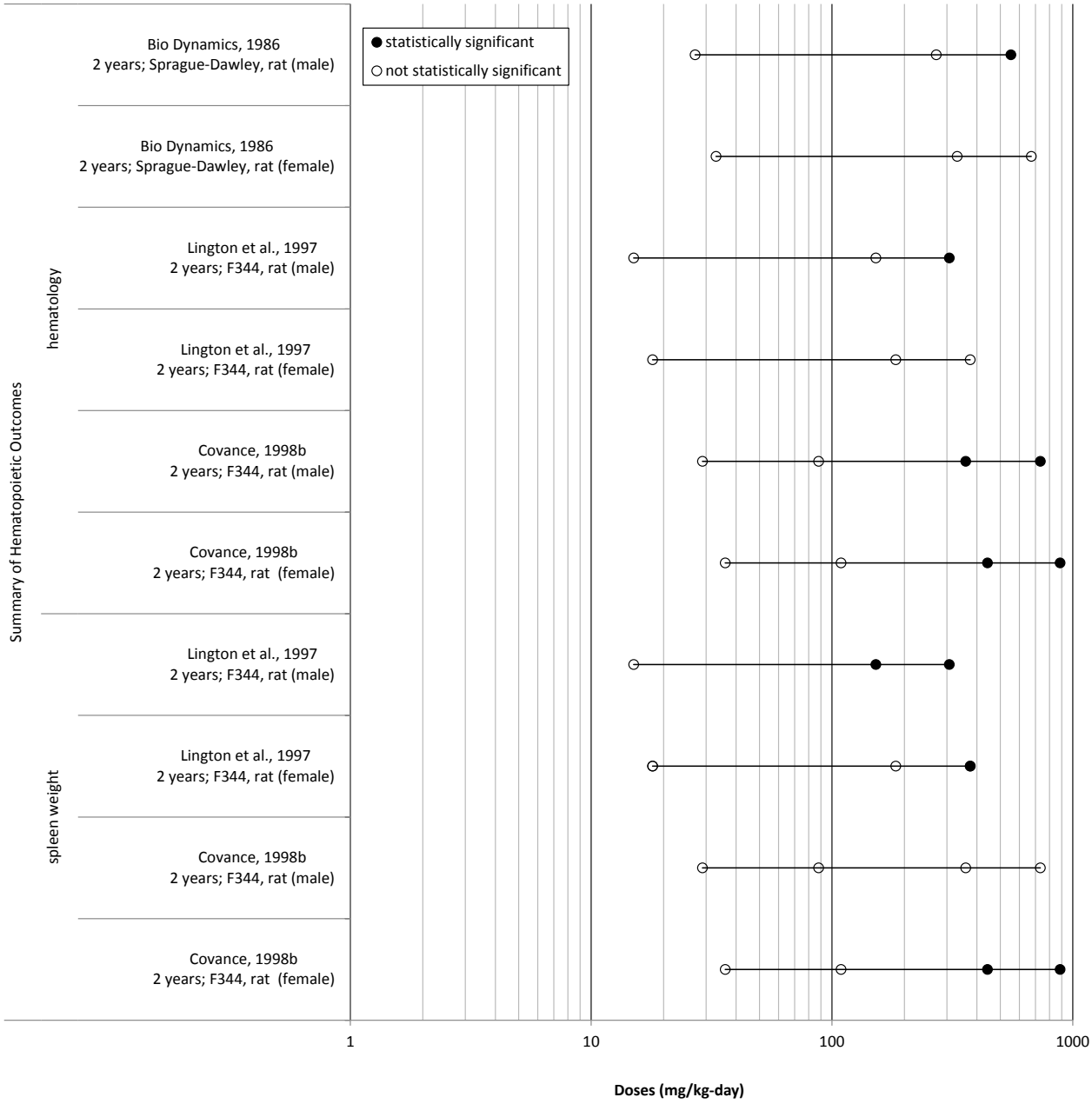


**Figure 3-14. Exposure-response array of hematopoietic effects following oral exposure to DINP.**

## 3.4. PRELIMINARY MECHANISTIC INFORMATION FOR DINP

The systematic literature search for DINP also identified studies evaluating mechanisms of action considered potentially relevant to effects observed following exposure to DINP. Studies were included if they evaluated mechanistic events following exposure to DINP formulations or metabolites, or contained information relevant to the mechanistic understanding of DINP toxicity. Reviews or analyses that do not contain original data are not included here, but may be considered in later stages of assessment development.

The diverse array of mechanistic studies presented here includes investigations of the cellular, biochemical, and molecular mechanisms underlying toxicological outcomes. For this preliminary evaluation, information reported in each study was extracted into a database (in the form of an Excel spreadsheet) that will facilitate future evaluation of mechanistic information. This information is being made available to provide an opportunity for stakeholder input, including the identification of relevant studies not captured here.

The information extracted from each study and included in the database, corresponds to the column headings in the spreadsheet, and is as follows: link to HERO record (contained within a URL that links to the study abstract in the HERO database), HERO ID, author(s), year, molecular formulation, in vitro/in vivo, species, cell type, endpoint(s) (i.e., mechanistic outcomes), assay, and mechanistic category. The database supports sorting capabilities, e.g., data can be organized by assay. The database is available through HERO at [http://hero.epa.gov/index.cfm?action=-reference.details&reference_id=2347390]. To access the database, click on the link at the top of the web page and select "download" and then "ok" to view the spreadsheet in Excel. This spreadsheet may also be saved to your desktop by downloading and selecting "save." The resulting inventory of DINP mechanistic studies consists of 60 mechanistic outcomes from 22 in vivo studies, as well as 45 mechanistic outcomes from 17 in vitro assays. Table 3-17 presents a summary of the mechanistic outcomes recorded in the database from each study identified.

The mechanistic categories developed here are not mutually exclusive and are designed to facilitate the analysis of similar studies and experimental observations in a systematic manner. This process will allow the identification of mechanistic events that contribute to mode(s) of action (MOAs) and/or adverse outcome pathways (AOPs) following DINP exposure. The mechanistic categories assigned to each mechanistic outcome reported by an individual study are as follows: 1) mutation, including investigations of gene and chromosomal mutation; 2) DNA damage, including indicator assays of genetic damage; 3) DNA repair; 4) oxidative stress; 5) cell death and division (this captures a broad range of assays, but it is useful to consider them together as observations resulting from cell cycle alterations; 6) pathology, which includes morphological evaluations pertaining to the dysfunction of organs, tissues, and cells; 7) epigenetic effects, which are observations of heritable changes in gene function that cannot be explained by changes in the DNA sequence; 8) receptor-mediated and cell signaling effects; 9) immune system effects; 10) cellular differentiation and transformation; 12) cellular energetics; and 13) "other," to capture those mechanistic outcomes not easily assigned to a defined category. Mechanistic outcomes in the

"other" category include gene expression from mouse liver and rat hypothalamus, rat serum hormone levels, rat kidney alpha2u globulin, and numerous measurements of rat testicular function (hormone, protein, and mRNA measurements).

Information summarized in Table 3-17 and Figure 3-15 and detailed in the mechanistic database can be used to ascertain the breadth and scope of available mechanistic studies. At this preliminary stage, study results are not presented. Additionally, the inclusion of a study in the spreadsheet does not reflect conclusions reached as to mechanistic study quality or relevance. After the epidemiological and experimental studies on each health effect have been synthesized, mechanistic studies will be reviewed and findings synthesized to evaluate potential MOAs and/or AOPs, which can be used to inform hazard identification and dose-response assessment, specifically addressing questions of human relevance, susceptibility, and dose-response relationships.

**Table 3-17. Summary of mechanistic outcomes evaluated following DINP administration**

| Mechanistic category | Total # mechanistic outcomes/ # studies | *In vivo (# mechanistic outcomes/# studies)* | | | | *In vitro (# mechanistic outcomes/ # studies)* | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Total | Primate | Rat | Mouse | Total | Human | Primate | Rat | Mouse |
| Mutation[a] | 9/6 | 2/2 | 0 | 1/1 | 1/1 | 7/5 | 0 | 0 | 0 | 3/3 |
| DNA damage | 1/1 | 0 | 0 | 0 | 0 | 1/1 | 0 | 0 | 1/1 | 0 |
| *DNA repair* | | | | | | | | | | |
| *Oxidative stress* | | | | | | | | | | |
| Cell death and division | 14/7 | 7/5 | 1/1 | 2/2 | 4/3 | 7/2 | 4/2 | 0 | 3/2 | 0 |
| Pathology | 20/8 | 20/8 | 0 | 19/8 | 1/1 | N/A | N/A | | | |
| *Epigenetics* | | | | | | | | | | |
| Receptor-mediated and cell signaling[b] | 26/8 | 9/5 | 3/2 | 4/3 | 2/2 | 17/5 | 5/4 | 3/2 | 6/5 | 2/2 |
| Immune system | 5/3 | 5/3 | 0 | 1/1 | 4/2 | 0 | 0 | 0 | 0 | 0 |
| Cellular differentiation and transformation[b] | 16/10 | 3/2 | 1/1 | 1/1 | 1/1 | 13/8 | 2/2 | 1/1 | 1/1 | 8/8 |
| *Cellular energetics* | | | | | | | | | | |
| Other | 14/6 | 14/6 | 0 | 13/5 | 1/1 | 0 | 0 | 0 | 0 | 0 |
| Total | 105/35 | 60/22 | | | | 45/17 | | | | |

[a]Database also included three experimental measures in two studies utilizing bacteria, and one experimental measure from one study using Chinese hamster ovary cells, not listed.

[b]Database also included one experimental measure in one study utilizing primary hepatocytes from Syrian golden hamsters, not listed.

Note: The shaded rows represent categories for which no experimental measures were identified in the database, from any species, in any kind of model system (e.g. in vitro, in vivo, biochemical, etc). Additionally, 10 studies did not have pdfs available to provide the information needed for collection into the spreadsheet (pdfs have been requested for a future data collection).

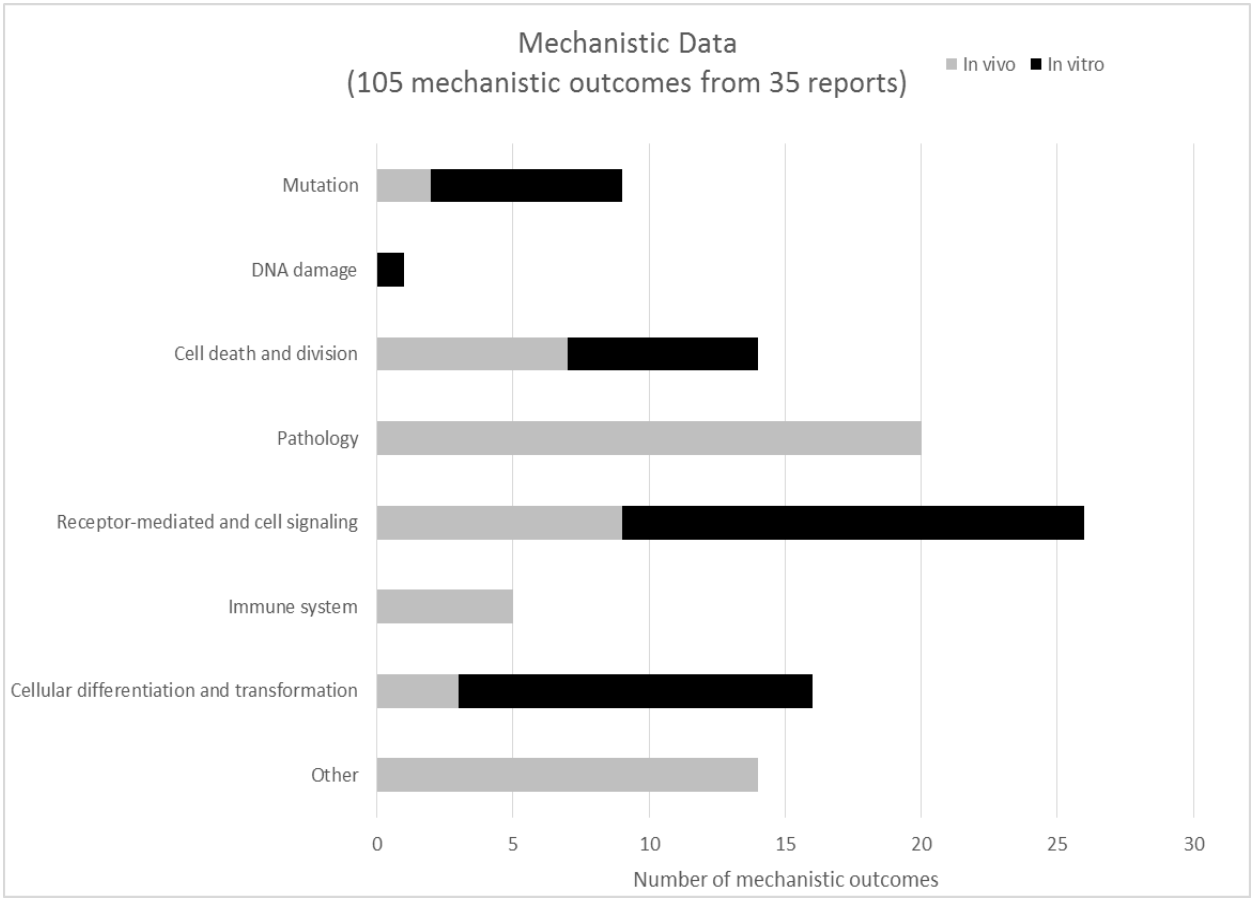


**Figure 3-15. Summary of in vivo and in vitro mechanistic data by mechanistic category**

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