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Preliminary Materials for the Integrated Risk Information System (IRIS) Toxicological Review of Dibutyl Phthalate (DBP)

[CASRN 84-74-2]

January 2015

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ABBREVIATIONS

AGD	anogenital distance
aOR	adjusted odds ratio
BASC-PRS	Behavior Assessment System for Children—Parent Rating Scales
BBP	butyl benzyl phthalate
BMI	body mass index
BP	blood pressure
BPA	bisphenol A
BRIEF	Behavior Rating Inventory of Executive Function
BW	body weight
CASRN	Chemical Abstracts Service Registry Number
CHAP	Chronic Hazard Advisory Panel
CI	confidence interval
CPSC	Consumer Product Safety Commission
DBP	dibutyl phthalate
DEP	di-ethyl phthalate
DEHP	di(2-ethylhexyl)phthalate
DHEAS	dehydroepiandrosterone
DIBP	diisobutyl phthalate
DINP	diisononyl phthalate
DnBP	dibutyl phthalate
DNA	deoxyribonucleic acid
DPP	dipentyl phthalate
DXA	dual energy x-ray absorptiometry
EPA	Environmental Protection Agency
FBG	fasting blood glucose
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GD	gestational day
HbA1c	glycosolated hemoglobin
HCG	human chorionic gonadotropin
HDL	high-density lipoprotein
HERO	Health and Environmental Research Online
Hgb	hemoglobin
HOMA	homeostatic model assessment
HOMA-IR	homeostatic model assessment of insulin resistance
HOME	Health Outcomes and Measures of the Environment
IgE	immunoglobulin E
ICC	intra-class correlation coefficient
IM-GSM	grey scale media of the intima media complex
IMT	intima media thickness
IQR	interquartile range
IRIS	Integrated Risk Information System
Koc	partition coefficient
LDL	low-density lipoprotein
LH	luteinizing hormone
LMW	low molecular weight
LOD	level of detection
LOQ	level of quantification
MBzP	mono-benzyl phthalate
MBP	monobutyl phthalate
MCPP	mono-(3-carboxypropyl) phthalate
MDI	mental delay index
MEHP	mono-(2-ethylhexyl) phthalate
MEP	monoethyl phthalate
MHBP	mono-3-(3-carboxypropyl)phthalate
MIBP	monoisobutyl phthalate
MMP	monomethyl phthalate
MOA	mode of action
MOINP	oxo-(mono-oxoisononyl) phthalate
MRI	magnetic resonance imaging
NCEA	National Center for Environmental Assessment
NHANES	National Health and Nutrition Examination Survey
NHS	Nurses' Health Study
NRC	National Research Council
OR	odds ratio
ORD	Office of Research and Development
PAH	polycyclic aromatic hydrocarbon
PCO	polycystic ovarian morphology
PCOS	polycystic ovarian syndrome
PDI	psychomotor delay index
PND	postnatal day
PPS	preputial separation
PVC	polyvinyl chloride
RBC	red blood cell
SD	standard deviation
SE	standard error
SHBG	sex-hormone binding globulin
T3	triiodothyronine
T4	thyroxine
TSH	thyroid stimulating hormone
VO	vaginal opening
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

PREFACE

This draft document presents preliminary materials for an assessment of dibutyl phthalate (DBP) 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 studies in evidence tables and exposure-response arrays, and mechanistic information for DBP. 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 DBP, occurrence of DBP 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 of 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 DBP 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 describe EPA's approach for the selection of studies to be included in the evidence tables. It also includes presentation of methodological details and results in tabular form, and describes the considerations that will be used to distinguish level of quality, informativeness, and bias in the set of collected studies. This evaluation will be incorporated into the 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;
- 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 dibutyl phthalate (DBP). The planning and scoping summary includes information on the properties, sources, and uses of DBP, occurrence and fate of DBP in the environment, potential for human exposure, and the rationale for the development of this assessment.

1.1. DBP IN THE ENVIRONMENT

1.1.1. Production and Use

DBP (Chemical Abstract Service Registry Number [CASRN] 84-74-2) is a plasticizer used in resins and polymers such as polyvinyl chloride (PVC) as well as, nitrocellulose paints, explosives, nail polish and solid rocket propellants. DBP is also used in the manufacture of printing inks, adhesives, sealants, film coatings, and safety glass and as a solvent and fixative for perfumes (HSDB, 2009). EPA's Office of Pollution Prevention and Toxics (OPPT) reported that more than 7 million pounds were imported or manufactured in the United States in 2012 (http://www.epa.gov/oppt/cdr/index.html).

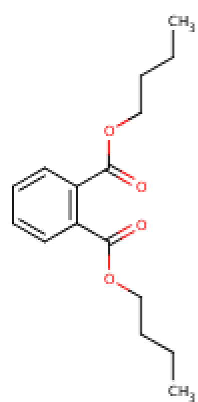


Figure 1-1. Chemical structure of DBP (HSDB, 2009).

1.1.2. Environmental Fate

If released to air, DBP will exist in both the vapor and particulate phases in the atmosphere. Vapor-phase DBP will be degraded with a half-life of about 42 days. Particulate-phase DBP will be removed from the atmosphere by wet or dry deposition. Once in soil, DBP has low mobility with an organic carbon partition coefficient (Koc) of 3.05-3.14. Biodegradation half-life in aerobic soil and water is estimated as 2.9 days. Anaerobic biodegradation half-life is approximately 14.4 days. If released into water, DBP is expected to adsorb to suspended solids and sediment. Measured bioconcentration factors suggest that concentrations in aquatic organisms may be low due to the ability of aquatic organisms to readily metabolize this class of compounds (HSDB, 2009). As noted by Wormuth et al. (2006), the majority of phthalates that are found in the environment come from slow release from plastics and other phthalate-containing articles. Certain waste streams, sludges, and contaminated sites, however, may contain higher levels of phthalates than other sites.

1.1.3. Human Exposure Pathways

The manner that humans are exposed to phthalates, along with the magnitude of exposures, has changed over time as the quantities and uses of phthalates have changed. Human exposure to phthalates occurs mainly in occupational or household settings because they are used and released from products in the home environment. Environmental concentrations of phthalates are typically the highest in house dust and they may be present in food due to the use of phthalates in packaging and food preparation materials. For most phthalates, food ingestion is the dominant pathway of exposure, with dust exposures (ingestion and dermal contact), use of personal care products, and inhalation also being important in some circumstances. Infant and toddler exposures occur due to teething and playing with plastic toys that contain phthalates (Wormuth et al., 2006).

The presence of phthalates or their metabolites in a body matrix, such as blood or urine, provides evidence of exposure to that chemical. The predominant metabolite of DBP in humans is monobutyl phthalate (MBP). The prevalence and temporal trends of MBP in urine samples collected as part of the biennial National Health and Nutrition Examination Survey (NHANES) conducted between 2001 and 2010 has been reported by the Centers for Disease Control (CDC, 2013). Concentrations were fairly stable between 2001 and 2008 (geometric mean approximately 20 ng/ml; 95th percentile approximately 110 ng/ml), but decreased in the 2009-2010 cycle (geometric mean 14.6 ng/ml; 95th percentile 75.9 ng/ml) (Zota et al., 2014).

Intake exposures can be estimated on a pathway-basis by combining exposure media concentrations and contact rates. Using this approach, Clark et al. (2011) determined a median intake of DBP of between 1.2 and 3.4 μg/kg-day for various lifestages as defined by the authors: adults (20-70 years of age), teens (12-19 years of age), children (5-11 years of age), toddlers (0.5-4 years of age), and infants (0-0.5 years of age). Toddlers had the highest intake noted. Ingestion of food accounted for 75% of the total exposure for all age groups except infants, with the remainder primarily due to incidental ingestion of dust and a minor contribution due to inhalation of indoor air. For formula-fed infants, ingestion of food accounted for approximately 46% of exposure, followed by ingestion of dust and inhalation of indoor air. For breast-fed infants, ingestion of dust represented approximately 62% of total exposure followed by inhalation of indoor air and ingestion of food. In another assessment, Wormuth et al. (2006) found that ingestion of food was the dominant exposure pathway for the adults while for teens, dermal contact, ingestion of personal care products, and inhalation of air were important exposure pathways. The Consumer Products Safety Commission (CPSC) developed a scenario based exposure assessment for phthalates in the context of a report from the Chronic Hazard Advisory Panel (CHAP, 2014). Their report focused on exposures to women of child-bearing age and to children (infants, toddlers, and older children), and included 8 phthalate esters (DEP, DBP, DiBP, BBP, DNOP, DEHP, DiNP, and DiDP). For women of child-bearing age specific to DBP, they found that personal care products explained 59% of exposures, with dietary exposures second at 26%. Indoor exposures, including toys and house dust, explained 61% of exposures for infants, 48% for toddlers, and 23% for children, with diet and personal care products explaining the remaining exposures for these groupings of individuals.

Wittassek et al. (2011) reported median intakes of DBP in the range of 0.8-7.6 μg/kg-day based on a literature survey or urinary biomonitoring data and intake estimates provided therein. Their review included U.S. estimates generated using data from the NHANES 2001-2002. Qian et al. (2014) used NHANES 2007-2008 data and found a median intake of 0.54 μg/kg-day and a 95th percentile intake of 2.43 μg/kg-day. 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 0.5 μg/kg-day and a 95th percentile intake of 2.1 μg/kg-day. The CPSC (CHAP, 2014) found a median and a 95th percentile intake for adults (age range 15-45) of 0.66 and 2.6 μg/kg-day based on NHANES 2005-2006 data; corresponding figures based on urine measures in infants were 1.7 (median) and 10.4 (95th percentile) μg/kg-day.

1.2. SCOPE OF THE ASSESSMENT

The National Research Council has recommended that, “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, 2008), p11]. They envisioned facilitating the process by “defining the groups of agents that should be included for a given outcome” [(NRC, 2008), p12]. In humans, the NRC cited results from the NHANES that demonstrate exposure to multiple phthalates in most people [(NRC, 2008), p23-25]. This IRIS assessment will help to inform EPA programs and regions of the potentially unique vulnerabilities of adults, especially women of reproductive age to DBP exposure and enable future cumulative risk assessments that assess effects on human health outcomes that might be associated with DBP and other phthalates. EPA’s previous IRIS assessment of DBP included an oral reference dose (RfD) and qualitative cancer assessment (classified as Group D, not classifiable). Since that time, a number of experimental animal and epidemiological studies have been published for DBP.

2. METHODS FOR IDENTIFYING AND SELECTING STUDIES

2.1. DRAFT LITERATURE SEARCH AND SCREENING STRATEGY

A literature search for DBP was conducted in four online scientific databases [PubMed, Web of Science, Toxline, and Toxic Substances Control Act Test Submissions (TSCATS2)[1]] in November 2012. The search was updated in June 2013 and in January 2014. The identification of the available literature captured in this document is complete through January 2014. A literature search update was recently performed in September 2014. EPA is currently reviewing the literature obtained from this update. As described below, an additional search strategy was developed to identify epidemiological studies, and was most recently updated in June 2014.

The detailed search approach, including the search strings and number of citations identified per database, is presented in Table 2-1. The search strings and search terms described for DBP captured studies using the parent compound and metabolites (i.e., the active metabolite, MBP). This search of online databases identified 3,090 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); 86 citations were obtained using these additional search strategies. In total, 3,176 citations were identified using online scientific databases and additional search strategies.

Table 2-1. Database search strategy for DBP

Database (search date)	Keywords[a]
PubMed 01/2014 06/2013 11/2012	("Dibutyl phthalate"[mh]) OR ((("Dibutyl phthalate"[mh]) OR ("Dibutyl phthalate"[tw] OR "Di-n-butyl phthalate"[tw] OR "Dibutyl 1,2-benzenedicarboxylate"[tw] OR "Phthalic acid dibutyl ester"[tw] OR "1,2-Benzenedicarboxylic acid dibutyl ester"[tw] OR "1,2-Benzenedicarboxylic acid 1,2-dibutyl ester"[tw] OR "o-Benzenedicarboxylic acid dibutyl ester"[tw] OR "Benzene-o-dicarboxylic acid di-n-butyl ester"[tw] OR "Dibutyl-o-phthalate"[tw] OR "ortho-Dibutyl phthalate" OR dibutylphthalate OR "N-Butylphthalate"[tw] OR "n-Butyl phthalate"[tw] OR "di-butyl phthalate"[tw]) OR ("Celluflex DPB"[tw] OR "Elaol"[tw] OR "Ergoplast FDB"[tw] OR "Ersoplast FDA"[tw] OR "Genoplast B"[tw] OR "Hatcol DBP"[tw] OR "Hexaplas M B"[tw] OR "Kodaflex DBP"[tw] OR "Palatinol C"[tw] OR "Polycizer DBP"[tw] OR "RC Plasticizer DBP"[tw] OR "Staflex DBP"[tw] OR "Uniflex DBP"[tw] OR "Unimoll db"[tw] OR "Witcizer 300"[tw]) OR (DBP[tw] AND (phthalic acids[mh] OR phthalate[tw] OR phthalates[tw]))) AND (to[sh] OR po[sh] OR ae[sh] OR pk[sh] OR me[sh] OR ci[sh] OR bl[sh] OR cf[sh] OR ur[sh] OR "Inhalation Exposure"[Mesh] OR "Maternal Exposure"[Mesh] OR "Maximum Allowable Concentration"[Mesh] OR "Occupational Exposure"[Mesh] OR "Paternal Exposure"[Mesh] OR "Environmental Exposure"[Mesh:noexp] OR ((pharmacokinetics[mh] OR metabolism[mh])

[1] The TSCATS2 database was accessed through Toxline (U.S. National Library of Medicine).

Database (search date)	Keywords[a]
	AND (humans[mh] OR animals[mh])) OR "dose-response relationship, drug"[mh] OR risk[mh] OR "toxicity tests"[mh] OR noxae[mh] OR cancer[sb] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR endocrine[tw] OR rat[tw] OR rats[tw] OR mouse[tw] OR mice[tw] OR "animals, laboratory"[mh])) OR ((("Dibutyl phthalate"[mh]) OR ("Dibutyl phthalate"[tw] OR "Di-n-butyl phthalate"[tw] OR "Dibutyl 1,2-benzenedicarboxylate"[tw] OR "Phthalic acid dibutyl ester"[tw] OR "1,2-Benzenedicarboxylic acid dibutyl ester"[tw] OR "1,2-Benzenedicarboxylic acid 1,2-dibutyl ester"[tw] OR "o-Benzenedicarboxylic acid dibutyl ester"[tw] OR "Benzene-o-dicarboxylic acid di-n-butyl ester"[tw] OR "Dibutyl-o-phthalate"[tw] OR "ortho-Dibutyl phthalate" OR dibutylphthalate OR "N-Butylphthalate"[tw] OR "n-Butyl phthalate"[tw] OR "di-butyl phthalate"[tw]) OR ("Celluflex DPB"[tw] OR "Elaol"[tw] OR "Ergoplast FDB"[tw] OR "Ersoplast FDA"[tw] OR "Genoplast B"[tw] OR "Hatcol DBP"[tw] OR "Hexaplas M B"[tw] OR "Kodaflex DBP"[tw] OR "Palatinol C"[tw] OR "Polycizer DBP"[tw] OR "RC Plasticizer DBP"[tw] OR "Staflex DBP"[tw] OR "Uniflex DBP"[tw] OR "Unimoll db"[tw] OR "Witcizer 300"[tw]) OR (DBP[tw] AND (phthalic acids[mh] OR phthalate[tw] OR phthalates[tw]))) AND "phthalic acids" AND /ai)
	(("Dibutyl phthalate"[mh]) OR ("Dibutyl phthalate"[tw] OR "Di-n-butyl phthalate"[tw] OR "Dibutyl 1,2-benzenedicarboxylate"[tw] OR "Phthalic acid dibutyl ester"[tw] OR "1,2-Benzenedicarboxylic acid dibutyl ester"[tw] OR "1,2-Benzenedicarboxylic acid 1,2-dibutyl ester"[tw] OR "o-Benzenedicarboxylic acid dibutyl ester"[tw] OR "Benzene-o-dicarboxylic acid di-n-butyl ester"[tw] OR "Dibutyl-o-phthalate"[tw] OR "ortho-Dibutyl phthalate" OR dibutylphthalate OR "N-Butylphthalate"[tw] OR "n-Butyl phthalate"[tw] OR "di-butyl phthalate"[tw]) OR ("Celluflex DPB"[tw] OR "Elaol"[tw] OR "Ergoplast FDB"[tw] OR "Ersoplast FDA"[tw] OR "Genoplast B"[tw] OR "Hatcol DBP"[tw] OR "Hexaplas M B"[tw] OR "Kodaflex DBP"[tw] OR "Palatinol C"[tw] OR "Polycizer DBP"[tw] OR "RC Plasticizer DBP"[tw] OR "Staflex DBP"[tw] OR "Uniflex DBP"[tw] OR "Unimoll db"[tw] OR "Witcizer 300"[tw]) OR (DBP[tw] AND (phthalic acids[mh] OR phthalate[tw] OR phthalates[tw]))) NOT medline[sb]
	(("Dibutyl phthalate"[mh]) OR ("Dibutyl phthalate"[tw] OR "Di-n-butyl phthalate"[tw] OR "Dibutyl 1,2-benzenedicarboxylate"[tw] OR "Phthalic acid dibutyl ester"[tw] OR "1,2-Benzenedicarboxylic acid dibutyl ester"[tw] OR "1,2-Benzenedicarboxylic acid 1,2-dibutyl ester"[tw] OR "o-Benzenedicarboxylic acid dibutyl ester"[tw] OR "Benzene-o-dicarboxylic acid di-n-butyl ester"[tw] OR "Dibutyl-o-phthalate"[tw] OR "ortho-Dibutyl phthalate" OR dibutylphthalate OR "N-Butylphthalate"[tw] OR "n-Butyl phthalate"[tw] OR "di-butyl phthalate"[tw]) OR ("Celluflex DPB"[tw] OR "Elaol"[tw] OR "Ergoplast FDB"[tw] OR "Ersoplast FDA"[tw] OR "Genoplast B"[tw] OR "Hatcol DBP"[tw] OR "Hexaplas M B"[tw] OR "Kodaflex DBP"[tw] OR "Palatinol C"[tw] OR "Polycizer DBP"[tw] OR "RC Plasticizer DBP"[tw] OR "Staflex DBP"[tw] OR "Uniflex DBP"[tw] OR "Unimoll db"[tw] OR "Witcizer 300"[tw]) OR (DBP[tw] AND (phthalic acids[mh] OR phthalate[tw] OR phthalates[tw]))) AND ("Computational biology"[mh] OR "Bio-Informatics"[mh] OR "Bioinformatics"[mh] OR "Computational Molecular Biology"[mh] OR "Molecular Biology, Computational"[mh] OR "Clinical Informatics"[mh] OR "Information Science, Medical"[mh] OR "Medical informatics"[mh] OR "Genomics"[mh] OR "Genome"[mh] OR "Proteomics"[mh] OR "Proteome"[mh] OR "Metabolomics"[mh] OR "Metabolic Profile"[mh] OR "Metabolome"[mh] OR "Microarray"[mh] OR "Nanoarray"[mh] OR "Gene"[mh] OR "Genes"[mh] OR "Gene expression"[mh] OR "Transcript expression"[mh] OR "transcriptomes"[mh] OR "Phenotype"[mh] OR "Transcription"[mh] OR "genetics"[mh] OR "genotype"[mh] OR "transcriptome"[mh] OR "Systems biology"[mh] OR "Biological systems AND (monitoring OR data OR analysis)"[mh] OR "Genetic transcription"[mh] OR "Gene transcription"[mh] OR "Gene Activation"[mh] OR "Genetic induction"[mh] OR "Reverse transcription"[mh] OR "Transcriptional activation"[mh] OR "Transcription factors"[mh] OR "Biosynthesis AND (RNA OR DNA)"[mh] OR "mRNA"[mh] OR "messenger RNA"[mh] OR

Database (search date)	Keywords[a]
	"transfer RNA"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "protein synthesis"[mh] OR "RT-PCR"[mh] OR "RTPCR"[mh] OR "Reverse Transcriptase Polymerase Chain Reaction"[mh] OR "DNA sequence"[mh] OR "Trans-activators"[mh])
Web of Science 01/2014 06/2013 11/2012	((TS=DBP AND TS=phthalat*) OR (TS="dibutyl phthalate" OR TS="di-n-butyl phthalate" OR TS="dibutyl 1,2-benzenedicarboxylate" OR TS="phthalic acid dibutyl ester" OR TS="1,2-benzenedicarboxylic acid dibutyl ester" OR TS="1,2-benzenedicarboxylic acid 1,2-dibutyl ester" OR TS="dibutyl-o-phthalate" OR TS=dibutylphthalate OR TS="n-butylphthalate" OR TS="n-butyl phthalate" OR TS="di-butyl phthalate")) AND (TS=chronic OR TS=immun* OR TS=lymph* OR TS=neurotox* OR TS=toxicokin* OR TS=pharmacokin* OR TS=biomarker* OR TS=neurolog* OR TS=subchronic OR TS=pbpk OR TS=epidemiolog* OR TS=acute OR TS=subacute OR TS=ld50)
	((TS=DBP AND TS=phthalat*) OR (TS="dibutyl phthalate" OR TS="di-n-butyl phthalate" OR TS="dibutyl 1,2-benzenedicarboxylate" OR TS="phthalic acid dibutyl ester" OR TS="1,2-benzenedicarboxylic acid dibutyl ester" OR TS="1,2-benzenedicarboxylic acid 1,2-dibutyl ester" OR TS="dibutyl-o-phthalate" OR TS=dibutylphthalate OR TS="n-butylphthalate" OR TS="n-butyl phthalate" OR TS="di-butyl phthalate")) AND (TS=lc50 OR TS=inhal* OR TS=pulmon* OR TS=nasal OR TS=lung* OR TS=respir* OR TS=occupation* OR TS=workplace OR TS=worker* OR TS=oral OR TS=orally OR TS=ingest* OR TS=gavage OR TS=diet OR TS=diets OR TS=dietary OR TS=drinking OR TS=gastr* OR TS=intestin*)
	((TS=DBP AND TS=phthalat*) OR (TS="dibutyl phthalate" OR TS="di-n-butyl phthalate" OR TS="dibutyl 1,2-benzenedicarboxylate" OR TS="phthalic acid dibutyl ester" OR TS="1,2-benzenedicarboxylic acid dibutyl ester" OR TS="1,2-benzenedicarboxylic acid 1,2-dibutyl ester" OR TS="dibutyl-o-phthalate" OR TS=dibutylphthalate OR TS="n-butylphthalate" OR TS="n-butyl phthalate" OR TS="di-butyl phthalate")) AND (TS=gut OR TS=sensitiz* OR TS=abort* OR TS=abnormalit* OR TS=embryo* OR TS=cleft* OR TS=fetus* OR TS=foetus* OR TS=fetal* OR TS=foetal* OR TS=fertil* OR TS=malform* OR TS=ovum OR TS=ova OR TS=ovary OR TS=placenta* OR TS=pregnan*)
	((TS=DBP AND TS=phthalat*) OR (TS="dibutyl phthalate" OR TS="di-n-butyl phthalate" OR TS="dibutyl 1,2-benzenedicarboxylate" OR TS="phthalic acid dibutyl ester" OR TS="1,2-benzenedicarboxylic acid dibutyl ester" OR TS="1,2-benzenedicarboxylic acid 1,2-dibutyl ester" OR TS="dibutyl-o-phthalate" OR TS=dibutylphthalate OR TS="n-butylphthalate" OR TS="n-butyl phthalate" OR TS="di-butyl phthalate")) AND (TS=dermal* OR TS=dermis OR TS=skin OR TS=epiderm* OR TS=cutaneous OR TS=carcinog* OR TS=cocarcinog* OR TS=cancer OR TS=precancer OR TS=neoplas* OR TS=tumor* OR TS=tumour* OR TS=oncogen* OR TS=lymphoma* OR TS=carcinom* OR TS=genetox* OR TS=genotox* OR TS=mutagen* OR TS=nephrotox* OR TS=hepatotox* OR TS=endocrin* OR TS=estrogen* OR TS=androgen*)
	((TS=DBP AND TS=phthalat*) OR (TS="dibutyl phthalate" OR TS="di-n-butyl phthalate" OR TS="dibutyl 1,2-benzenedicarboxylate" OR TS="phthalic acid dibutyl ester" OR TS="1,2-benzenedicarboxylic acid dibutyl ester" OR TS="1,2-benzenedicarboxylic acid 1,2-dibutyl ester" OR TS="dibutyl-o-phthalate" OR TS=dibutylphthalate OR TS="n-butylphthalate" OR TS="n-butyl phthalate" OR TS="di-butyl phthalate")) AND (TS=hormon* OR TS=blood OR TS=serum OR TS=urine OR TS=bone OR TS=bones OR TS=skelet* OR TS=rat OR TS=rats OR TS=mouse)
	((TS=DBP AND TS=phthalat*) OR (TS="dibutyl phthalate" OR TS="di-n-butyl phthalate" OR TS="dibutyl 1,2-benzenedicarboxylate" OR TS="phthalic acid dibutyl ester" OR TS="1,2-benzenedicarboxylic acid dibutyl ester" OR TS="1,2-benzenedicarboxylic acid 1,2-dibutyl ester" OR TS="dibutyl-o-phthalate" OR TS=dibutylphthalate OR TS="n-butylphthalate" OR TS="n-butyl phthalate" OR TS="di-butyl phthalate")) AND (TS=mice OR TS=guinea OR

Database (search date)	Keywords[a]
	TS=muridae OR TS=rabbit* OR TS=lagomorph* OR TS=hamster* OR TS=ferret* OR TS=gerbil* OR TS=rodent* OR TS=dog OR TS=dogs OR TS=beagle* OR TS=canine OR TS=cats OR TS=feline OR TS=pig OR TS=pigs OR TS=swine OR TS=porcine OR TS=monkey* OR TS=macaque* OR TS=baboon* OR TS=marmoset* OR TS=toxic* OR TS=adverse OR TS=poisoning)
	((TS=DBP AND TS=phthalat*) OR (TS="dibutyl phthalate" OR TS="di-n-butyl phthalate" OR TS="dibutyl 1,2-benzenedicarboxylate" OR TS="phthalic acid dibutyl ester" OR TS="1,2-benzenedicarboxylic acid dibutyl ester" OR TS="1,2-benzenedicarboxylic acid 1,2-dibutyl ester" OR TS="dibutyl-o-phthalate" OR TS=dibutylphthalate OR TS="n-butylphthalate" OR TS="n-butyl phthalate" OR TS="di-butyl phthalate")) AND (TS=prenatal OR TS=perinatal OR TS=postnatal OR TS=reproduc* OR TS=steril* OR TS=teratogen* OR TS=sperm* OR TS=neonat* OR TS=newborn* OR TS=development* OR TS=zygote* OR TS=child OR TS=children OR TS=adolescen* OR TS=infant* OR TS=wean* OR TS=offspring OR TS=age)
	((TS=DBP AND TS=phthalat*) OR (TS="dibutyl phthalate" OR TS="di-n-butyl phthalate" OR TS="dibutyl 1,2-benzenedicarboxylate" OR TS="phthalic acid dibutyl ester" OR TS="1,2-benzenedicarboxylic acid dibutyl ester" OR TS="1,2-benzenedicarboxylic acid 1,2-dibutyl ester" OR TS="dibutyl-o-phthalate" OR TS=dibutylphthalate OR TS="n-butylphthalate" OR TS="n-butyl phthalate" OR TS="di-butyl phthalate")) AND (TS="Genomics" OR TS="Proteomics" OR TS="Metabolic Profile" OR TS="Metabolome" OR TS="Metabolomics" OR TS="Microarray" OR TS="Nanoarray")
	((TS=DBP AND TS=phthalat*) OR (TS="dibutyl phthalate" OR TS="di-n-butyl phthalate" OR TS="dibutyl 1,2-benzenedicarboxylate" OR TS="phthalic acid dibutyl ester" OR TS="1,2-benzenedicarboxylic acid dibutyl ester" OR TS="1,2-benzenedicarboxylic acid 1,2-dibutyl ester" OR TS="dibutyl-o-phthalate" OR TS=dibutylphthalate OR TS="n-butylphthalate" OR TS="n-butyl phthalate" OR TS="di-butyl phthalate")) AND (TS="Gene expression" OR TS="Transcript expression" OR TS="transcriptomes" OR TS="transcriptome" OR TS="Phenotype" OR TS="Transcription" OR TS="Trans-act*" OR TS="transact*" OR TS="trans act*" OR TS=genetic OR TS="genetics" OR TS="genotype")
	((TS=DBP AND TS=phthalat*) OR (TS="dibutyl phthalate" OR TS="di-n-butyl phthalate" OR TS="dibutyl 1,2-benzenedicarboxylate" OR TS="phthalic acid dibutyl ester" OR TS="1,2-benzenedicarboxylic acid dibutyl ester" OR TS="1,2-benzenedicarboxylic acid 1,2-dibutyl ester" OR TS="dibutyl-o-phthalate" OR TS=dibutylphthalate OR TS="n-butylphthalate" OR TS="n-butyl phthalate" OR TS="di-butyl phthalate")) AND (TS="Genetic transcription" OR TS="Gene transcription" OR TS="Gene Activation" OR TS="Genetic induction" OR TS="Reverse transcription" OR TS="Transcriptional activation" OR TS="Transcription factors" OR (TS="Biosynthesis" AND (TS=RNA OR TS=DNA)) OR TS="mRNA")
	((TS=DBP AND TS=phthalat*) OR (TS="dibutyl phthalate" OR TS="di-n-butyl phthalate" OR TS="dibutyl 1,2-benzenedicarboxylate" OR TS="phthalic acid dibutyl ester" OR TS="1,2-benzenedicarboxylic acid dibutyl ester" OR TS="1,2-benzenedicarboxylic acid 1,2-dibutyl ester" OR TS="dibutyl-o-phthalate" OR TS="dibutylphthalate" OR TS="n-butylphthalate" OR TS="n-butyl phthalate" OR TS="di-butyl phthalate")) AND (TS="messenger RNA" OR TS="transfer RNA" OR TS="peptide biosynthesis" OR TS="protein biosynthesis" OR TS="protein synthesis" OR TS="RT-PCR" OR TS="RTPCR" OR TS="Reverse Transcriptase Polymerase Chain Reaction" OR TS="DNA sequence")
Toxline 01/2014 06/2013 11/2012	@OR+("dibutyl+phthalate" + "di-n-butyl+phthalate" + "dibutyl+1,2-benzenedicarboxylate" + "phthalic+acid+dibutyl+ester" + "1,2-benzenedicarboxylic+acid+dibutyl+ester" + "1,2-benzenedicarboxylic+ acid+1,2-dibutyl+ester" + "o-benzenedicarboxylic + acid+dibutyl+ester"+ "benzene-o-dicarboxylic+acid+di-n-butyl+ester" + "dibutyl-o-phthalate" + "ortho-dibutyl+phthalate" + dibutylphthalate + "n-butylphthalate" + "n-butyl+phthalate" +

Database (search date)	Keywords[a]
	"di-butyl+phthalate" + "celluflex+dpb"+ "elaol" + "ergoplast+fdb" + "ersoplast+fda" + "genoplast+b" + "hatcol+dbp" + "hexaplas+m+b" + "kodaflex+dbp" + "palatinol+c"+ "polycizer+dbp"+ "rc+plasticizer+dbp" + "staflex+dbp" + "uniflex+dbp"+ "unimoll+db" + "witcizer+300"+"84 74 2"+ @term+@rn+84-74-2)+@NOT+ @org+pubmed+pubdart+crisp+tscats
TSCATS2 via ToxLine 11/2012	@term+@rn+84-74-2+@AND+@org+tscats

1 [a]The search strings and search terms described in the table captured studies using the parent compound and the
2 metabolite MBP.

3 **Table 2-2. Summary of additional search strategies for DBP**

Approach used	Source(s)	Date performed	Number of additional citations identified
Manual search of citations from regulatory documents	Toxicological Profile: ATSDR (2001) "Toxicological Profile for Di-n-butyl Phthalate"	05/2013	31 citations added
	Toxicity Review: CPSC (2010) "Toxicity Review for Di-n-butyl Phthalate"	05/2013	8 citations added
Web of Science, forward search	Mahood et al. (2007)[2] In utero exposure to di(n-butyl) phthalate and testicular dysgenesis: comparison of fetal and adult end points and their dose sensitivity. Environ Health Perspect. 115: 55-61.	05/2013	3 citations added
	Mylchreest et al. (2000)[3] Dose-dependent alterations in androgen-regulated male reproductive development in rats exposed to Di(n-butyl) phthalate during late gestation. Toxicol Sci. 55(1):143-51.	05/2013	29 citations added
Web of Science, backward search	Mahood et al. (2007) In utero exposure to di(n-butyl) phthalate and testicular dysgenesis: comparison of fetal and adult end points and their dose sensitivity. Environ Health Perspect. 115: 55-61.	05/2013	0 citations added
	Mylchreest et al. (2000) Dose-dependent alterations in androgen-regulated male reproductive development in rats exposed to Di(n-butyl) phthalate during late gestation. Toxicol Sci. 55(1):143-51.	05/2013	2 citations added

[2] Key study identified in CPSC (2010)

[3] Key study identified in ATSDR (2001)

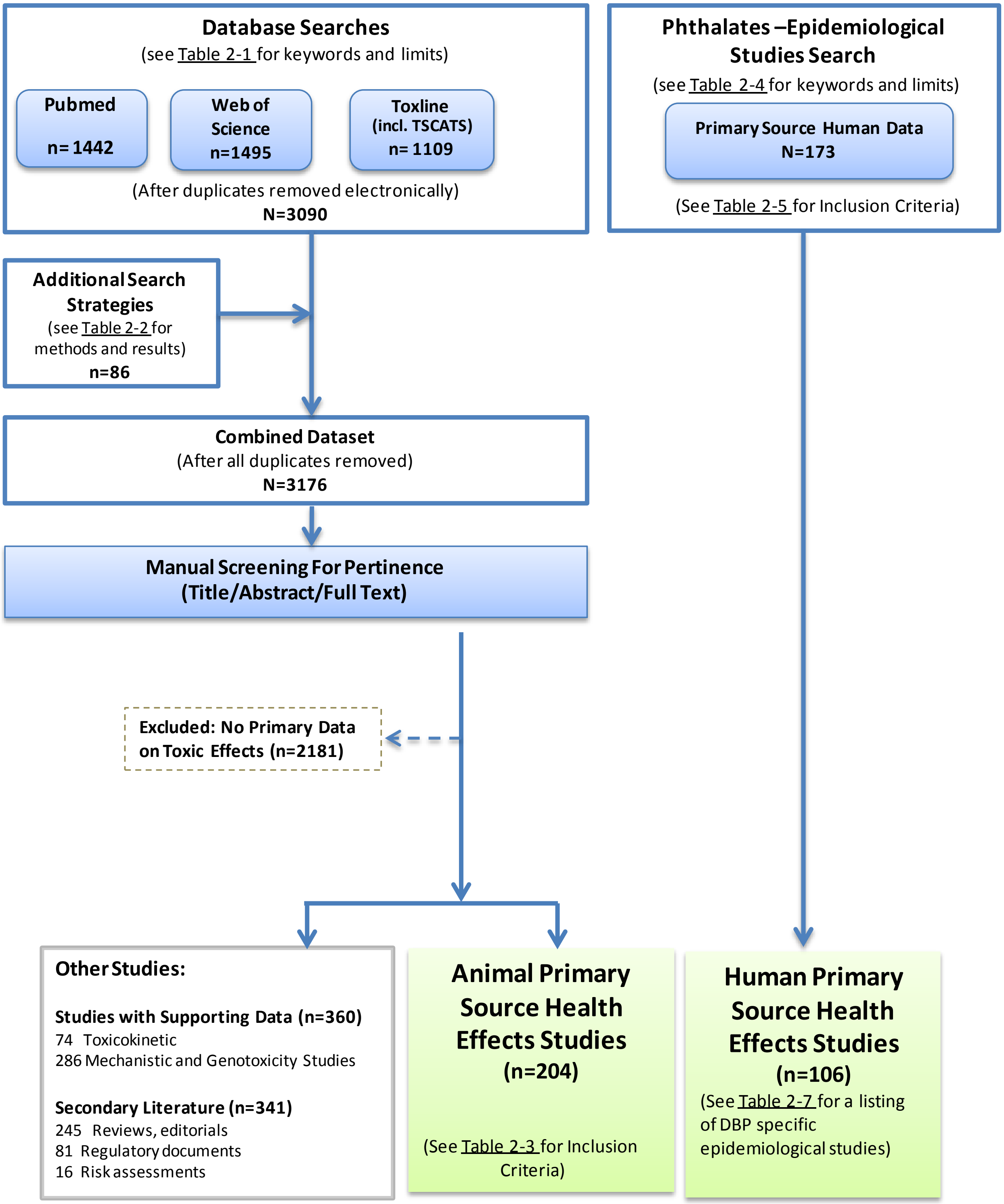
Approach used	Source(s)	Date performed	Number of additional citations identified
References obtained during the assessment process	DBP references in previous assessment or previously added to the HERO project page	11/2014	8 citations added
Background check	Searched a combination of CASRNs and synonyms on the following databases: ACGIH (http://www.acgih.org/home.htm) ATSDR (http://www.atsdr.cdc.gov/substances/index.asp) CalEPA Office of Environmental Health Hazard Assessment (http://www.oehha.ca.gov/risk.html) OEHHA Toxicity Criteria Database (http://www.oehha.ca.gov/tcdb/index.asp) Biomonitoring California-Priority Chemicals (http://www.oehha.ca.gov/multimedia/biomon/pdf/PriorityChemsCurrent.pdf) Biomonitoring California-Designated Chemicals (http://www.oehha.ca.gov/multimedia/biomon/pdf/DesignatedChemCurrent.pdf) Cal/Ecotox database (http://www.oehha.ca.gov/scripts/cal_ecotox/CHEMLIST.ASP) OEHHA Fact Sheets (http://www.oehha.ca.gov/public_info/facts/index.html) 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) CPSC (http://www.cpsc.gov) eChemPortal (http://www.echemportal.org/echemportal/participant/page.action?pageID=9) Environment Canada – Search entire site if not found below: (http://www.ec.gc.ca/default.asp?lang=En&n=ECD35C36) Toxic Substances Managed under CEPA (http://www.ec.gc.ca/toxiques-toxics/Default.asp?lang=En&n=98E80CC6-1) Screening Assessment reports Risk Management reports Final Assessments (http://www.ec.gc.ca/lcpe-cepa/default.asp?lang=En&xml=09F567A7-B1EE-1FEE-73DB-8AE6C1EB7658)	03/2013	5 citations added

Approach used	Source(s)	Date performed	Number of additional citations identified
	Draft Assessments (http://www.ec.gc.ca/lcpe-cepa/default.asp?lang=En&xml=6892C255-5597-C162-95FC-4B905320F8C9) EPA Acute Exposure Guideline Levels (http://www.epa.gov/oppt/aegl/pubs/chemlist.htm) EPA – IRISTrack/New Assessments and Reviews EPA NSCEP (http://www.epa.gov/ncepihom/) EPA RfD/RfC and CRAVE meeting notes EPA Science Inventory (http://cfpub.epa.gov/si/) FDA (http://www.fda.gov/) Federal Docket (www.regulations.gov) Health Canada First Priority List Assessments (http://www.hc-sc.gc.ca/ewh-semt/pubs/contaminants/psl1-lsp1/index-eng.php) Health Canada Second Priority List Assessments (http://www.hc-sc.gc.ca/ewh-semt/pubs/contaminants/psl2-lsp2/index-eng.php) IARC (http://monographs.iarc.fr/htdig/search.html) ITER (TERA database) (http://iter.ctcnet.net/publicurl/pub_search_list.cfm) NAP – Search Site (http://www.nap.edu/) NRC – AEGLs via NAP search for "Acute Exposure Guideline Level" and the chemical NCI (http://www.cancer.gov) NCTR (http://www.fda.gov/AboutFDA/CentersOffices/OC/OfficeofScientificandMedicalPrograms/NCTR/default.htm) National Institute for Environmental Health Sciences (NIEHS) http://www.niehs.nih.gov/ NICNAS (PEC only covered by eChemPortal) (http://www.nicnas.gov.au/industry/aics/search.asp) NIOSH (http://www.cdc.gov/niosh/topics/) NIOSHTIC 2 (http://www2a.cdc.gov/nioshtic-2/) NTP - RoC, status, results, and management reports (http://ntpsearch.niehs.nih.gov/query.html) OSHA (http://www.osha.gov/dts/chemicalsampling/toc/toc_chemsamp.html) RTECS http://www.ccohs.ca/search.html		

These citations were screened using the title, abstract, and in some instances, full text for pertinence to examine the health effects of DBP exposure. The citations were 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 DBP package. The process for screening the literature search is described below and is shown graphically in Figure 2-1:

- 204 references were identified as animal studies with health effects data and were considered for data extraction to evidence tables and exposure-response arrays.
- 360 references were identified as supporting studies; of these, 74 were toxicokinetic studies and 286 were mechanistic and genotoxicity studies.
- 341 references were identified as secondary literature (e.g., reviews and editorials, risk assessments, regulatory documents); these references are not included in the set of primary source health effects studies but were considered as additional resources.
- 2,181 references were excluded because these studies did not include primary source data evaluating DBP in relation to any kind of toxicity or health endpoint, and did not provide either supporting information (e.g., toxicokinetic or mechanistic/genotoxicity data) or secondary literature information.

Note that some studies were identified as belonging to multiple categories. As a result, the total number of studies in a given category may be less than the sum of the individual studies listed in subcategories.



Note: Studies containing multiple information categories were sorted into multiple tags. For this reason, the subcategory numbers do not always add up to the category total.

Figure 2-1. Literature search approach for DBP.

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

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

A total 180 foreign language studies were identified in the literature search. Fifty-four of these publications report pertinent evidence for hazard characterization and/or dose-response. These studies [(Li et al., 2013; Zhou et al., 2013; Zhang et al., 2012; Zhou et al., 2012; Chang et al., 2010; Chen et al. (2010); Dobrzyńska et al., 2010; Hu et al., 2010; Man et al., 2010; Zhang et al., 2009a; Brucker-Davis et al., 2008a; Li et al., 2008; Lin et al., 2008a; Lin et al., 2008b; Long et al., 2008; Xu et al., 2008; Ao et al., 2007; Chang et al. (2007); Qiao et al., 2007; Wu et al., 2006; Shi et al., 2005; Wang et al., 2005; Wang et al., 2004b; Wang et al., 2004a; Zhang et al., 2004a; Zhang et al., 2004c; Kobayashi et al., 2003; Nakahara et al., 2003; Yu et al., 2003b; Yu et al., 2003c; Yu et al., 2003a; Eom et al., 2002; Kleinsasser et al., 2001; Yuan et al., 2001; Kleinsasser et al., 1999b; Kleinsasser et al., 1999a; Wan et al., 1998; Astapova et al., 1990; Wang and Zhang, 1989; Ikemoto et al., 1988; Timofievskaya et al., 1988; Zinchenko, 1986; Turbin et al., 1983; Kawano, 1980a, b; Timofievskaya et al., 1980; Lagente et al., 1978; Hamano et al., 1977; Shcherbak, 1977; Balynina and Berezovskaia, 1976; Antoniuk and Aldyreva, 1973; Piekacz, 1971a, b; Cagianut, 1954)] were tagged under "Kept for Further Review" in HERO but are not shown in the figure. The available foreign language studies will be considered individually for translation and inclusion in evidence tables during development of the draft assessment of the available evidence of DBP-induced health effects.

Seventy-six 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 DBP 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., diisobutyl phthalate [DiBP], DBP, butyl benzyl phthalate [BBP], di(2-ethylhexyl)phthalate [DEHP], di-ethyl phthalate [DEP], diisononyl phthalate [DINP], and dipentyl phthalate [DPP]). 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 is 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 DBP 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 and in June 2014. 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 PubMed 06/2013 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 After duplicates deleted: 2,482
Web of Science 06/2013 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 After duplicates deleted: 1,836
ToxNet 06/2013 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 After duplicates deleted: 2,426
Merged Reference Set	Merged dataset, with duplicates eliminated through electronic screen **Epidemiology articles meeting inclusion criteria**	4,127 **127**

Database, search date	Terms	Hits
December 2013 search	PubMed Web of Science ToxNet Merged dataset **Epidemiology articles meeting inclusion criteria**	155 249 114 350 **22**
June 2014 Search[a]	PubMed Web of Science Merged dataset **Epidemiology articles meeting inclusion criteria**	184 409 494 **24**
Total (through June 2014)		173

[a]ToxNet was not searched in June 2014 because no articles had been identified solely through this source in all the previous searches.

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. Earlier analyses that are updated in a subsequent paper (e.g., with a larger sample size) are not included as a primary paper, but may be used as background material regarding study methods.

One hundred and seventy-three epidemiological studies examining one or more phthalates in relation to one or more endpoints were identified by the searches conducted through June 2014 (127 in the initial search, 22 in the December 2013 update, and 24 in the June 2014 update; Figure 2-1). Other strategies to supplement this broad search for epidemiology studies of phthalates, such as review of citations noted in the background or discussion sections in the identified primary source studies (i.e., a “backward search”), have been used (or are currently in process) (see Table 2-6), resulting in the identification of 12 additional publications (Table 2-6), for a total of 185 epidemiological studies. From this set of all of the epidemiological studies examining any phthalate, 106 studies analyzed one or more health effects in relation to a measure of DBP (Table 2-7).

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

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

[a]For DBP, the primary metabolite of interest is MBP.

Table 2-6. 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	6
Review of references cited in the identified list of epidemiology studies ("backward" search)	July 2014	1
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
Inquiry of corresponding authors of primary source epidemiology articles pertaining to phthalates and selected outcomes[b] asking for missed papers or unpublished studies	November 2014	Review in process

[a]The following studies were used to conduct the forward searches: (Trasande et al. (2013b); 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. (2006a); 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)).

[b]Sexual differentiation measures, male reproductive effects, male or female pubertal development, immune (allergic conditions, asthma), neurodevelopment, diabetes, and obesity.

Table 2-7. Primary source epidemiological studies examining health effects of DBP

Outcome category	Reference[a]	DBP measure
Sexual differentiation measures (Table 3-1)	Brucker-Davis et al. (2008b) Carran and Shaw (2012) Choi et al. (2012) Huang et al. (2009) Lin et al. (2011a) Main et al. (2006) Suzuki et al. (2012) Swan (2008) Swan et al. (2010)	MBP (cord blood, colostrum) Father's history ofDBP use in military MBP (mothers and infants; urine and plasma) MBP (amniotic fluid) MBP (maternal urine) MBP (breast milk) MBP (maternal urine) MBP (maternal urine) MBP (maternal urine)
Male reproductive (semen parameters, infertility, and hormones) (Tables 3-2 and 3-4)	Buck Louis et al. (2014) Han et al. (2014) Hauser et al. (2007) Hauser et al. (2006) Joensen et al. (2012) Jonsson et al. (2005) Jurewicz et al. (2013) Kranvogl et al. (2014) Li et al. (2011) Liu et al. (2012) Meeker et al. (2009a) Mendiola et al. (2012)	MBP (urine) MBP (urine) MBP (urine) MBP (urine) MBP (urine) MBP (urine) MBP (urine) MBP (urine) DBP (serum, serum) MBP (urine) MBP (urine) MnBP + MIBP (urine)

Outcome category	Reference[a]	DBP measure
	Pan et al. (2006) Pant et al. (2014) Pant et al. (2011) Pant et al. (2008) Toshima et al. (2012) Tranfo et al. (2012) Wirth et al. (2008) Zhang et al. (2006)	MBP (urine) DBP (semen) DBP (semen) DBP (semen) MBP (urine) MBP (urine) MnBP + MIBP (urine) DBP (semen)
Male pubertal development (Table 3-3)	Ferguson et al. (2014c) Mieritz et al. (2012)	MBP (maternal and child's urine) MBP (urine)
Female pubertal development (Table 3-6)	Chen et al. (2013) Chou et al. (2009) Hart et al. (2013) Lomenick et al. (2010) Yum et al. (2013)	MBP (urine) MBP (urine MBP (maternal serum) MBP (urine) MBP (plasma)
Female reproductive (infertility, hormones, gynecological conditions) (Tables 3-5 and 3-7)	Buck Louis et al. (2013) Hart et al. (2013) Huang et al. (2010) Itoh et al. (2009) Reddy et al. (2006a) Reddy et al. (2006b) Sathyanarayana et al. (2014) Upson et al. (2013) Weuve et al. (2010)	MBP (urine) MBP (serum) MBP (urine) MBP (urine) DBP (plasma) DBP (plasma) MBP (urine) MBP (urine) MBP + MIBP (urine)
Pregnancy outcomes (fetal growth, preterm birth) (Table 3-8)	Brucker-Davis et al. (2010) Ferguson et al. (2014b) and Ferguson et al. (2014a) Huang et al. (2014b) Huang et al. (2009) Meeker et al. (2009b) Philippat et al. (2012) Suzuki et al. (2010) Toft et al. (2012) Weinberger et al. (2014) Wolff et al. (2008) Zhang et al. (2009b)	MBP (cord blood) MBP (maternal urine) DBP (cord blood) MBP (amniotic fluid) MBP (maternal urine) MBP (maternal urine) MBP (maternal urine) MBP (maternal urine) MBP (maternal urine) MBP (maternal urine) DBP (cord blood), MBP (meconium)
Immune: allergy (rhinitis, eczema) (Table 3-9)	Ait Bamai et al. (2014) Bornehag et al. (2004) Callesen et al. (2014a) Callesen et al. (2014b) Hoppin et al. (2013a) Hsu et al. (2012) Kanazawa et al. (2010) Kolarik et al. (2008) Sun et al. (2009) Wang et al. (2014)	DBP (dust) DBP (dust) MBP (urine) DBP (dust) MBP (urine) DBP (dust), MBP (urine) DBP (dust) DBP (dust) DBP (dust) MBP (maternal urine)
Immune: asthma (Table 3-10)	Ait Bamai et al. (2014) Bertelsen et al. (2013) Callesen et al. (2014a)	DBP (dust) MBP (urine) MBP (urine)

Outcome category	Reference[a]	DBP measure
	Callesen et al. (2014b) Hoppin et al. (2013a) Hsu et al. (2012) Kolarik et al. (2008) Sun et al. (2009)	DBP (dust) MBP (urine) DBP (dust), MBP (urine) DBP (dust) DBP (dust)
Thyroid (Table 3-11)	Boas et al. (2010) Brucker-Davis et al. (2011) Dirtu et al. (2013) Huang et al. (2007) Meeker et al. (2007) Jung et al. (2013) Meeker and Ferguson (2011)	MBP (urine) MBP (breast milk) MBP (urine) MBP (urine) MBP (urine) DBP, MBP (plasma) MBP (urine)
Pulmonary Function (Table 3-12)	Cakmak et al. (2014) Hoppin et al. (2004) Kolena et al. (2014) Park et al. (2013)	MBP (urine) MBP (urine) MBP (urine) MBP (urine)
Neurodevelopment (Table 3-13)	Braun et al. (2014) Cho et al. (2010) Chopra et al. (2014) Engel et al. (2010) Kim et al. (2009) Kim et al. (2011) Kobrosly et al. (2014) Miodovnik et al. (2011) Park et al. (2014) Téllez-Rojo et al. (2013) Whyatt et al. (2012)	MBP (maternal urine) MBP (child's urine) MBP + MIBP (child's urine) MBP (maternal urine) MBP (child's urine) MBP (maternal urine) MBP (maternal urine) MBP (maternal urine) MBP (child's urine) MBP (maternal urine) MBP (maternal urine)
Obesity (Table 3-14)	Buser et al. (2014) Dirtu et al. (2013) Hart et al. (2013) Hatch et al. (2008) Kasper-Sonnenberg et al. (2012) Song et al. (2014) Stahlhut et al. (2007) Svensson et al. (2011) Teitelbaum et al. (2012) Trasande et al. (2013a) Wang et al. (2013)	MBP (urine) MBP (urine) MBP (maternal serum) MBP (urine) MBP (urine) MBP + MIBP (urine) MBP + MIBP (urine) MBP (urine) MBP (urine) MBP (urine) MBP (urine)
Diabetes and insulin resistance (Table 3-15)	Hong et al. (2009) Huang et al. (2014a) James-Todd et al. (2012) Kim et al. (2013) Sun et al. (2014) Svensson et al. (2011) Stahlhut et al. (2007) Trasande et al. (2013c)	MBP (urine) MBP (urine) MBP (urine) MBP (urine) MBP + MIBP (urine) MBP (urine) MBP + MIBP (urine) MBP (urine)
Other cardiovascular disease risk factors (Table 3-16)	Shiue (2014) Trasande et al. (2013b)	MBP (urine) MBP (urine)

Outcome category	Reference[a]	DBP measure
Cancer (Table 3-17)	Carran and Shaw (2012) Lopez-Carrillo et al. (2010)	Father's history of DBP use in military MBP (urine)

[a]This listing is arranged alphabetically within each outcome category.

The literature for both epidemiological and animal studies will be regularly monitored for the publication of new studies. The documentation and results for this supplementary search can be found on the Health and Environmental Research On-line (HERO) website[4] (http://hero.epa.gov/DBP and http://hero.epa.gov/phthalates-humanstudies).

2.2. SELECTION OF STUDIES IN EARLY STAGES OF DRAFT DEVELOPMENT

2.2.1. General Approach

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 could 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. Evaluation of "quality" is generally not used as a basis for exclusion at this stage. However, the large number (204) of available animal studies examining the same or similar outcomes (e.g. reproductive, developmental, liver and kidney effects) necessitated development of a strategy to reduce the number of studies to be practically presented in this set of evidence tables. The criteria used for this process are documented in the following section (Section 2.2.2).

2.2.2. Approach for Selection of Experimental Studies

The DBP database consists of experimental studies using animal models and designed to examine repeat-dose intraperitoneal, subcutaneous or oral toxicity (including chronic, subchronic, and short-term duration studies) and endpoint-specific toxicities (including reproductive and

[4]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 DBP may not match the numbers of references identified in Figure 2-1 (current through January 2014).

developmental toxicity). Studies in which DBP was administered via the intraperitoneal or subcutaneous route of exposure were excluded from the DBP evidence tables because the intraperitoneal route of exposure is generally considered less relevant to human exposure. The remaining studies involved administration of DBP in the diet or via gavage administration. Inhalation exposure studies of chronic, or sub-chronic duration were not identified.

The DBP database is extensive and includes many multiple-dose experimental studies using the same or similar protocols and test species, and evaluate the same or simlar endpoints. Due to the size of the database of experimental studies, an approach was developed to capture the DBP-induced health effects reported in the scientific literature and pragmatically presented these effects in evidence tables. Thus, the dose ranges employed in the available studies were used to select studies for presentation in evidence tables; focusing on multi-dose studies that initiated exposure at lower levels as these studies may be more informative for human exposure. Care was taken to select a dose-range inclusive of all major health effects and to include both positive and negative data. This approach included all studies within the specified dose range regardless of the direction of the measured outcome. For development of evidence tables on effects in the male reproductive system, studies which initiated exposure at doses ≤ 100 mg/kg-day were selected for presentation in the evidence tables. This dose range was selected to capture all types of male reproductive effects reported in the scientific literature on DBP. In general, single dose and multi-dose studies that initiated exposure to animals at levels > 100 mg-kg-day were not included in the preliminary evidence tables for the male reproductive system. For all other health outcomes, studies which initiated exposure at doses ≤ 250 mg/kg-day were selected for presentation in the evidence tables.

Studies that were not presented in the evidence tables are included in the HERO database (Studies with Health Effects Data). Based upon a preliminary screening of the database, the higher dose studies are generally supportive of the studies presented in the evidence tables. The findings reported in the higher dose studies will be considered along with the lower dose studies and incorporated as part of the evaluation and integration of evidence during assessment development.

To confirm that relevant, low-dose, DBP-induced health effects identified from the literature search are captured in the preliminary evidence tables, EPA reviewed both the ATSDR (2001) and CPSC (2010) assessments. In evaluating these assessments, EPA identified one additional endpoint (cleft palate) reported in two studies (Ema et al., 1997; Ema et al., 1994) that had not been included using the dose range approach described above. Both studies were included in the preliminary evidence tables.

Additionally, human testicular tissue xenograft studies have raised questions about the human relevance of androgen-dependent male reproductive effects reported in rat studies where animals were exposed to DBP or MBP during gestation (Heger et al., 2012; Mitchell et al., 2012). It has been proposed that responses observed in mouse fetal testis may serve as more informative model of the potential DBP-induced adverse effects to the human male reproductive system (Johnson et al., 2012). Thus, in vivo mouse studies reporting effects to the male reproductive system after gestational exposure to DBP were also included in the preliminary evidence tables. Although these mouse studies included single dose and higher dose studies outside the dose range specified for the male reproductive effects, these studies were included for purposes of comparison of exposure outcomes among different species.

Overall, application of the study approach described above resulted in the selection of 71 studies for presentation in evidence tables out of a total 204 studies experimental studies identified in the literature search and tagged as Studies with Health Effects Data/Animal toxicology studies.

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 EPIDEMIOLOGICAL STUDIES FOR DBP

Several considerations will be used in EPA's evaluation of epidemiological studies of human health effects of DBP. These considerations include 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. These issues are outlined in the IRIS Preamble, and are described below, with a specific focus on data pertaining to DBP.

2.3.1. 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 internal 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, missing data, and loss to follow-up. This information is used to evaluate internal study validity related to selection bias. Different types of selection bias that may occur include the healthy worker effect, differential loss to follow up, Berkson's bias (relating to selection of participants in hospital-based case-control studies), 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, is 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. An example of differential participation would be when people with high levels of exposure and the outcome of interest are more likely to participate than people with low levels of exposure and the outcome.

The available DBP studies have generally examined metabolites from many different phthalates within the context of research on environmental exposures. 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 generally do not have knowledge of the study hypothesis or their exposure to DBP 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 DBP, 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 (for example, evidence of differences in exposure levels among people who did and did not participate in a cohort follow-up). 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.

2.3.2. Exposure Considerations

General considerations for evaluating exposure include: (1) identifying how exposure can occur (e.g., exposure sources, routes, and media); (2) determining appropriate critical exposure period(s) for the outcomes under study; (3) evaluating variability in the exposure metrics of interest (e.g., temporal and spatial variability for environmental measures or inter-individual variability for biomonitoring data) that can impact different types of exposure metrics (e.g., cumulative, average, or peak exposure); (4) determining if an appropriate analytical methodology was employed (e.g., choice of biological matrix, sampling protocol, quantification approach); (5) evaluating the choice of exposure surrogate evaluated (e.g., constituent chemical or group/mixture); and (6) evaluating the classification of individuals into exposure categories. These six considerations help determine the accuracy and precision of the exposure estimates, and the likelihood of measurement error with respect to the exposure metrics used. Nondifferential misclassification of exposure categories, for example, can also result from measurement error and is expected to predominantly result in attenuated effect estimates (Blair et al., 2007).

Some common sources of exposure to DBP include food and food packaging and dust from specific building materials, with the primary route of exposure occurring through ingestion and some exposure occurring via inhalation and dermal routes (see Section 1.1.3). Thus, exposure to DBP is typically from multiple sources, many of which result in repeated but episodic exposure on a daily basis.

Urine provides an integrated measure of phthalate exposure from all sources. Measurement of DBP metabolites, rather than the parent compound, is preferred because the parent compound is metabolized very quickly and does not provide an accurate measure of exposure. The simple monoester metabolite, MBP is the most commonly measured DBP metabolite in epidemiologic studies. The monoester metabolite is considered the primary biomarker for exposure to the low molecular weight phthalates such as DBP. MBP accounts for an estimated 84% of the urinary excretion of DBP (Koch et al., 2012). This value is based on human data from a controlled dosing study in a single volunteer (Koch et al., 2012). MBP can also be a minor metabolite of butyl benzyl phthalate (BBP): MBP represented 6% of the monoester excretion in the high BBP dose group (506 μg/day), but was not seen in the low BBP dose group (253 μg/day) in a controlled-dosing study (n=8 adults per group) (Anderson et al., 2001). EPA considers the use of

MBP to be a good proxy for total DBP exposure and does not consider the potential contribution of BBzP to observed concentrations 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. Studies examining DBP metabolites in breast milk or serum have generally reported low levels of detection (i.e., 25-50%). Hogberg et al. (2008) reported that relatively few breast milk (11 out of 42) or serum (17 out of 36) samples in a study in Sweden had detectable MBP concentrations. One study in Taiwan reported that MBP above the limit of detection was found in 33.3% of breast milk samples from 30 women. The detection rate in 30 cord blood samples in this study was 100%, but the correlation between MBP measured in cord blood and maternal urine was -0.01 (Pearson correlation of log-transformed levels) (Lin et al., 2011b). Among 60 men ages 18-26 years, 40.7% of serum samples and 13.3% of seminal plasma samples had MBP concentrations above the limit of detection (Frederiksen et al., 2010). The Spearman correlation between urine and serum and between urine and seminal plasma concentrations were reported to be non-significant (correlation coefficients not provided) (Frederiksen et al., 2010). The lower detection rate in tissues other than urine reduces EPA's confidence in DBP metabolite measures in these biological matrices.

Given their first-order kinetics with half-lives on the order of hours [2.6 hours for MBP in (Koch et al., 2012)] 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 139 pregnant women in Puerto Rico included measurement of MBP and found little difference in specific gravity-adjusted concentrations in samples collected in early morning, mid-morning, early afternoon, or evening (Cantonwine et al., 2014). Urinary measures of DBP 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., 2012) and that a single spot sample was reliable in ranking subjects according to tertile of MBP (Teitelbaum et al., 2008). Based on this information, EPA does not consider the reliance on spot urine samples for exposure estimation (including ranking of individuals into different DBP 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, outliers) when evaluating analyses based on use of DBP metabolites as continuous measures.

Another potential limitation of measurement of DBP 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). There is some indication of an inverse association between ICC and length of time between measurements taken over a period of less than one week to several months) (i.e., higher ICCs seen with shorter time periods) (Figure 2-2). The lowest ICC (0.17) was in a study of pregnancy women comparing samples taken in the first to third trimester (Irvin et al., 2010), and the highest ICC (0.80) was in a study comparing samples taken two days apart (Hoppin et al., 2002). Most results were in the moderate to high range (median ICC 0.55). One study analyzed samples taken 1 to 3 years apart among participants in the Nurses Health Study (and Nurses Health Study II), and reported an ICC of 0.53 for all samples (Townsend et al., 2013). Only two of these studies focused on men (Hauser et al., 2004) or children (Teitelbaum et al., 2008); although data are more limited in these populations, the ICC results were similar to those seen in other populations (Figure 2-2).

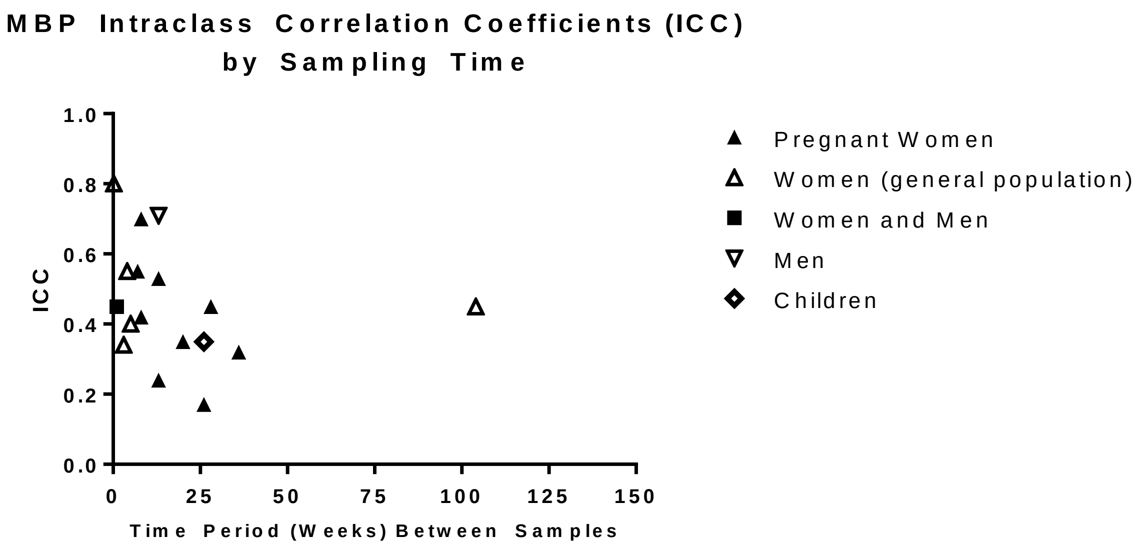


Figure 2-2. Summary of studies of reliability of MBP measures in humans.

The Intraclass Correlation Coefficient (ICC) is a measure of between- and within-person variability; a higher ICC indicates greater reproducibility (i.e., lower within-person variance). Studies of pregnant women: Adibi et al. (2008) [n = 28]; Braun et al. (2012) [n=137]; Cantonwine et al. (2014) [n=139]; Fisher and Eugster (2014) [n = 70]; Irvin et al. (2010) [n=64]; Suzuki et al. (2009) [n=120]. Studies of general population women: Baird et al. (2010) [n = 60]; Braun et al. (2012) [n=137]; Hoppin et al. (2002) [n = 46]; Peck et al. (2010) [n = 45]; Townsend et al. (2013) [n = 45]. Studies of general population women and men: Fromme et al., 2007 [n = 50]. Studies of general population men: Hauser et al. (2004) [n = 11]. Studies of children: Teitelbaum et al. (2008) [n = 60].

The available data highlight the value of repeated exposure measures collected during the appropriate critical period for the outcome(s) under study. Based on these studies, however, EPA does not consider the use of a single measurement to be a major limitation in studies in adults in which the measure of exposure is closely aligned (within a few months) with the relevant window(s) of exposure, if known, for the effect under study. EPA has greater uncertainty, however, about measurements taken outside of the relevant time window (e.g., several years after diagnosis, or the difference between first and third trimesters of pregnancy).

Some studies present analyses using a combined measure based on summation of MIBP and MBP, as a measure of both DIBP and DBP, respectively. The relative contribution of DBP to this total has varied over time (as the use of DIBP has increased), and can vary between populations (e.g., greater use of DIBP compared with DBP in some countries). Some studies do not specifically distinguish between MBP and MIBP; NHANES did not make this distinction until the 2001-2002 collection cycle (Figure 2-3). EPA includes studies in the DBP evidence tables using this summed exposure measure except in situations in which the concentration of MIBP is expected to be greater than that of MBP (based on specific data provided from the study or from other studies conducted in a similar population and time period). EPA recognizes that this combined measure introduces an additional source of exposure misclassification, but does not consider this to be a major limitation affecting the interpretation of these studies.

Other studies present analyses using a combined "low molecular weight" phthalate measure based on the summation of MIBP, MBP, and monoethyl phthalate (MEP) (reflecting exposure to the parent compounds of DIBP, DBP, and DEP, respectively). Because MBP does not represent a major contributor to this summation measurement, EPA has not included data from these studies in the DBP evidence tables.

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 lead to a behavioral change that results in a change in DBP exposure. This type of scenario adds an additional challenge, and greater uncertainty, to the interpretation of the DBP metabolites as valid measures of exposure in a relevant time window(s) with respect to disease development.

The distribution of exposure will also be considered 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.

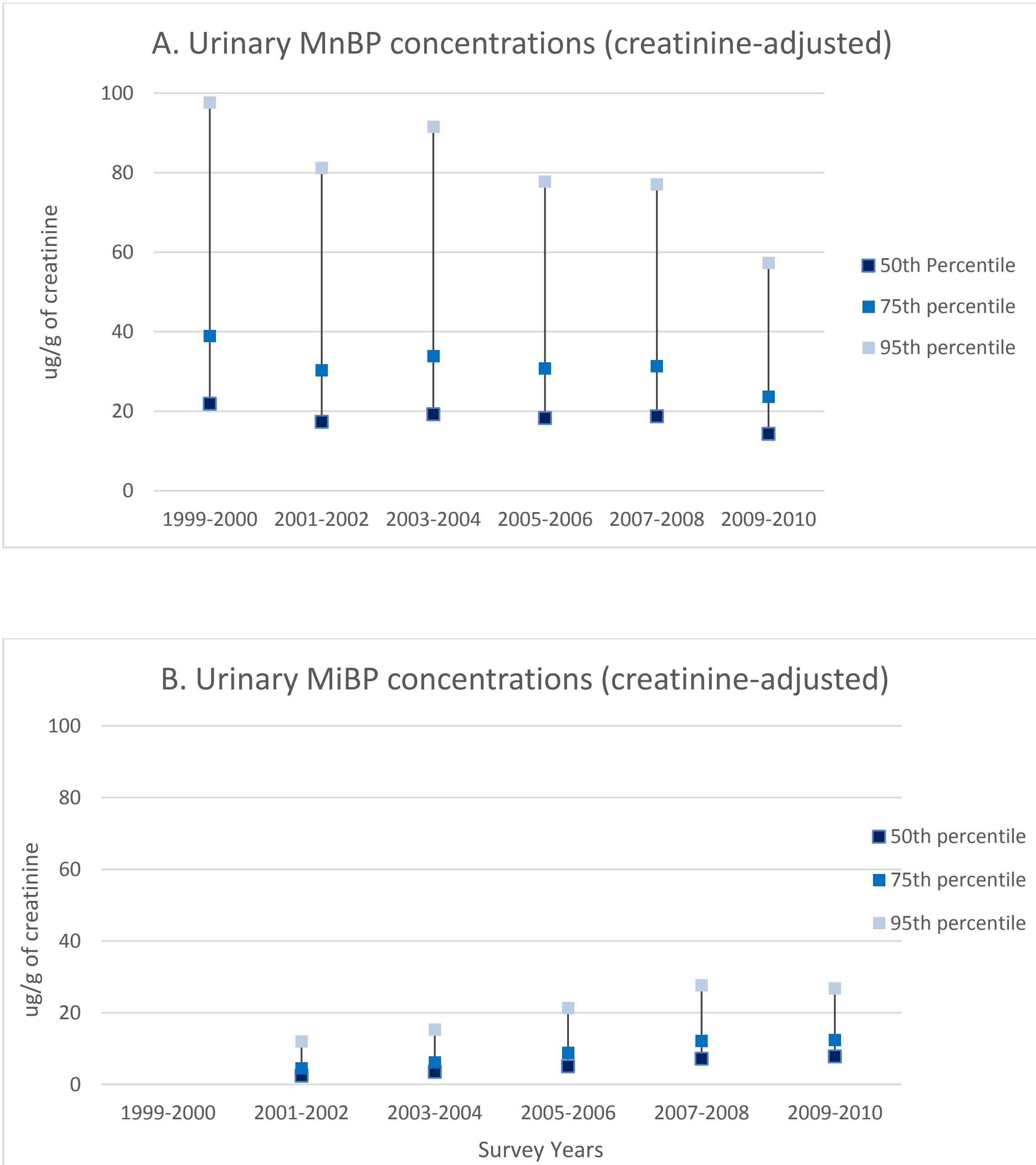


Figure 2-3. Urinary concentration of MnBP (Panel A) and MIBP (Panel B) in United States population.

Data from National Health and Nutrition Examination Survey (NHANES), 1999 to 2010 (CDC, 2013).

2.3.3. Primary Outcome Measures

The general considerations for evaluating issues relating to accuracy, reliability, and biological relevance of outcomes include adequate length of follow-up 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). With respect to continuous measures, such as hormone concentrations or semen parameters, EPA will consider, in addition to assessing whether reported parameters are outside normal physiological range, evidence of smaller changes in the distribution of a parameter that may represent an effect on a population level [e.g., as is the case for early childhood exposure to lead and decrements in intelligence as measured by IQ (U.S. EPA, 2013)].

Issues relating to assessment of the specific primary health effects are discussed below and summarized in Table 2-8 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 or over a narrow age range and lesser confidence in studies among a group spanning a larger age range.

Gender-related behaviors, as measured by the Pre-School Activities Inventory (Golombok and Rust, 1993) or other scales, has been examined in relation to direct or indirect measures of fetal testosterone levels, including studies of DBP. This outcome measure has been examined in studies of relatively rare genetic conditions (e.g., congenital adrenal hyperplasia and complete androgen insensitivity syndrome), as well as in studies focusing on the normal variability seen in the general population [reviewed in (Hines, 2006)]. EPA will consider evidence pertaining to the reliability and validity of the Pre-School Activities Inventory in its evaluation of studies using this scale.

Male and Female Reproductive Outcomes

The DBP literature includes studies of reproductive and gonadotropin hormone levels in men and studies of semen parameters that can be indicative of reduced fertility. 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. 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.

Much of the focus of the research on male steroidal and gonadotropin hormones in the DBP 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.

The DBP literature also includes studies of reproductive hormones in women. In addition to the general considerations regarding hormone assays noted above, timing within a menstrual cycle for studies of pre- and peri-menopausal women, and timing with respect to gestational age for studies of women during pregnancy, are also be an important considerations for interpretation of reproductive hormone concentrations.

Another female reproductive outcome included in the DBP literature is endometriosis. 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.

Infertility is generally defined clinically and for research purposes as the inability to conceive a clinically-recognized pregnancy after 12 months of intercourse of regular frequency without use of contraceptives. Fecundity or fecundability are terms for the capacity for reproduction. “Time to pregnancy” (i.e., the number of cycles of unprotected intercourse before conception) has been used as a measure of fecundability in studies of environmental and occupational exposures (Baird et al., 1986; Baird and Wilcox, 1985). Time to pregnancy is a measure of a couple’s fecundability, incorporating effects that can be manifested through the male or female (or both). Considerations in time to pregnancy studies include the source of data (i.e., retrospective or prospective designs) and incorporation of information on “non-pregnancy planners” (Weinberg et al., 1994).

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 males 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.

Pregnancy-Related Outcomes

Infant birth weight and gestational age are two outcomes commonly used in reproductive epidemiology studies. EPA considers analyses of the various indices for both outcomes (fetal growth and gestational age) to be informative with respect to hazard identification, but will consider each separately as they address different issues. Gestational duration can be measured as a continuous outcome or dichotomous outcome such as preterm birth. Preterm births include infants delivered earlier than 37 gestational weeks, and those delivered earlier than 32 gestational weeks are classified as very preterm births. Different measures of fetal growth restriction are often examined in epidemiological studies. In addition to the continuous measure of birth weight, another commonly used measure of fetal growth restriction is the categorical variable of low birth weight (defined as <2,500 g). Small for gestational age (defined as birth weight less than the 10^{th} percentile for the gestational birth weight distribution) is considered a better measure of fetal growth rate as it takes into consideration gestational duration, and would be preferred over a measure of birth weight in a study that includes preterm births. Birth weight and gestational duration can also be examined as continuous variables, often in analysis that excludes preterm or low birth weight births, so that the focus of the analysis is on variability within the "normal" range.

EPA considers birth weight obtained from medical records 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). Menstrual dating of gestational age dependent on maternal recall of the last menstrual period can be subject to considerable measurement error in some cases, so ultrasonography-based estimates may be considered more accurate (Savitz et al., 2002; Taipale and Hiilesmaa, 2001).

Immune-Related Outcomes: Allergy and Asthma

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).

Neurodevelopment

With respect to neurodevelopmental outcomes, a major consideration is the assessment tool(s) used by the study investigators; details of the assessment method, or references providing this information, should be provided. In addition, EPA also looks for discussion of (or reference to) validation studies and the appropriateness of the tool for evaluation in the specific study population (e.g., age range, language).

Thyroid

Thyroid-related endpoints examined in epidemiological studies of DBP 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. A study 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 DBP (i.e., whether DBP 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 DBP. 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. EPA has not found studies examining seasonal variation in DBP levels. Based on these data, EPA has greater confidence in thyroid hormone studies that consider time of sample collection in the analysis, but recognizes the limited nature of the available data pertaining to this issue. One study conducted among 139 pregnant women in Puerto Rico included measurement of MBP and found little difference in specific gravity-adjusted concentrations in samples collected in early morning, mid-morning, early afternoon, or evening.

Obesity

Most of the studies of obesity measures in the DBP database are based on body mass index (BMI, calculated as kg/m^2) or waist circumference using measurements taken as part of the data collection protocol. BMI is highly correlated with body fat, and standardized cut-points have been established for characterization of "normal" (BMI between 18.5 and 24.9 kg/m^2), "overweight" (BMI between 25.0 and 29.9 kg/m^2) and "obese" (BMI ≥ 30.0 kg/m^2) categories. Waist circumference is also highly correlated with body fat, and is a more direct measure of abdominal obesity. 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.

Diabetes and Measure of Insulin Resistance

In the DBP database, diabetes has been assessed by a variety of biomarkers of glucose and insulin and by self-report of diabetes diagnosis. Oral glucose tolerance testing and glycosolated hemoglobin (HbA1c) are used clinically and in epidemiological research (Selvin et al., 2011). Self-report of prevalent diabetes can have high sensitivity and specificity in comparison to diagnosed diabetes based on validated medical record data (Oksanen et al., 2010; Leikauf and Federman, 2009). The biomarker-based classifications, however, offer an added advantage of being able to include undiagnosed disease. EPA will consider these points in assessing the reliability and validity of the diabetes measures used in the studies. None of the currently available studies assessed diabetes through cause of death data; sensitivity of diabetes assessed using cause of death data is low, even if underlying and other contributing cause of death fields are included (Cheng et al., 2008).

Insulin resistance, a marker of diabetes risk, can be measured using the homeostatic model assessment (HOMA) method, a physiologically-based structural model, using fasting glucose and insulin or C-peptide concentrations. HOMA is a validated tool for the estimation of insulin resistance in epidemiology studies, and requires a single measurement of fasting glucose and insulin (Wallace et al., 2004). Although the mean of three samples taken at 5-minute intervals results in a more precise estimate, insulin resistance estimated using a single baseline measurement is well correlated with that using the mean of three measurements when used to estimate a group mean. Therefore, EPA does not consider the use of a single measurement as an input to the HOMA model to be a limitation.

Cancer

With respect to studies of cancer, EPA considers the source of the outcome data (e.g., cause of death data, hospital cancer registry data, hospital discharge data, histopathology reports) in its evaluation of the accuracy of the data. An additional issue is the validity of mortality data as a representation of cancer incidence; mortality data for cancer types with a high survival rate may underrepresent disease incidence, require additional considerations with respect to determining appropriate time windows of exposure, and may lead to biased risk estimates if survival is related to exposure.

2.3.4. 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 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. When evaluating the potential for confounding, it is the strength of the relationship (i.e., risk estimate or correlation coefficient) between variables, rather than the value of a test of statistical significance, that is considered. Uncontrolled confounding by factors that are positively associated with both the exposure (e.g., DBP) 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 exposure and inversely associated with the health endpoint (or vice versa) will result in a downward bias of the effect estimate.

Potential Confounding by Other Phthalates

The correlation between MBP and other phthalates has been examined in a variety of populations. In an analysis conducted by EPA of 5,109 samples from the 2003-2008 National Health and Nutrition Examination Survey (NHANES) participants aged ≥6 years, the pairwise Spearman correlation coefficient between MBP and MEP (the primary metabolite of DEP) was low (0.38). A more moderate correlation was seen with the DEHP metabolites (correlations ranging from 0.44 to 0.58) and with MCOP, the secondary metabolite of DINP (r = 0.44); higher correlations were seen with MBzP (the primary metabolite of BBP, correlation coefficient = 0.70) and MIBP (the primary metabolite of DIBP; correlation = 0.72). Similar patterns have been seen in other studies, based on the review of the epidemiology studies identified in EPA's literature search (Figure 2-4). The median correlation between MBP and MIBP was 0.63 (based on 11 studies), 0.50 for MBzP (based on 17 studies), 0.32 for MEP (based on 18 studies), 0.36 for MCOP or MINP (metabolites of DINP, based on 3 studies) and 0.39 for MEOHP (a secondary oxidative metabolite of DEHP, based on 15 studies). An exception is in a study based on samples collected in the Nurses Health Study (and Nurses Health Study II), in which the correlation between MBP and MIBP was higher than that seen in these other studies (Spearman r = 0.98) (Sun et al., 2014). Based on these data, EPA is most concerned about MIBP (DIBP) and MBzP (BBP), and possibly DEHP metabolites, as potential confounders, and will evaluate the potential for confounding by examining the similarity of the results seen with MBP and these different metabolites. Thus, for example, lack of adjustment for mono-benzyl phthalate (MBzP) would not be considered a limitation in a study in which an association was seen with MBP that was not seen with MBzP; however this lack of adjustment would be considered a limitation if an association of similar or higher magnitude was seen for both metabolites.

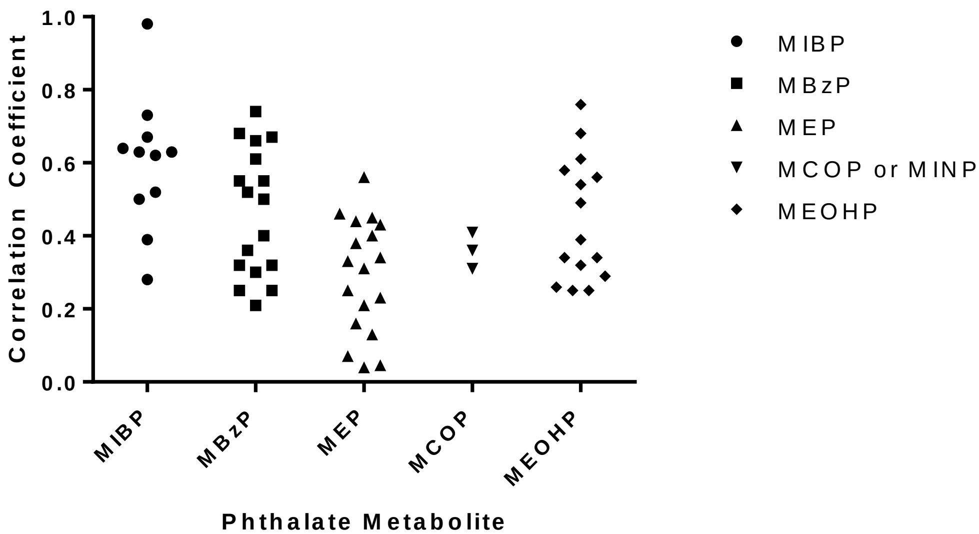


Figure 2-4. Correlation between MBP and other phthalate metabolites.

Data are from studies identified in the literature search that presented quantitative analysis of the correlation between urinary concentration of different metabolites as either Spearman correlation or Pearson correlation of log- or ln-transformed data. Studies in pregnant women: Huang et al. (2007); Kobrosly et al. (2014); Just et al. (2012); Whyatt et al. (2012); Suzuki et al. (2010). Studies in general population women: Buck Louis et al. (2013); Svensson et al. (2011); Sun et al. (2014); Itoh et al. (2009). Studies in general population men: Frederiksen et al. (2010). Studies in men, infertility setting: Hauser et al. (2006); Jurewicz et al. (2013); Liu et al. (2012). Studies in children: Bertelsen et al. (2013), Teitelbaum et al. (2012) (separate results for boys and girls).

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 MBP levels was highest in young children (geometric means of 28.3, 15.2, and 14.3 µg/g-creatinine, respectively, in ages 6-11, 12-19 and ≥20 years) (CDC, 2013). Concentrations were lower in males compared with females (geometric means of 13.0 and 17.8 µg/g-creatinine, respectively, in males and females). A modest degree of variability by ethnicity was also observed, with higher levels in Mexican Americans (geometric mean of 17.1 µg/g-creatinine) compared with non-Hispanic blacks or non-Hispanic whites (geometric means of 15.9 and 14.6 µg/g-creatinine, respectively). EPA will consider these differences in assessing the potential influence of demographic factors on observed effect estimates for DBP.

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 DBP (or its metabolites).

2.3.5. 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 the DBP 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 2-8. General and outcome-specific considerations for DBP 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) • Recruitment process; exclusion and inclusion criteria, knowledge of study hypothesis; knowledge of exposure and outcome • Participation rates: total eligible; participation at each stage and for final analysis group and denominators used to make these calculations • Length of follow-up, loss to follow-up • Comparability: participant characteristic data by group, data on non-participants
Exposure	• Biological matrix or target tissue/organ (e.g., urine, serum, semen, breast milk) • Level of detection (LOD) or level of quantitation (LOQ) • Exposure distribution (e.g., central tendency, interquartile range), proportion < LOD

Analysis	• Consideration of data distribution including skewness of exposure and outcome measures • Consideration of influence of "tails" in analysis based on continuous exposure measure • Consideration of analytic approaches exploring different shapes of exposure-response • Consideration of values below LOD or LOQ • 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 **Measures**	• AGD: protocol, training procedures, standardization and inter-rater reliability • Cryptorchidism: definition • Gender related play behavior: reliability and validity of measurement scale
Consideration of confounding	• AGD: variability by size (e.g., birth weight), sex, age; temporal trends in DBP exposure if study spans several years and includes a wide age range • 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) **Measures**	• Type of assay • 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 months preceding hormone sample collection
Sperm parameters **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 months preceding semen sample collection
Infertility **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 and during attempt to become pregnant

Timing of puberty **Measures**	• Source of data (e.g., self-report, physician assessment)
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 months preceding transition from one stage to another stage?
Gestational age **Measures**	• Source of data 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
Birth weight **Measures**	• Source of data (e.g., medical records, birth certificate)
Consideration of confounding	• Gestational age, maternal age, ethnicity, nutritional intake, smoking, maternal height/BMI, (consider if these are related to exposure)
Relevant exposure time window(s)	• In utero
Immune – allergy and asthma **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 months): up to 12 months preceding outcome assessment
Neurobehavioral **Measures**	• Standardized assessment tool, validation studies for specific study population (e.g., age group, geographic location) • Blinding of assessor to exposure
Consideration of confounding	• Age, sex, socioeconomic status
Relevant exposure time window(s)	• In utero; early childhood

Thyroid	
Measures	• Assay used and evidence from validation studies, if available • Sensitivity/detection limits, coefficient of variation; number of samples below LOD • 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)	• Varies by lifestage (i.e., infants, children, adults)
Obesity	
Measures	• Source of data (e.g., measured or self-reported weight and height)
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, including in utero)
Diabetes and insulin resistance	
Measures	• Source of data (e.g., biomarkers of insulin or glucose, medical records, self-report)
Consideration of confounding	• Age, sex, ethnicity
Relevant exposure time window(s)	• Not established (likely to be more than one, including in utero)

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

Beyond the initial 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 2-9. These questions are, for the most part, broadly applicable to all experimental studies.

Table 2-9. 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 2-9 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 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 EXPERIMENTAL 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 serve as an additional method for presenting and evaluating the suitability of the data to inform hazard identification for dibutyl phthalate (DBP) during the analysis of hazard potential and utility of the data for dose-response evaluation. For each 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 DBP are summarized in preliminary evidence tables.

Epidemiological studies are presented first where each study per table is listed in reverse chronological order. The specific metabolite(s) measured in a study, as reported in the study methods, are noted (i.e., MnBP, MnBP + MIBP, or MBP without further specification). Animal studies are then presented where each study per health endpoint is presented in order by dose. Finally, animal studies using MBP are also presented as this is DBP's primary metabolite and is thought to contribute to developmental toxicity. Inclusion of these studies may help to inform the hazard identification for DBP. 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 for DBP 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. Due to the large number of endpoints, for the purposes of practical presentation, for studies that report on multiple endpoints related to the same effect, the most sensitive endpoint was selected for representation in the exposure arrays. The complete list of references considered in preparation of these materials can be found on the Health and Environmental Research On-line (HERO) website at http://hero.epa.gov/DBP and http://hero.epa.gov/phthalates-humanstudies.

3.2. EPIDEMIOLOGICAL STUDIES

3.2.1. Sexual Differentiation Methods

Table 3-1. Evidence pertaining to DBP and sexual differentiation effects in humans

<table>
<tr><th>Reference and study design</th><th>Results</th></tr>
<tr><td colspan="2">Anogenital distance (AGD)</td></tr>
<tr><td><u>Suzuki et al. (2012)</u> (Japan)
Population: 111 male infants from birth cohort study, time period not given
Outcome: AGD measured 1-3 d after birth (AGD 1 to anterior genitalia, mean 45.8 mm, 14.8 mm/kg; AGD 2 to posterior genitalia, mean 20.3 mm, 6.6 mm/kg)
Exposure: Maternal urine samples, mean 29 wks of gestation
MnBP in urine (ng/mL):
<table><tr><th></th><th>Median</th><th>75th percentile</th></tr><tr><td>Unadjusted</td><td>46.6</td><td>65.3</td></tr><tr><td>SG-adjusted</td><td>50.8</td><td>92.9</td></tr></table>Analysis: Linear regression, considering gestational week, birth order, maternal age, maternal smoking during pregnancy, maternal urinary daidzein (soy isoflavone) and equol (a urinary metabolite of daidzein) concentrations and environmental tobacco smoke (smoking status of husbands of non-smoking women) as potential cofounders</td><td>Association between MnBP and AGD measures reported as not statistically significant (quantitative results not reported).</td></tr>
<tr><td><u>Huang et al. (2009)</u> (Taiwan)
Population: 65 infants (32 girls, 33 boys) from birth cohort study
Outcome: AGD (to posterior genitalia) measured at birth; two measures per infant (mean 23 mm, 7.2 mm/kg in boys; mean 16 mm, 5.4 mm/kg in girls)
Exposure: Maternal urine and amniotic fluid samples, 1st trimester
MBP in urine (ng/mL):
<table><tr><th></th><th>Median</th><th>90th percentile</th></tr><tr><td>Females</td><td>78.0</td><td>309*</td></tr><tr><td>Males</td><td>79.6</td><td>232.6</td></tr></table>MBP in amniotic fluid (ng/mL):
<table><tr><th></th><th>Median</th><th>90th percentile</th></tr><tr><td>Females</td><td>85.5</td><td>134.6</td></tr><tr><td>Males</td><td>81.3</td><td>127.8</td></tr></table>Analysis: Stratified into low and high exposure groups by median MBP concentration in amniotic fluid; AGD compared between the two exposure groups using</td><td>AGD by sex and concentration of MBP in amniotic fluid
<table><tr><th>Exposure group</th><th>Median MBP in exposure group (ng/mL)</th><th>AGD (mm)</th><th>AGD/ weight (mm/kg)</th><th>AGD/ length (x 10^3)</th></tr><tr><td>Boys</td><td></td><td></td><td></td><td></td></tr><tr><td>Low (n = 16)</td><td>63.8</td><td>21.2</td><td>6.6</td><td>4.3</td></tr><tr><td>High (n = 17)</td><td>98.7</td><td>24.1</td><td>7.7</td><td>4.8</td></tr><tr><td>Girls</td><td></td><td></td><td></td><td></td></tr><tr><td>Low (n = 15)</td><td>67</td><td>17.6</td><td>6.2</td><td>3.7</td></tr><tr><td>High (n = 16)</td><td>104</td><td>13.9*</td><td>4.5*</td><td>2.8*</td></tr></table>*p < 0.05 compared with low exposure group

Association between log MBP in amniotic fluid (ng/mL) and AGD in female infants (n = 29)
<table><tr><th>Analysis</th><th>AGD (mm)</th><th>AGD/weight (mm/kg)</th><th>AGD/length (x 10^3)</th></tr></table></td></tr>
</table>

This document is a draft for review purposes only and does not constitute Agency policy.

<table>
<tr><th>Reference and study design</th><th>Results</th></tr>
<tr><td>Wilcoxon rank-sum test. Spearman correlation analysis and linear regression for association between MBP and continuous variables.
*Report of 30.9 in the paper appears to be in error given the other values reported in the distribution</td><td>

Spearman correlation coefficient	-0.31	-0.32*	-0.33*
Regression R^2	Not reported	0.143*	0.159*

*$p < 0.05$
After adjustment for gestational age and other phthalate metabolites, linear regression of AGD/weight on MBP in amniotic fluid yielded significant ($p = 0.043$) R^2 of 0.36 (regression coefficient = -2.73).</td></tr>
<tr><td>**Swan (2008)** (United States; Minnesota, Missouri, California)
Population: 106 boys from birth cohort study (Study for Future Families), 2000-2002, mean age 12.8 mo (0-36 mo)
Outcome: AGD (to posterior genitalia) measured at 0-36 mo (mean 70.4 mm, 7.1 mm/kg)
Exposure: Maternal urine sample, 3rd trimester
MnBP in urine (ng/mL):
Median 13.5; 75th percentile unadjusted 30.9
Analysis: Regression analysis using mixed model adjusting for age and weight percentile
Related references: Swan et al. (2005) (exposure data and analysis of smaller sample size with less robust method of adjustment for variation by size)</td><td>Percent change in AGD per interquartile increase in MnBP concentration (*p*-value)
MnBP -3.2 (0.049)</td></tr>
<tr><td colspan="2">*Cryptorchidism or testicular position, hypospadias*</td></tr>
<tr><td>**Carran and Shaw (2012)** (New Zealand)
Population: 79 male offspring born to New Zealand soldiers exposed to DBP during military service in Malaya from 1948-1960
Outcome: Hypospadias or other penis defects or cryptorchidism. Assessed via questionnaire sent to the veterans in 2009 (age 70-> 80 yrs), followed up with personal interview. Low response rate: of 252 veterans contacted, 85 responded, of whom 71 reported DBP exposure; 58 of these had children (n=155; 79 male, 76 female) after return to New Zealand following military service.
Exposure: Exposure to DBP self-reported via questionnaire (DBP used as insect repellant and Acaricide; applied through painting of seams of clothes before military operations in jungle areas of Malaysia). Authors performed dose reconstruction experiments using DBP-treated clothing; estimated daily exposure 64 mg/kg-day.</td><td>Frequency in births in general population and in exposed cohort

	General population	Exposed cohort
Cryptorchidism	0.91-1.09%	5.1* (4/79)
Hypospadias	0.30-0.33%	2.5* (2/70)

*$p < 0.05$ when compared with either 2000 or 2005 incidence in general population</td></tr>
</table>

Reference and study design	Results
Analysis: Incidence in exposed individuals compared to New Zealand general population incidence rates in 2000 and 2005 using binomial test	
Choi et al. (2012) (Korea) **Population:** 80 hypospadias cases, 40 cases' mothers, and 80 controls; recruited at a medical college in Seoul; demographics and time period of recruitment not reported. **Outcome:** Hypospadias **Exposure**: DBP and MBP in urine (ng/mL) and plasma (ng/mL) Mean ± SD MBP in urine of controls 142.38 ± 500.45 MBP in plasma of controls 72.34 ± 74.28 **Analysis:** Concentrations in urine and plasma of cases compared with controls (details not reported)	Mean ± SD of DBP and MBP in urine (ng/mL) and plasma (ng/mL) | | Controls | Hypospadias cases | Mothers of hypospadias cases | MBP in urine: 142.38 ± 500.45 | 86.51 ± 127.09 | 165.01 ± 421.41 MBP in plasma: 72.34 ± 74.28 | 47.49 ± 62.73 | 15.25 ± 43.27
Brucker-Davis et al. (2008b) (France) **Population:** 36 cryptorchidism cases and 49 controls, 2002-2005, ≥ 34 wks gestation, born at one hospital. Controls matched by place and date of birth, birth weight, gestational age, and when possible parental origin. [MBP analysis was added later in the study, so sample size is less than total of 78 cases and 86 controls.] **Outcome:** Cryptorchidism at birth and 3 mo of age, based on two concordant examinations before discharge (n = 108 cases); follow-up at 3 and 12 mo (n = 50 permanent cases). Undescended testis defined as non-palpable, inguinal, supra-scrotal, high scrotal and ectopic testis. Retractable testis excluded from cases and controls. **Exposure**: Cord blood and colostrum samples Concentration in cord blood (ng/mL): Median 75th percentile MBP Controls 2.9 4.9 Cases 2.4 3.1 Concentration in colostrum (ng/g milk): Median 75th percentile MBP Controls 10.6 20.3 Cases 17.3 32.6 **Analysis:** Exposure concentrations compared using Kruskal-Wallis nonparametric test; exposure scores defined as unquantifiable (0), below median (1), or above median (2) concentration in milk; categorical analysis by logistic regression, adjusting for variables shown in results column	OR (95% CI) for cryptorchidism and MBP in milk (exposure score of 2; above median)[a] (adjusted for gestational age, birth weight, pre-pregnancy maternal BMI, maternal age, parity, paternal history of cryptorchidism, season of birth, and city of birth) At birth 2.13 (0.66, 6.83) At 3 mo 2.38 (0.40, 14.22) [a]n = 34 infants (18 case and 16 controls) had MBP exposure scores of 2; n = 35 (12 case and 23 controls) had scores of 1; and n = 2 infants (1 case and 1 control) had scores of 0. No differences in MBP concentrations (in cord blood or colostrum) were observed in comparisons between cases and controls ($p > 0.1$; see Exposure in Reference and study design column).

Reference and study design	Results
Swan (2008) (United States; Minnesota, Missouri, California) **Population:** 106 boys from birth cohort study (Study for Future Families), 2000-2002, mean age 12.8 mo (0-36 mo) **Outcome:** Incomplete testicular descent assessed at clinical exam (one or both testes classified in category other than normal or normal retractile) (10% prevalence) **Exposure:** Maternal urine sample, 3rd trimester MnBP in urine (ng/mL): Median / 75th percentile Unadjusted 13.5 / 30.9 **Analysis:** Logistic regression, adjusting for age and weight percentile **Related references:** Swan et al. (2005) (exposure data)	MnBP reported as not associated with testicular position or penile width or length (quantitative results not reported).
Main et al. (2006) (Denmark, Finland) **Population:** 62 cases, 68 controls from two pregnancy cohorts, born 1997-2001, age 3 mo **Outcome:** Cryptorchidism, at birth and/or 3 mo. Undescended testis defined as non-palpable, inguinal, supra-scrotal, high scrotal and ectopic testis. **Exposure:** Breast milk samples collected 1-3 mo of age MBP in breast milk (µg/L), all samples: Median (range) Denmark 4.3 (0.6-10,900) Finland 12 (2.4-123) **Analysis:** Mann-Whitney U-test for comparison of MBP concentrations in boys with and without cryptorchidism **Related references:** Boisen et al. (2004) (study design, case-control description)	Median MBP in breast milk (µg/L) Controls: 9.09 / Cases: 10.25 ($p > 0.40$)

Reference and study design	Results
Infant hormone levels	
Lin et al. (2011a) (Taiwan) **Population:** 155 infants (81 boys, 74 girls) from birth cohort, born 2000-2001 **Outcome:** Cord blood hormone levels **Exposure:** Maternal urine sample 3rd trimester MBP in urine (percentile): Median / 75th / 95th Unadjusted (ng/mL): 65.5 / 121 / 275 Cr-adjusted (μg/g Cr): 95.9 / 169 / 507 **Analysis:** Pearson correlation analysis and linear regression adjusted for variables shown in the results column	Pearson correlation coefficient (r) and regression coefficient (β), log-MBP (μg/g Cr) and cord blood hormone level (regression adjusted for maternal age, BMI, smoking habit, gestational age, parity, and use of contraceptive drugs) (r / β) Boys Free testosterone (ng/dL): -0.11 / NR Estradiol (pg/mL): 0.05 / -0.02 Free testosterone:estradiol ratio: -0.15 / -0.22 Girls Free testosterone (ng/dL): -0.07 / -0.01 Estradiol (pg/mL): -0.07 / NR Free testosterone:estradiol ratio: -0.06 / -0.01 NR = not reported All *p*-values > 0.10
Main et al. (2006) (Denmark, Finland) **Population:** 130 male infants from two pregnancy cohorts (cryptorchidism cases and controls combined for this analysis), born 1997-2001, age 3 mo **Outcome:** Serum steroidal and gonadotropin hormone levels in infants, samples collected when breast milk samples delivered to hospital **Exposure:** Breast milk samples collected 1-3 mo of age MBP in breast milk (μg/L), all samples: Median (range) Denmark: 4.3 (0.6-10,900) Finland: 12 (2.4-123) **Analysis:** Cases and controls combined for analysis of association between metabolite concentration and hormone analysis using partial Spearman correlation coefficients adjusted for country of birth; linear regression, considering gestational age, weight for gestational age, parity, smoking, diabetes, and country of origin as potential covariates	Spearman correlation coefficient (*p*-value), MBP (μg/L) and serum hormone level (n = 96 boys) SHBG (nmol/L): 0.272 (0.01) Free testosterone (nmol/L): -0.220 (0.03) Testosterone (nmol/L): -0.040 (0.71) LH (IU/L): 0.076 (0.47) FSH (IU/L): -0.083 (0.42) Estimated percent change (95% CI) in hormone level with 10-fold increase in MBP SHBG (nmol/L): 8% (-1 to 18%) LH:free testosterone ratio: 18% (-2 to 44%) Free testosterone (nmol/L): -15% (-29 to ±1%)

<table>
<tr><th>Reference and study design</th><th>Results</th></tr>
<tr><td colspan="2">Gender-related play</td></tr>
<tr><td>Swan et al. (2010) (United States; Minnesota, Missouri, California, Iowa)

Population: 145 children from birth cohort study (Study for Future Families), 2000-2002 and 2002-2005 (Iowa), ages 4-7 yrs; second follow-up

Outcome: Gender-specific play based on Pre-School Activities Inventory (24 items completed by parent or caregiver; subscores of male-oriented items and female-oriented items and a composite score consisting of male summation minus the female summation scores)

Exposure: Maternal urine sample, 3rd trimester

MBP in urine (ng/mL); distribution not reported for this analysis; EPA assumed similar distribution as seen in Swan et al. (2005)

Unadjusted MnBP in urine (ng/mL):
Median / 75th percentile
Boys: 12.5 / 28.3
Girls: 18.0 / 32.3

Analysis: Regression analysis using Generalized Linear Models, considering creatinine, sex and age of child, maternal age, parental education, number of same and opposite sex siblings, ethnicity, clinic location, and parental attitude as potential covariates

Related references: Swan et al. (2005) (exposure data)</td><td>Regression coefficient (95% CI) for pre-school activities index scores and log-transformed MnBP (adjusted for child's age, mother's age, mother's education, parents' attitude toward boy's play, and interaction between education and attitude; negative value indicates less masculine play behavior with higher metabolite level)

| | Boys | Girls |
Masculine: -2.21 (-5.29, 0.87) | 0.21 (-2.69, 3.10)
Composite: -3.61 (-7.48, 0.26) | -1.07 (-5.46, 3.32)</td></tr>
</table>

3.2.2. Male Reproductive Effects in Humans

Table 3-2. Evidence pertaining to DBP and reproductive hormones in adult men

Reference and study design	Results
Han et al. (2014) (China) **Population:** 232 men without reproductive or urological diseases or occupational exposure to phthalates, recruited by Chongqing Institute of Science and Technology for Population and Family Planning; mean age 32 yrs (range 20-40 yrs); 2007 **Outcome:** Serum testosterone, estradiol, FSH, and LH **Exposure:** Urine sample, collected at same time as serum sample MBP in urine: Median / 95th percentile Unadjusted (µg/L): 18.72 / 129.34 Cr-adjusted (µg/g Cr): 23.26 / 157.33 **Analysis:** Spearman correlation analysis with standardized partial correlation analysis considering age, BMI, smoking status and alcohol consumption as potential cofounders	Partial correlation coefficient for increase in hormone unit change in Cr-adjusted urine MBP (adjusted for age, body mass index, and smoking status) Testosterone (nmol/L): 0.01 E_2 (pg/mL): 0.01 FSH (IU/L): 0.05 LH (IU/L): 0.04 Free androgen index (FAI): 0.01 ($p > 0.05$ for all)
Pant et al. (2014) (India) **Population:** 60 male partners of infertile couples; mean age 32 yrs; time period not reported **Outcome:** Serum testosterone **Exposure:** Semen sample DBP in semen (µg/mL): Mean ± SD DBP: 0.97 ± 0.55 **Analysis:** Linear regression adjusting for variables shown in results column.	Regression coefficient (95% CI) between serum testosterone (ng/mL) and DBP in semen (µg/mL) (adjusted for age, body mass index, tobacco and alcohol use, and diet) -0.61 (-1.20, -0.02)
Jurewicz et al. (2013) (Poland) **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; time period not reported; MBP measured in 268 samples **Outcome:** Plasma testosterone, E2, and FSH **Exposure:** Urine sample, collected at same time as plasma sample MnBP in urine: Geometric mean (SD) Unadjusted (µg/L): 108.5 (1.9) Cr-adjusted (µg/g Cr): 81.9 (1.8) **Analysis:** Linear regression, adjusting for variables shown in results column	Regression coefficient (*p*-value) for increase in hormone unit change in log-MnBP (adjusted for age, smoking, medical history [mumps, cryptorchidism, testes surgery, testes trauma], abstinence time, and urinary creatinine) Testosterone (ng/mL): 0.02 (0.95) E_2 (pg/mL): 0.86 (0.43) FSH (IU/L): 0.24 (0.47)

Reference and study design	Results
Joensen et al. (2012) (Denmark) **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) **Outcome:** Serum steroidal and gonadotropin hormones **Exposure:** Urine sample, collected at same time as serum sample for hormone analysis MnBP in urine (ng/mL): Median 95^{th} percentile Unadjusted 28 91 **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 *As reported by Ravnborg et al. (2011)	Percent difference (95% CI), highest compared with lowest quartile of MnBP (ng/mL) (adjusted for age, BMI, smoking, alcohol consumption, and time of blood sampling [and assay type for inhibin-B only]) LH (IU/L) 9% (1-18%) No other significant differences in hormone levels (free testosterone, estradiol, SHBG, inhibin-B, or FSH) seen (quantitative results not reported).
Mendiola et al. (2012) (United States; Minnesota, Missouri, California, Iowa) **Populations:** 425 fertile men with pregnant partners enrolled in birth cohort study (Study for Future Families[SFF]), 1999-2005; mean age 32 yrs; 425 men who were male partners of infertile couples seeking evaluation (Massachusetts General Hospital [MGH]; 2000-2004, mean age 36 yrs **Outcome:** Serum steroidal and gonadotropin hormones **Exposure:** Urine sample, collected at same time as serum sample for hormone analysis Sum of MBP and MIBP) in urine (ng/mL): Median 90^{th} percentile SFF: Unadjusted 24.5 65.3 MGH: Unadjusted 17.7 50.8 All: Unadjusted 18.8 58.2 **Analysis:** Pearson correlation coefficients of log(10)-transformed MBP and hormone measures (bivariate analysis); linear regression considering age, age square, BMI, smoking status, ethnicity, urinary creatinine concentration (SFF models) or specific gravity (MGH models), time of sample collection, time of collection squared, and study center (SFF vs MGH) for each population separately and for the pooled population **Related references:** This is a pooled analysis of a study of fertile men (Mendiola et al., 2011) and men from infertile couples (Meeker et al., 2009a). The analysis in Mendiola et al., 2011 was conducted for MnBP (no associations noted; quantitative results not reported).	Authors report "no associations between any hormone levels [testosterone, estradiol, SHBG, LH, inhibin-B, or FSH] and any urinary metabolites of phthalates other than DEHP" [including MBP+MIBP summation] (quantitative results not reported).
Li et al. (2011) (China)	Spearman correlation coefficient, DBP (µg/L) and serum hormone level

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Reference and study design	Results
Population: 118 male partners seen in subfertility clinic 2007-2008; mean age 30 yrs **Outcome:** Serum steroidal and gonadotropin hormones, prolactin. **Exposure:** Semen and serum samples DBP (µg/mL): Median / 75th percentile / 95th percentile Semen 0.02 / 0.08 / 0.20 Serum 0.05 / 0.07 / 0.32 **Analysis:** Spearman correlation analysis; linear regression adjusting for variables shown in results column (samples with undetectable DBP were assigned a value of one-half the limit of detection); logistic regression for change in prolactin by exposure tertile only	(DBP in semen / DBP in serum) Testosterone (ng/mL): -0.21* / -0.08 Estradiol (pg/mL): 0.07 / 0.06 FSH (IU/L): -0.15 / -0.05 LH (IU/L): <0.01 / 0.04 Prolactin (ng/mL): 0.13 / 0.23* *$p < 0.05$ Regression coefficient (95% CI) for change in hormone level per unit increase in ln-transformed DBP (adjusted for age, BMI, education, smoking, and drinking). (DBP in semen / DBP in serum) Testosterone (ng/mL): -0.17 (-0.36, 0.02) / -0.07 (-0.26, 0.12) Estradiol (pg/mL): 0.54 (-0.65, 1.74) / 0.45 (-0.72, 1.62) FSH (IU/L): -0.06 (-0.13, 0.01) / -0.02 (-0.08, 0.05) LH (IU/L): -0.01 (-0.05, 0.04) / 0.01 (-0.04, 0.05) Prolactin (ng/mL): 0.03 (-0.03, 0.09) / 0.06 (0.01, 0.12) OR (95% CI) for increased serum prolactin by tertile of DBP (DBP in semen / DBP in serum) 1 (<LOD): 1.0 (Ref) / 1.0 (Ref) 2 (0.01-0.05 µg/L): 1.07 (0.43, 2.67) / 1.10 (0.41-2.96) 3 (0.06-1.40 µg/L): 2.11 (0.85, 5.24) / 2.62 (1.04-6.64) (trend *p*): (0.10) / (0.04)
Meeker et al. (2009a) (United States; Boston) **Population:** 425 men from subfertility clinic, 2000-2004; mean age 36 yrs **Outcome:** Serum steroidal and gonadotropin hormones **Exposure:** Urine sample, collected at same time as serum sample MBP in urine (ng/mL) (percentile): Median / 75th percentile / 95th percentile SG-adjusted 17.7 / 32.7 / 69.9 **Analysis:** Linear regression using untransformed (testosterone, estradiol) or natural logarithm transformed (free androgen index, FSH, LH) hormone	Regression coefficient (95% CI) for change in hormone with interquartile range (IQR) increase in adjusted MBP concentration (adjusted for age, BMI, smoking, season and time of day sample was collected, and [for testosterone and estradiol only] SHBG) Untransformed hormone level (0.0 = no effect) Testosterone (ng/dL): -4.65 (-15.7, 6.33) Estradiol (pg/mL): -0.47 (-1.62, 0.68) Inhibin B (pg/mL): 1.34 (-5.98, 8.66) Ln-transformed hormone level (1.0 = no effect) Free androgen index: 0.98 (0.94, 1.01)

Reference and study design	Results
levels; considering age, BMI, smoking status, race, previous infertility example, prior ability to impregnate partner, and season and time of sample collection as potential covariates **Related references:** Duty et al. (2005)	FSH (IU/L) 1.02 (0.97, 1.08) LH (IU/L) 1.01 (0.97, 1.06) SHBG (nmol/mL) 1.02 (0.98, 1.06) Prolactin (ng/mL) 1.00 (0.96, 1.04)
Pan et al. (2006) (China) **Population:** 74 exposed workers (PVC flooring factory, mean work duration 1 yr); 63 controls (construction workers, matched by age and smoking); mean age 33.9 yrs, time period not reported **Outcome:** serum steroidal and gonadotropin hormones **Exposure:** Urine sample, collected at the same time as serum samples for hormone analysis MBP in urine (μg/g Cr): Median / 75th percentile / 95th percentile Exposed: 548 / 1,493 / 8,781 Controls: 114 / 207 / 435 **Analysis:** Two-sample t-test for comparing concentrations between groups; standardized partial correlation coefficient for association between hormone levels and exposure, adjusting for variables shown in results column	Mean ± SD log-transformed serum hormone levels: Controls / Exposed FSH (mIU/mL): 5.4 ± 1.7 / 5.0 ± 1.5 LH (mIU/mL): 4.9 ± 1.7 / 4.3 ± 1.5 Free Testosterone (pg/mL): 9.7 ± 1.4 / 8.4 ± 1.5* Estradiol (pg/mL): 20 ± 1.7 / 22.4 ± 1.6 Standardized partial correlation coefficients between log-serum hormone levels and log-MBP in urine (μg/g Cr) (adjusted for age and alcohol consumption status [yes/no]) Controls / Exposed / All FSH (mIU/mL): 0.002 / -0.180 / -0.103 LH (mIU/mL): 0.078 / 0.087 / -0.042 Free Testosterone (pg/mL): 0.095 / -0.253* / -0.237* Estradiol (pg/mL): -0.061 / -0.029 / 0.032 *p < 0.05
Jonsson et al. (2005) (Sweden) **Population:** 234 men from general population, assessed at military conscription exam in 2000; ages 18-21 yrs **Outcome:** Serum steroidal and gonadotropin hormones **Exposure:** Urine sample, collected at same time as serum sample for hormone analysis MnBP in urine (percentile) Median / 75th / 95th Unadjusted (ng/mL): 78 / 140 / 330 Adjusted (nmol/mmol Cr): 24 / 36 / 81 **Analysis:** Mean difference between high and low quartiles	Mean difference (95% CI), highest (≥36.31 nmol/mmol Cr) compared with lowest quartile of MnBP (≤12.4 nmol/mmol Cr) (positive difference indicates lower value in highest exposure quartile. Testosterone (nM) -0.7 (-1.2, 2.7) Free testosterone (T/SHBG) 0.09 (-0.02, 0.2) Estradiol (pM) 4.5 (-1.6, 11) FSH (IU/L) -0.5 (-1.1, 0.2) LH (IU/L) 0.2 (-0.4, 0.6)

3.2.3. Male Pubertal Development in Humans

Table 3-3. Evidence pertaining to DBP and the timing of male puberty or sex hormones in boys

Reference and study design	Results
Ferguson et al. (2014c) (Mexico) **Population:** 115 boys ages 8-14 yrs from a birth cohort (Early Life Exposure in Mexico to Environmental Toxicants, participants enrolled during first trimester 1994-2004); follow up initiated in 2010 **Outcome:** Adrenarche or puberty, based on Tanner staging by physician (pubic hair stage ≥2; genitalia stage ≥2 or testicular volume >3 mL); serum hormone level **Exposure:** Maternal urine sample (n = 107) from third trimester or child's urine sample (n = 113) collected at time of Tanner staging and serum collection Unadjusted MnBP in urine (ng/mL): Median / 95th percentile Maternal sample: 57.6 / 299 Child's sample: 102 / 477 **Analysis:** Logistic regression for analysis of puberty onset, adjusting for variables shown in results column; linear regression for analysis of hormone levels, considering age, BMI z-score, socioeconomic status, and maternal smoking potential covariates	OR (95% CI) for adrenarche or puberty per interquartile increase in ln-transformed MnBP (adjusted for child age, BMI z-score, and urine specific gravity) Exposure basis — Tanner stage or testicular volume: Maternal urine (prenatal) / Child urine Pubic hair (stage ≥2): 0.42 (0.14, 1.29) / 1.57 (0.52, 4.75) Genitalia (stage ≥2): 0.61 (0.32, 1.16) / 1.15 (0.58, 2.30) Testicular volume (>3 mL): 1.01 (0.49, 2.08) / 3.45 (1.26, 9.42) Percent change (95% CI) in serum hormone level per interquartile increase in ln-transformed MBP (adjusted for urine specific gravity, child age, and BMI z-score): Exposure basis — Serum hormone: Maternal urine (prenatal) / Child urine Testosterone: -10.4 (-33.9, 21.5) / 7.13 (-22.4, 47.9) Free testosterone: -16.9 (-39.4, 13.9) / 9.71 (-21.9, 54.1) SHBG: 12.3 (1.29, 24.6) / -3.41 (-13.8, 8.22) DHEAS: -13.9 (-25.5, -0.48) / 2.67 (-12.2, 20.1) Estradiol: 8.11 (-1.63, 18.8) / -3.51 (-12.9, 6.82) Inhibin B: -3.53 (-13.8, 7.90) / 2.02 (-9.27, 14.7)
Mieritz et al. (2012) (Denmark) **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 **Outcome:** Anthropometry, pubertal stage (pubic hair and genital development), presence of gynecomastia, and serum testosterone **Exposure:** Urine sample, first morning sample MnBP in urine (ng/mL): Median / 95th percentile Group 3: 45.14 / 148.2	MnBP concentration (ng/mL) by group Group 1 (n = 38) / Group 2 (n = 189) / Group 3 (n = 517) Median: 44.3 / 41.7 / 45.1 95th percentile: 108.3 / 119.5 / 148.2 Group 1 = boys with palpable gynecomastia Group 2 = boys without palpable gynecomastia (age-matched) Group 3 = boys without palpable gynecomastia (all ages)

Reference and study design	Results
(boys without gynecomastia, all ages) **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	No association between MBP concentration and timing of puberty or serum testosterone level; however authors reported that more boys in the 2nd quartile of urinary (MBP+MIBP) had testicular volume >3 mL compared with boys in the 4th quartile (quantitative results not reported).

3.2.4. Semen Parameters and Infertility

Table 3-4. Evidence pertaining to DBP and semen parameters or infertility in adult men or couples

Reference and study design	Results
Sperm parameters	
Han et al. (2014) (China) **Population:** 232 men without reproductive or urological diseases or occupational exposure to phthalates, recruited by Chongqing Institute of Science and Technology for Population and Family Planning; mean age 32 yrs (range 20-40 yrs); 2007 **Outcome:** Semen analysis, and sperm DNA damage assessed by alkaline comet assay **Exposure:** Urine sample, collected at same time as semen sample MBP in urine: Median / 95th percentile Unadjusted (µg/L): 18.72 / 129.34 Cr-adjusted (µg/g Cr): 23.26 / 157.33 **Analysis:** Logistic regression, adjusting for variables shown in results column; Spearman correlation analysis with standardized partial correlation analysis considering age, BMI, abstinence time, smoking status and alcohol consumption as potential cofounders	OR (95% CI) for semen parameter below WHO reference value, comparing Cr-adjusted urine MBP above and below the median (adjusted for age and abstinence time) Sperm concentration: 1.97 (0.95, 4.08) Sperm motility: 1.08 (0.69, 1.69) Sperm morphology: 1.53 (0.76, 3.09) Partial correlation coefficient for Cr-adjusted urine MBP and DNA damage to sperm (adjusted for age, abstinence time, and smoking status) Tail %: -0.00 Tail length: -0.03 Tail distributed moment (TDM): -0.02 (p > 0.05 for all)
Kranvogl et al. (2014) (Slovenia) **Population:** 136 men from couples seeking infertility treatment (mean age 36.2 yrs, range 24-54 yrs), 2012 **Outcome:** Semen analysis **Exposure:** Urine sample, collected at same time as semen sample MnBP in urine Median / Maximum Unadjusted (µg/L): 18.3 / 199.8 Cr-adjusted (µg/g Cr): 14.9 / 104.7 **Analysis:** Spearman correlation	Spearman correlation coefficient, MnBP and sperm parameters: Sperm concentration: -0.006 Sperm motility: -0.127 (p > 0.05 for both parameters)

Reference and study design	Results
Pant et al. (2014) (India) **Population:** 60 male partners of infertile couples; mean age 32 yrs; time period not reported **Outcome:** Semen analysis and sperm DNA damage assessed by comet assay **Exposure:** Semen sample DBP in semen (µg/mL): Mean ± SD DBP 0.97 ± 0.55 **Analysis:** Linear regression (unadjusted)	Regression coefficient (95% CI) between sperm parameter and DBP in semen Sperm concentration (× 10^6/mL) -6.42 (-13.69, -0.84) Sperm motility (%) -10.05 (-20.22, -0.12) Normal morphology -3.96 (-8.79, 0.87) Comet tail length 12.45 (-0.71, 25.6) % DNA in comet tail 4.63 (-0.21, 9.48) Comet tail moment 2.40 (-1.76, 6.57)
Jurewicz et al. (2013) (Poland) **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; time period not reported; MBP measured in 268 samples **Outcome:** Semen analysis **Exposure:** Urine sample, collected at same time as semen sample MnBP in urine: Geometric mean (SD) Unadjusted (µg/L) 108.5 (1.9) Cr-adjusted (µg/g Cr) 81.9 (1.8) **Analysis:** Linear regression, adjusting for variables shown in results column	Regression coefficient (*p*-value) for change in sperm parameter with unit change in log-MnBP (adjusted for age, smoking, medical history [mumps, cryptorchidism, testes surgery, testes trauma], abstinence time, and urinary creatinine) Log-transformed sperm concentration (million/mL) -0.21 (0.11) Sperm motility (%) -1.55 (0.51) Abnormal sperm morphology (%) -2.68 (0.24) Several measures of sperm aneuploidy also examined.
Joensen et al. (2012) (Denmark) **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) **Outcome:** Semen analysis **Exposure:** Urine sample, collected at same time as semen sample MnBP in urine (ng/mL): Median 95^{th} percentile Unadjusted 28 91 **Analysis:** Linear regression, considering age, BMI, smoking, alcohol consumption, 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 *As reported by Ravnborg et al. (2011)	Results for individual phthalate metabolites (including MnBP) reported as "few significant associations" with sperm volume, count, or percentage progressively motile sperm (quantitative results not reported; analyses adjusted for abstinence time [volume, concentration, and count] or time from ejaculation to analysis [progressively motile]; percent of morphologically normal sperm was left unadjusted).

<table>
<tr><th>Reference and study design</th><th>Results</th></tr>
<tr>
<td>
Liu et al. (2012) (China)
Population: 97 men from subfertility clinic, 2009-2010; mean age 32 yrs
Outcome: Semen analysis; results dichotomized above and below WHO reference values; n = 43 with normal semen parameters
Exposure: Urine sample, collected at same time as semen sample
MBP in urine:
<table>
<tr><th></th><th>Median</th><th>66th percentile</th></tr>
<tr><td>Unadjusted (ng/mL)</td><td>10.1</td><td>15.8</td></tr>
<tr><td>Cr-adjusted (µg/g Cr)</td><td>14.2</td><td>24.2</td></tr>
</table>
Analysis: Logistic regression, considering age, BMI, abstinence time, smoking, alcohol use, and education as potential covariates
</td>
<td>
OR (95% CI) by tertile of MBP (adjusted for age, BMI, abstinence time, smoking, and alcohol use)
<table>
<tr><th>MBP Tertile</th><th>Sperm concentration <20 x 10^6/mL (n = 11)</th><th>Sperm motility <50% motile (n = 34)</th><th>Semen volume <2 mL (n = 15)</th></tr>
<tr><td>1 (low)</td><td>1.0 (referent)</td><td>1.0 (referent)</td><td>1.0 (referent)</td></tr>
<tr><td>2</td><td>6.8 (1.0, 75.3)</td><td>0.5 (0.2, 1.4)</td><td>1.0 (0.3, 4.1)</td></tr>
<tr><td>3 (high)</td><td>12.0 (1.0, 143)</td><td>0.7 (0.3, 2.1)</td><td>0.4 (0.1, 2.1)</td></tr>
<tr><td>(trend p)</td><td>(0.05)</td><td>(0.56)</td><td>(0.29)</td></tr>
</table>
</td>
</tr>
<tr>
<td>
Toshima et al. (2012) (Japan)
Population: 42 men visiting gynecology clinic for infertility consultation in 2010; mean age 37 yrs
Outcome: Semen analysis; results also dichotomized above and below WHO reference values (semen volume of 1.5 mL, sperm concentration of 15 x 10^6/mL, and motility of 40%)
Exposure: Urine sample, collected on same day as semen sample
MnBP in urine (ng/mL):
<table>
<tr><th></th><th>Geometric mean (SD)</th></tr>
<tr><td>SG-adjusted</td><td>62.4 (1.82)</td></tr>
</table>
Analysis: Urine concentrations compared between dichotomized groups using t-test; linear regression between SG-adjusted MBP and continuous outcome variables, considering age, abstinence time, BMI, smoking status, frequency of consumption of vegetables, fruits, and coffee, and presence of detectable levels of equol potential covariates
</td>
<td>
SG-adjusted MnBP concentration in urine was higher among men with high semen volume (greater than WHO reference value, n = 39) than with among men with low semen volume (less than WHO reference value, n = 2; $p < 0.05$; quantitative results not reported).

No statistically significant differences in urinary MBP concentrations were observed in groups dichotomized on sperm concentration or motility (quantitative results not reported by the study authors).

Regression coefficient (p-value) for change in sperm parameter per unit change in log-MBP (adjusted for fruit and coffee consumption, and urinary daidzein levels).
<table>
<tr><td>Sperm concentration</td><td>0.294 ($p < 0.05$)</td></tr>
</table>
Authors reported no statistically significant association between urinary MBP and semen volume or sperm motility analyzed by linear regression (quantitative results not reported).
</td>
</tr>
</table>

Reference and study design	Results
Pant et al. (2011) (India) **Population:** 180 male partners 50 fertile, 130 infertile (65 oligoasthenospermic; 65 asthenospermic) seen in Lucknow obstetrics and gynecology department; mean age 28-29 yrs; time period not reported **Outcome:** Semen analysis **Exposure:** Semen sample DBP in semen (µg/mL) (percentile): Median / 75th / 95th Fertile: 0.07 / 0.33 / 0.69 Oligoastheno-spermic: 1.23 / 2.42 / 7.48 Astheno-spermic: 0.17 / 0.57 / 3.03 **Analysis:** Pearson correlation analysis	Pearson correlation coefficient (*p*-value), semen DBP (µg/mL) and sperm parameter Oligoasthenospermic men: -0.25 (<0.01) Asthenospermic men: -0.20 (<0.01) There were no significant differences between fertile and infertile men when other semen parameters (color, odor, viscosity, liquefaction time, pH, volume) were assessed (quantitative results not reported).
Pant et al. (2008) (India) **Population:** 300 male partners (n = 100 fertile, 200 infertile) seen in obstetrics and gynecology department from both urban and rural areas; mean age 29 yrs; time period not reported **Outcome:** Semen analysis **Exposure:** Semen sample DBP in semen (µg/mL), mean ± SE: Fertile / Infertile Rural areas: 0.18 ± 0.03 / 1.10 ± 0.16 Urban areas: 0.63 ± 0.10 / 1.65 ± 0.22 **Analysis:** Pearson correlation analysis	Pearson correlation coefficient between semen DBP and sperm parameter: r Sperm concentration (× 10^6/mL): -0.20* Sperm motility (%): -0.18* Morphology (percent abnormal): -0.01 DNA fragmentation index (chromatin integrity): 0.18* *$p < 0.05$
Wirth et al. (2008) (United States, Michigan) **Population:** 45 male partners seen in infertility clinic, time period not reported; mean age 34 yrs **Outcome:** Semen analysis **Exposure:** Urine sample, collected at same time as semen sample (all between 7 and 11 am) MnBP in urine (ng/mL) (percentile): Median / 75th / 95th 24.7 / 44.3 / 144.5 MIBP in urine (ng/mL) (percentile): Median / 75th / 95th 5.8 / 10.0 / 17.9 **Analysis:** Dichotomized outcomes (above and below WHO reference values), DBP metabolites (sum of MBP and MIBP) dichotomized at median or divided into tertiles; age, education (3 levels), income (3 levels), race, BMI (3 levels), current smoking status, and alcohol use (2 levels) considered as potential confounders; specific gravity also included in all models	OR (95% CI) for DBP metabolites (sum of MnBP and MIBP) above versus below median Low sperm concentration <20 x 10^6/mL: 0.5 (0.1, 3.6)[a] Low sperm motility <50% motile: 0.8 (0.2, 3.9)[b] Abnormal sperm morphology: 3.3 (0.7, 16.2)[c] [a]Adjusted for race (whites, nonwhites) and specific gravity [b]Adjusted for age, alcohol use (≤3 and >3 servings/wk), and specific gravity [c]Adjusted for specific gravity Results of tertile analysis not reported.

<table>
<tr><th>Reference and study design</th><th>Results</th></tr>
<tr><td>
Hauser et al. (2007) (United States; Boston)
Population: 379 male partners from subfertility clinic, 2000-2004; mean age 36 yrs
Outcome: Sperm DNA damage assessed by neutral comet assay
Exposure: Urine sample, collected at same time as semen sample
MBP in urine (ng/mL) (percentile):
<table>
<tr><th></th><th>Median</th><th>75th.</th><th>95th</th></tr>
<tr><td>SG-adjusted</td><td>18.4</td><td>32.3</td><td>72.8</td></tr>
</table>
Analysis: Linear regression, considering age, abstinence time, smoking status, and race as potential covariates
Related reference: Duty et al. (2003b)
</td><td>
Regression coefficient (95% CI) for DNA damage associated with interquartile range increase in ln-MBP (adjusted for age and smoking status).
<table>
<tr><th>Comet extent (µm)</th><th>Tail distribution (µm)</th><th>%DNA tail</th></tr>
<tr><td>0.17 (-3.46, 3.79)</td><td>-0.22 (-1.69, 1.23)</td><td>1.63 (0.20, 3.08)</td></tr>
</table>
</td></tr>
<tr><td>
Hauser et al. (2006) (United States; Boston)
Population: 443 male partners from subfertility clinic 2000-2004; mean age 36 yrs
Outcome: Semen analysis; results dichotomized above and below WHO reference values
Exposure: Urine sample, collected at same time as serum sample for hormone analysis
MBP in urine (ng/mL) (percentile):
<table>
<tr><th></th><th>Median</th><th>75th</th><th>95th</th></tr>
<tr><td>SG-adjusted</td><td>17.7</td><td>31.7</td><td>69.9</td></tr>
</table>
Analysis: Logistic regression, considering age, race, BMI, abstinence time, and smoking as potential covariates
Related references:
Hauser et al. (2005)
Duty et al. (2004)
Duty et al. (2003a)
</td><td>
OR (95% CI) by quartile of MBP (ng/mL) (adjusted for age, abstinence time, and smoking; comparison group = 210 men without deficiencies on any of these three parameters)
<table>
<tr><th>MBP quartile</th><th>Sperm concentration <20 x 10⁶/mL</th><th>Sperm motility <50% motile</th><th>Sperm morphology <4% normal</th></tr>
<tr><td>1 (low)</td><td>1.0 (referent)</td><td>1.0 (referent)</td><td>1.0 (referent)</td></tr>
<tr><td>2</td><td>3.1 (1.2, 8.1)</td><td>1.5 (0.8, 2.6)</td><td>0.8 (0.4, 1.6)</td></tr>
<tr><td>3</td><td>2.5 (0.9, 6.7)</td><td>1.5 (0.8, 2.6)</td><td>0.9 (0.5, 1.7)</td></tr>
<tr><td>4 (high)</td><td>3.3 (1.2, 8.5)</td><td>1.8 (1.1, 3.2)</td><td>0.8 (0.4, 1.6)</td></tr>
<tr><td>(trend p)</td><td>(0.04)</td><td>(0.04)</td><td>(0.59)</td></tr>
</table>
Regression coefficient (95% CI) for sperm motion parameters by quartile of MBP (ng/mL) (adjusted for age, smoking, and abstinence time)
<table>
<tr><th>MBP (ng/mL) quartile</th><th>Straight line velocity (µm/s)</th><th>Curvilinear velocity (µm/s)</th><th>Linearity (%)</th></tr>
<tr><td>1 (low)</td><td>1.0 (referent)</td><td>1.0 (referent)</td><td>1.0 (referent)</td></tr>
<tr><td>2</td><td>-0.97
(-3.68, 1.74)</td><td>-3.46
(-8.05, 1.14)</td><td>1.11
(-0.80, 3.02)</td></tr>
<tr><td>3</td><td>-0.11
(-2.79, 2.58)</td><td>-1.32
(-5.87, 3.24)</td><td>0.84
(-1.06, 2.73)</td></tr>
<tr><td>4 (high)</td><td>-0.88
(-3.57, 1.81)</td><td>-1.65
(-6.20, 2.91)</td><td>0.38
(-1.52, 2.27)</td></tr>
<tr><td>(trend p)</td><td>0.68</td><td>0.71</td><td>0.78</td></tr>
</table>
</td></tr>
</table>

Reference and study design	Results
	MBP quartile cut points: 0.3-10.6, 10.6-17.7, 17.7 -31.7, 31.7-14,459 ng/mL No interaction with polychlorinated biphenyls (PCBs) was identified in this study; however, an interaction was reported by Hauser et al. (2005) for below reference sperm motility.
Zhang et al. (2006) (China) **Population:** 52 men seen in Shanghai Institute of Planned Parenthood Research in 2002, mean age 32 yrs **Outcome:** Semen analysis **Exposure:** Semen samples Mean (range) DBP (mg/L) 0.16 (0.09-0.57) **Analysis:** Spearman correlation analysis	Spearman correlation coefficient (*p*-value), semen DBP (mg/L) and sperm parameter: Sperm density (× 10^6/mL) -0.26 (0.13) Sperm livability (%) -0.25 (0.15) Sperm rate of malformations (%) 0.29 (0.09)
Jonsson et al. (2005) (Sweden) **Population:** 234 men from general population, assessed at military conscription exam in 2000; ages 18-21 yrs **Outcome:** Semen analysis **Exposure:** Urine sample, collected at same time as semen sample MBP in urine (percentile): Median 75th 95th . Unadjusted (ng/mL) 78 140 330 Adjusted (nmol/mmol Cr) 24 36 81 **Analysis:** Mean difference between high and low quartiles	Mean difference (95% CI), highest (≥36.31 nmol/mmol Cr) compared with lowest (≤12.4 nmol/mmol Cr) quartile MBP (positive difference indicates lower value in highest exposure quartile) Sperm concentration (× 10^6/mL) -7.9 (-33, 17) Sperm motility (%) 2.1 (-4.0, 8.2) Sperm damage (chromatin integrity) -2.6 (-6.2, 1.0)
Infertility	
Buck Louis et al. (2014) (United States; Michigan and Texas) **Population:** 501 couples discontinuing contraception and attempting to achieve pregnancy; recruited from 16 counties using population sampling. Women's mean age 30.0 yrs, men's mean age 31.8 yrs; 2005-2009 **Outcome:** Time to pregnancy as assessed by diaries recording intercourse and menstruation,	Fecundability OR (95% CI) per unit increase in log-transformed MnBP scaled by SD (adjusted for female age, difference in couples' ages, research site, and both partners' urinary creatinine, BMI, and serum cotinine; in addition, results for exposure in each partner adjusted for exposure in the other partner, and models accounted for left truncation or time off contraception) Women 0.95 (0.78, 1.16) Men 0.87 (0.73, 1.04)

<table>
<tr><th>Reference and study design</th><th>Results</th></tr>
<tr><td>home-fertility monitoring to detect ovulation, and home pregnancy tests
Exposure: Urine samples from both partners, collected at enrollment (beginning of pregnancy attempt)
Unadjusted MnBP in urine (ng/mL) among couples achieving pregnancy:
Geometric mean (95% CI)
Women 9.97 (8.96-11.09)
Men 5.94 (5.30-6.67)
Analysis: Fecundability ORs calculated using Cox models, adjusting for variables shown in results column</td><td></td></tr>
<tr><td>Tranfo et al. (2012) (Italy)
Population: 56 infertile couples from assisted reproduction center, 56 fertile couples (parents of one or more children, living in same area), time period not reported; mean age 39-40 yrs in both groups
Outcome: Primary or secondary infertility as assessed by WHO criteria (cause attributed to males in 8/56 couples)
Exposure: Urine sample
MnBP in urine, fertile couples:
Median 95th percentile
Cr-adjusted (μg/g Cr) 31.16 146.11
Analysis: Mann-Whitney U-test for comparison of MBP concentrations by group</td><td>MnBP concentration in urine (μg/g Cr) in fertile and infertile couples
<table><tr><th></th><th>Fertile</th><th>Infertile</th><th>p-value</th></tr><tr><td>Median</td><td>31.16</td><td>53.76*</td><td><0.001</td></tr><tr><td>95th percentile</td><td>146.11</td><td>244.10</td><td></td></tr></table>Sex-stratified comparison was also significant for men (p = 0.008, quantitative results not reported).</td></tr>
<tr><td>Pant et al. (2008) (India)
Population: 100 fertile and 200 infertile men visiting obstetrics and gynecology department from both urban and rural areas; mean age 29 yrs; time period not reported
Outcome: Infertility based on female partners who had not conceived after 1-yr unprotected intercourse and who had no diagnosed fertility disorder
Exposure: Semen samples
DBP in semen (μg/mL), mean ± SE:
<table><tr><th></th><th>Fertile</th><th>Infertile</th></tr><tr><td>Rural areas</td><td>0.18 ± 0.03</td><td>1.10 ± 0.16</td></tr><tr><td>Urban areas</td><td>0.63 ± 0.10</td><td>1.65 ± 0.22</td></tr></table>Analysis: Two-way ANOVA for difference in DBP concentrations between fertile and infertile with rural/urban as additional variable</td><td>DBP concentration in semen (μg/mL), mean ± SE, in fertile and infertile men
Rural
<table><tr><th>Fertile (n = 40)</th><th>Infertile (n = 88)</th></tr><tr><td>0.18 ± 0.03</td><td>1.10 ± 0.16*</td></tr></table>Urban
<table><tr><th>Fertile (n = 60)</th><th>Infertile (n = 112)</th></tr><tr><td>0.63 ± 0.10</td><td>1.65 ± 0.22*</td></tr></table>*p < 0.05</td></tr>
</table>

3.2.5. Female Reproductive Effects in Humans

Table 3-5. Evidence pertaining to DBP and reproductive hormones in adult women

<table>
<tr><th>Reference and study design</th><th colspan="3">Results</th></tr>
<tr><td colspan="4">Maternal hormones during pregnancy</td></tr>
<tr><td rowspan="5">Sathyanarayana et al. (2014) (United States; Minnesota, Missouri, California)
Population: 180 mothers from birth cohort (Study for Future Families), recruited during pregnancy, 1999-2002
Outcome: Serum hormone levels, samples collected during prenatal clinic visit
Exposure: Maternal urine sample, collected during 2nd or 3rd trimester
MnBP in urine (ng/mL):
Median / 75th percentile
Unadjusted: 17.35 / 54.85
Analysis: Linear regression, log-transformed MnBP and log-transformed hormone level</td><td colspan="3">Regression coefficient (95% CI) for change in maternal log-transformed serum hormone level with unit increase in log-transformed MnBP, stratified by sex of fetus</td></tr>
<tr><td></td><td>Mothers with male fetus (n = 94)</td><td>Mothers with female fetus (n = 86)</td></tr>
<tr><td>Testosterone (total)</td><td>0.15 (-0.04, 0.33)</td><td>-0.20 (-0.39, -0.01)</td></tr>
<tr><td>Testosterone (free)</td><td>0.13 (-0.07, 0.33)</td><td>-0.21 (-0.42, 0.004)</td></tr>
<tr><td>Estradiol</td><td>0.04 (-0.10, 0.18)</td><td>-0.002 (-0.18, 0.17)</td></tr>
<tr><td rowspan="10">Hart et al. (2013) (Australia)
Population: 123 mothers from birth cohort (Western Australian Pregnancy Cohort), whose mothers were recruited at 18 wks of gestation between 1989 and 1991
Outcome: Reproductive and gonadotropin hormone levels in maternal serum collected at 18 and 34-36 wks of gestation
Exposure: Maternal serum samples (n = 123) collected at 18 and 34-36 wks of gestation (combined aliquot from both time periods)
MnBP in serum (ng/mL):
Median / 90th percentile
MnBP: 2.46 / 10.99
Analysis: Correlation between quartiles of serum MnBP and log-transformed hormone levels</td><td colspan="3">Correlation coefficient between log-transformed maternal serum hormone level and quartiles of MnBP in maternal serum</td></tr>
<tr><td></td><td>At 18 wks of gestation (n = 119)</td><td>At 34-36 wks of gestation (n = 114)</td></tr>
<tr><td>Androstene-dione (nmol/L)</td><td>-0.030</td><td>-0.035</td></tr>
<tr><td>DHEAS (μmol/L)</td><td>-0.112</td><td>-0.058</td></tr>
<tr><td>Testosterone (pmol/L)</td><td>-0.022</td><td>-0.052</td></tr>
<tr><td>SHBG (nmol/L)</td><td>0.048</td><td>-0.101</td></tr>
<tr><td>Free testosterone (pmol/L)</td><td>-0.053</td><td>0.010</td></tr>
<tr><td>Free testosterone index</td><td>-0.041</td><td>0.016</td></tr>
<tr><td colspan="3">p > 0.10 for all correlations</td></tr>
</table>

3.2.6. Female Pubertal Development in Humans

Table 3-6. Evidence pertaining to DBP and timing of female puberty or sex hormones in girls

Reference and study design	Results
Precocious puberty or thelarche	
Chen et al. (2013) (Taiwan) **Population:** 71 girls with central precocious puberty from pediatric endocrinology clinic and 29 controls from schools recruited 2006-2009; mean ages 8.1 and 6.8 yrs, respectively **Outcome:** Premature puberty based on appearance of thelarche, pubic hair or menarche before 8 yrs of age; Tanner staging and serum levels of LH releasing hormone used for additional classification **Exposure:** Urine sample (child's), collected at same time as clinical assessment MBP in urine of controls: Mean (95% CI) Unadjusted (ng/mL) 40.2 (9.93, 163) Cr-adjusted (µg/g Cr) 67.2 (20.5, 275) **Analysis:** MBP concentrations in cases and controls compared with Mann-Whitney U-test	Mean (95% CI) MBP in cases and controls Controls / Cases / (*p*-value) Unadjusted (ng/mL): 40.2 (9.93, 163) / 60.4 (6.14, 1,324) / (0.049) Cr-adjusted (µg/g Cr): 67.2 (20.5, 275) / 94.6 (22.3, 910) / (0.195)
Yum et al. (2013) (Korea) **Population:** Case control study; n = 150 precocious puberty cases and 90 healthy controls visiting pediatric endocrine clinic in 2009 **Outcome:** Precocious puberty defined as development of secondary sex characteristics before 8 yrs of age or menarche before 9.5 yrs of age **Exposure:** Plasma sample (child's) MBP and DBP in plasma (ng/mL) of controls: Mean ± SD MBP 22.80 ± 30.42 DBP 36.65 ± 41.25 **Analysis:** Two-sample t-test for comparisons between concentrations	DBP and MBP in plasma, mean ± SD (ng/mL) Controls / Precocious puberty cases MBP: 22.80 ± 30.42 / 29.81 ± 33.56 DBP: 36.65 ± 41.25 / 29.00 ± 27.49 ($p > 0.1$)
Lomenick et al. (2010) (United States, Ohio, Kentucky) **Population:** 28 girls with central precocious puberty, 28 age- and race-matched controls; all recruited from pediatric endocrinology clinic, 2005-2008; mean age 7 yrs **Outcome:** Central precocious puberty defined based on clinical standards (appearance of physical characteristics of puberty before 8 yrs of age, with laboratory confirmation of central origin of breast	Mean ± SE MnBP in cases and controls Controls / Central precocious puberty / (*p*-value) Unadjusted (ng/mL): 47.2 ± 8.7 / 43.2 ± 7.3 / (0.90) Cr-adjusted (µg/g Cr): 45.1 ± 5.9 / 47.4 ± 6.2 / (0.88)

Reference and study design	Results
development); no cases had received medical treatment prior to urine sample collection **Exposure:** Urine sample (child's), collected at clinical evaluation MnBP in urine of controls: Mean ± SE Unadjusted (ng/mL) 47.2 ± 8.7 Cr-adjusted (μg/g Cr) 45.1 ± 5.9 **Analysis:** MnBP concentrations in cases and controls compared with Wilcoxon rank-sum test	
Chou et al. (2009) (Taiwan) **Population:** 30 girls with premature thelarche and 26 girls with central precocious puberty from pediatric endocrinology clinic; 33 controls from school exams; mean ages 6.7, 8.0, and 8.2 yrs, respectively, in the groups, time period not reported **Outcome:** Premature puberty based on appearance of any physical characteristics of puberty before 8 yrs of age **Exposure:** Urine sample (child's) collected at same time as clinical assessment MBP in urine (ng/mL), controls: Mean ± SD Unadjusted 303.7 ± 176.2 **Analysis:** One-way ANOVA comparing MBP concentrations between groups	Unadjusted MBP in urine; mean ± SD (ng/mL) Controls / Central precocious puberty cases / Premature thelarche cases 303.7 ± 176.2 / 172.5 ± 122.6* / 181.1 ± 131.9* $^*p$ = 0.001 compared to controls
Pubertal development (general population)	
Hart et al. (2013) (Australia) **Population:** 121 girls from birth cohort study (Western Australian Pregnancy Cohort), whose mothers were recruited at 18 wks of gestation 1989-1991; follow-up at ages 14-16 yrs **Outcome:** Age at menarche **Exposure:** Maternal serum samples (n = 123) collected at 18 and 34-36 wks of gestation (combined aliquot from both time periods) MnBP in serum (ng/mL): Median 90th percentile Unadjusted 2.46 10.99 **Analysis:** Correlation between log-transformed MnBP and age at menarche or serum hormones	Authors reported no association between MnBP and age at menarche (quantitative results not reported). Authors reported no correlation between MnBP and serum SHBG, FSH, total testosterone, free androgen index, anti-Müllerian hormone, or inhibin B in adolescents (quantitative results not reported by study authors).

3.2.7. Gynecological Conditions in Humans

Table 3-7. Evidence pertaining to DBP and gynecological conditions in humans

Reference and study design	Results
Endometriosis and fibroids	
Buck Louis et al. (2013) (United States, California and Utah) **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 **Outcome:** Endometriosis confirmed by surgery (operative cohort) or MRI (population cohort) **Exposure:** Urine sample MnBP in urine (ng/mL), unadjusted: Geometric mean Operative cohort-controls 11.01 Population cohort-controls 11.24 **Analysis:** Student's t-test or Wilcoxon test for continuous data; logistic regression, adjusting for age, BMI, and creatinine; 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-MnBP, by cohort (adjusted for age, BMI, and creatinine) Operative cohort 1.11 (0.86, 1.43) Population cohort 2.62 (1.14, 6.05) Adjusted OR (95% CI) for endometriosis per unit increase in ln-MnBP in operative cohort (sensitivity analysis) Endometriosis stage 3 and 4 (n = 339) 1.04 (0.71, 1.53) Visual/histological confirmed endometriosis (n = 473) 0.91 (0.64, 1.31) Comparison with women with postoperative diagnosis normal pelvis (n = 320) 1.13 (0.84, 1.52) Note: Concentrations were log transformed and rescaled by their SDs for analysis.
Upson et al. (2013) (United States, Washington) **Population:** 92 incident endometriosis cases, 195 controls frequency-matched on age, all members of a large health care system and enrolled in Women's Risk of Endometriosis Study, 1996-2001; ages 18-49 yrs **Outcome:** Endometriosis confirmed by surgery; for each case, reference date assigned by date of first visit for symptoms leading to diagnosis; reference dates randomly assigned to controls based on case distribution **Exposure:** Urine sample, collected after enrollment (2001-2002) MnBP in urine, controls: Median (interquartile range) Unadjusted (ng/mL) 10.0 (4.9-23.5) **Analysis:** Logistic regression (quartiles of exposure), covariates considered based on directed acyclic graph; final model adjusted for variables shown in results column	OR (95% CI) for endometriosis by quartile MBP (adjusted for ln-transformed urinary creatinine, age, and reference year) MnBP quartile (ng/mL) — OR (95% CI) 1 (≤4.9) — 1.0 (referent) 2 (4.9-10.0) — 1.2 (0.5, 2.8) 3 (10.0-23.5) — 1.5 (0.6, 3.9) 4 (>23.5) — 1.3 (0.4, 3.9) (trend *p*) — (0.96) Adjustment for education, smoking status and alcohol consumption did not alter the results; similar results in analyses based on summation of MIBP and MnBP.

Reference and study design	Results
Huang et al. (2010) (Taiwan) **Population:** Case-control study, n = 28 endometriosis cases, n = 36 leiomyoma cases, n = 16 adenomyosis cases, and n = 29 controls. Mean ages ~38, 41, and 36 yrs, respectively; recruited from laparotomy patients in medical center, 2005-2007 **Outcome:** Clinical diagnosis of endometriosis, leiomyoma, or adenomyosis confirmed by pathology **Exposure:** Urine sample MnBP in urine, controls Median (range) Unadjusted (ng/mL) 35.4 (5.2-247.2) Cr-adjusted (μg/g Cr) 58.0 (9.8-479.0) **Analysis:** Logistic regression considering age, BMI, and GSTM1 polymorphism as potential covariates	OR (95% CI) for case status by MnBP above compared with below the median(for endometriosis, adjusted for GSTM1 polymorphism and BMI; for leiomyomas and adenomyosis, adjusted for GSTM1 polymorphism and age) Endometriosis / Leiomyomata / Adenomyosis 2.93 (0.92, 9.31) / 1.36 (0.46, 4.00) / 0.78 (0.18, 3.33)
Weuve et al. (2010) (United States, NHANES) **Population:** 87 endometriosis cases, 151 leiomyomata cases, 1,020 controls from population-based survey (NHANES), 1999-2004; ages 20-54 yrs, mean age ~36 yrs **Outcome:** Self-reported diagnosis of endometriosis or leiomyomata; median time since diagnosis, 9 yrs **Exposure:** Urine sample, collected at time of survey MnBP + MIBP in urine, controls: Geometric mean (SE) Cr-adjusted (ng/mg Cr) 25.5 (1.0) **Analysis:** Logistic regression, adjusting for variables shown in results column	OR (95% CI) for gynecological condition by quartile of MBP (summed MnBP and MIBP) (ng/mg Cr) (adjusted for age, race/ethnicity, age at menarche, current pregnancy status and current breast-feeding status) MBP quartile / Endometriosis / Leiomyomata 1 (low) / 1.0 (referent) / 1.0 (referent) 2 / 0.75 (0.38, 1.47) / 0.66 (0.40, 1.10) 3 / 0.96 (0.49, 1.91) / 0.76 (0.46, 1.28) 4 (high) / 1.24 (0.65, 2.34) / 1.26 (0.70, 2.27) (trend *p*) / (0.3) / (0.2)
Itoh et al. (2009) (Japan) **Population:** 57 endometriosis cases, 80 controls; all seeking evaluation for infertility **Outcome:** Clinical diagnosis of endometriosis (American Fertility Society stages II-IV) by laparoscopy; controls were stages 0-1 **Exposure:** Urine sample MnBP in urine, controls: Median / 75th percentile Unadjusted (μg/L) 84.3 / 127.9 Cr-adjusted (μg/g Cr) 43.3 / 67.1 **Analysis:** Logistic regression, adjusting for variables shown in the results column	OR for endometriosis by MnBP (μg/g Cr), above compared with below the median (adjusted for menstrual regularity and average menstrual cycle length) OR (95% CI) = 1.14 (0.54, 2.39) Median MBP in urine by stage of endometriosis Endometriosis stage / Unadjusted (μg/L) / Cr-adjusted (μg/g Cr) 0 / 81.0 / 44.1 I / 92.5 / 42.4 II / 89.7 / 51.7 III / 82.6 / 48.1 IV / 94.7 / 41.6 (trend *p*) / (0.35) / (0.84)

Reference and study design	Results
Reddy et al. (2006a) (India) **Population:** 49 endometriosis cases, 38 gynecology patient controls (group 1), 21 tubal sterilization controls (group 2), time period not reported; mean age ~27 yrs **Outcome:** Endometriosis based on laparoscopy (American Fertility Society severity staging) **Exposure:** Plasma sample DBP in plasma (µg/mL): Mean ± SD Control group 1 0.08 ± 0.14 Control group 2 0.15 ± 0.21 **Analysis:** Two-sample t-test for comparisons between groups; correlation analysis for association with severity (details not reported)	Plasma DBP, mean ± SD, µg/mL Control 1 / Control 2 / Endometriosis 0.08 ± 0.14 / 0.15 ± 0.21 / 0.44 ± 0.41* *$p \leq 0.004$ compared with either control group DBP concentration positively correlated with severity (r = 0.73).
Reddy et al. (2006b) (India) **Population:** 85 endometriosis cases, 135 tubal sterilization controls, from subfertility clinic, 1999-2005; mean age ~31 yrs **Outcome:** Endometriosis based on laparoscopy (American Fertility Society severity staging) **Exposure:** Plasma sample DBP in plasma (µg/mL): Mean ± SD Controls 0.11 ± 0.21 **Analysis:** ANOVA for concentration comparisons across stages	Plasma DBP, mean ± SD (µg/mL), by stage of endometriosis Controls 0.11 ± 0.21 Stage I 0.19 ± 0.17 Stage II 0.29 ± 0.23 Stage III 0.52 ± 0.18 Stage IV 1.05 ± 0.44 $p < 0.05$ for difference between means
Polycystic ovarian syndrome	
	Correlation coefficient (*p*-value) between log-transformed MnBP and pubertal development parameter Uterine volume (mL) r ≤ 0.20 ($p \geq 0.17$) Ovarian volume (cm^3) r ≤ 0.10 ($p \geq 0.29$) Antral follicle count r ≤ 0.12 ($p \geq 0.20$) Authors reported no association between MnBP and polycystic ovarian syndrome using either definition (quantitative results not reported).

Reference and study design	Results
Hart et al. (2013) (Australia) **Population:** 121 girls from birth cohort study (Western Australian Pregnancy Cohort), whose mothers were recruited at 18 wks of gestation between 1989 and 1991; follow-up at ages 14-16 yrs **Outcome:** Uterine volume, ovarian volume, and antral follicle count measured by ultrasound; polycystic ovarian morphology (PCO) defined as ≥1 ovary more than 10 cm^3 or ≥12 follicles between 2 and 9 mm in diameter; polycystic ovarian syndrome or PCOS defined either as (1) presence of at least two of: polycystic ovarian morphology, clinical or biochemical hyperandrogenism, or oligo-anovulation; or (2) oligo-anovulatory menstrual cycles with either clinical or biochemical hyperandrogenism; all clinical assessments conducted on d 2-5 of menstrual cycle **Exposure:** Maternal serum samples (n = 123) collected at 18 and 34-36 wks of gestation (combined aliquot from both time periods) MnBP in serum (ng/mL): Median 90th percentile MnBP 2.46 10.99 **Analysis:** Correlation between log-transformed MBP and uterine volume, ovarian volume, and antral follicle counts; MnBP concentrations in PCO or PCOS cases and controls compared calculated using t-tests or Mann-Whitney U-tests	

3.2.8. Pregnancy-Related Outcomes

Table 3-8. Evidence pertaining to DBP and pregnancy outcomes in humans

Reference and study design	Results
Fetal growth (birth weight, birth length, head circumference)	
Huang et al. (2014b) (China) **Population:** 207 women delivering at 1 hospital in Chongqing between 2011 and 2012, aged 18-35 yrs, with no history of tobacco or alcohol use; mean age 28 yrs **Outcome:** Standard clinical measures at birth **Exposure:** Cord blood sample DBP in cord blood (μg/L): Median / 75th percentile / 95th percentile All samples: 36.21 / 72.03 / 265.40 **Analysis:** Linear regression, adjusting for variables shown in results column	Regression coefficient (95% CI) for change in clinical measurement at birth per unit increase in ln-transformed DBP (μg/L) (adjusted for gestational age): (Girls / Boys) Birth weight (g): -18 (-74, 38) / 10 (-76, 97) Birth length (cm): -0.20 (-0.55, 0.14) / -0.26 (-0.75, 0.23) Head circumference (mm): -3.87 (-8.97, 1.23) / -2.18 (-6.66, 2.31)
Philippat et al. (2012) (France) **Population:** 72 cases with undescended testis or hypospadias, 215 matched controls from two birth cohorts (EDEN and PELAGIE), 2002-2006 **Outcome:** Standard clinical measurements at birth **Exposure:** Maternal urine sample, collected between 6 and 19 (PELAGIE) or between 24 and 30 (EDEN) wks of gestation MnBP in urine (ng/mL): Median / 95th percentile Measured: 48.1 / 398 Standardized*: 58.1 / 488 **Analysis:** Cases and controls combined for this analysis; weighted linear regression using tertiles or ln-transformed urine concentrations, adjusting for variables shown in results column; analysis by tertiles for evaluation of possible non-monotonic relationship; analyses corrected for oversampling of malformation cases *Standardized for sampling conditions and gestational age at collection	Regression coefficient (95% CI) for change in birth outcome by MnBP tertile and per unit change in ln-MnBP (standardized, ng/mL) (adjusted for gestational duration, maternal pre-pregnancy weight and height, maternal smoking, maternal education, parity, recruitment center, urine creatinine, and mode of delivery as potential covariate; head circumference model also adjusted for mode of delivery) MnBP tertile (μg/L) / Birth weight (g) / Birth length (cm) / Head circumference (cm) 1 (<45.6): 0 (referent) / 0 (referent) / 0 (referent) 2 (45.6-85.5): 52 (-101, 206) / 0.3 (-0.4, 0.9) / 0.1 (-0.5, 0.6) 3 (≥85.5): -30 (-174, 114) / 0.1 (-0.6, 0.7) / 0.1 (-0.4, 0.7) (trend *p*): (0.42) / (0.91) / (0.63) ln(MnBP): -13 (-61, 35) / 0.1 (-0.2, 0.3) / 0.0 (-0.2, 0.2)

<table>
<tr><th>Reference and study design</th><th>Results</th></tr>
<tr><td>Brucker-Davis et al. (2010) (France)
Population: 49 healthy newborn boys from prospective study of cryptorchidism (Brucker-Davis et al., 2008b). [MBP analysis was added later in the study, so sample size is less than total of 86 participants.]
Outcome: Standard clinical measurements at birth
Exposure: Cord blood sample at birth and maternal milk sample 2-5 d postpartum
Phthalate in cord blood (ng/mL):
Median / 75th percentile
MBP 2.9 / 4.9
Phthalate in milk (ng/g fat):
Median / 75th percentile
MBP 10.6 / 20.3
Analysis: Spearman correlation analysis</td><td>Spearman correlation coefficient (p-value) between birth outcome and MBP in cord blood (ng/mL)
Birth weight (g) 0.27 (0.085)
Birth length (cm) 0.29 (0.070)
Head circumference (cm) 0.43 (0.005)
Results of analyses (if any) of correlation between milk concentrations and birth outcomes or between DBP in cord blood and birth outcomes were not reported.</td></tr>
<tr><td>Suzuki et al. (2010) (Japan)
Population: 149 infants from birth cohort, 2005-2008
Outcome: Standard clinical measurements at birth
Exposure: Maternal urine sample, gestation wks 9-40 (mean ± SD = 29 ± 8 wks)
MBP in urine:
Median / 75th percentile
Unadjusted (ng/mL) 48.1 / 96.5
Cr-adjusted (mg/g Cr) 52.2 / 91.3
Analysis: Pearson's correlation analysis for individual metabolites and low MW phthalates (∑MMP, MEP, and MBP molar concentrations)</td><td>Pearson's correlation coefficient between MBP (mg/g Cr) or low MW phthalate (molar concentration) and birth outcome
Birth outcome: MBP (mg/g Cr)
Birth weight (g) -0.104
Birth length (cm) -0.096
Head circumference (cm) -0.082
p > 0.05 for all correlations</td></tr>
<tr><td>Huang et al. (2009) (Taiwan)
Population: Birth cohort study; 65 infants (32 girls, 33 boys)
Outcome: Standard clinical measurements at birth
Exposure: Maternal urine and amniotic fluid
MBP in urine (ng/mL):
Median / 90th percentile
Females 78.0 / 309[a]
Males 79.6 / 232.6
MBP in amniotic fluid (ng/mL):
Median / 90th percentile
Females 85.5 / 134.6
Males 81.3 / 127.8
Analysis: Stratified into low and high exposure groups by median MBP concentration in amniotic fluid; AGD compared between the two exposure groups using Wilcoxon rank-sum test; Spearman correlation analysis for association between MBP and continuous variables</td><td>Clinical measurement at birth by sex and concentration of MBP in amniotic fluid
Exposure group | Median MBP in exposure group (ng/mL) | Birth weight (g) | Birth length (cm)
Boys
Low (n = 16) | 63.8 | 3,146 | 49.2
High (n = 17) | 98.7 | 3,194 | 50.0
Girls
Low (n = 15) | 67 | 2,810 | 47.3
High (n = 16) | 104 | 3,172* | 49.2*
*p < 0.05
Spearman correlation coefficient between MBP in amniotic fluid (ng/mL) and clinical measurement at birth in female infants (n = 29)
Birth weight (g) | Birth length (cm)</td></tr>
</table>

<table>
<tr><th>Reference and study design</th><th>Results</th></tr>
<tr><td></td><td>0.16   0.20</td></tr>
<tr><td>Zhang et al. (2009b) (Shanghai, China)
Population: 88 low birth weight infants and 113 controls from birth cohort, 2005-2006
Outcome: Low birth weight defined as <2,500 g among infants born ≥37 wks gestation; birth length
Exposure: Cord blood sample
DBP in cord blood (mg/L):
Median / 75th percentile
Controls 1.8 / 2.7
Cases 2.7 / 3.0
MBP in meconium (mg/g):
Controls 1.7 / 2.4
Cases 2.2 / 3.6
Analysis: Spearman correlation analysis; conditional logistic regression, considering gestational age, pregnancy complications, exposure to tobacco smoke, socioeconomic level, and pre-pregnancy BMI as potential covariates</td><td>OR for low birth weight by quartile of DBP in cord blood (mg/L) (adjusted for gestational age, smoking, socioeconomic level, pre-pregnancy BMI, and other phthalates)
<table>
<tr><td></td><td>OR (95% CI) DBP – cord blood</td><td>OR (95% CI) MBP – meconium</td></tr>
<tr><td>1 (low)</td><td>1.0 (referent)</td><td>1.0 (referent)</td></tr>
<tr><td>2</td><td>0.54 (0.45, 1.47)</td><td>1.58 (1.08, 2.46)</td></tr>
<tr><td>3</td><td>2.69 (1.30, 4.74)</td><td>2.84 (1.19, 4.82)</td></tr>
<tr><td>4 (high)</td><td>3.54 (1.54, 6.15)</td><td>4.68 (2.14, 6.85)</td></tr>
<tr><td>(trend p)</td><td>(0.008)</td><td>(<0.001)</td></tr>
</table>
Spearman coefficient (p-value) by ln-DBP in cord blood (mg/L) or ln-MBP in meconium (adjusted for gestational age, smoking, socioeconomic level, pre-pregnancy BMI, and other phthalates)
<table>
<tr><td></td><td>DBP – cord blood</td><td>MBP – meconium</td></tr>
<tr><td>Birth weight</td><td>-0.23 (0.01)</td><td>-0.56 (<0.001)</td></tr>
<tr><td>Birth length</td><td>-0.09 (0.23)</td><td>-0.11 (0.16)</td></tr>
</table></td></tr>
<tr><td>Wolff et al. (2008) (United States, New York City)
Population: 382 singleton live births without medical complications from birth cohort (Mt. Sinai Children's Environmental Health study), 1998-2002
Outcome: Standard clinical measurements at birth
Exposure: Maternal urine sample, third trimester
MnBP in urine (ng/mL):
Median / 75th percentile
Unadjusted 36 / 75
Analysis: Linear regression, adjusting for variables shown in results column</td><td>Regression coefficient (95% CI) for change in birth outcome with unit increase in ln-MnBP (ng/mL) (adjusted for race/ethnicity, infant sex, gestational age at delivery, ln-creatinine, prenatal smoking, pre-pregnancy BMI, maternal education, and marital status)
<table>
<tr><td>Birth weight (g)</td><td>-5.5 (-45, 34)</td></tr>
<tr><td>Birth length (cm)</td><td>0.15 (-0.07 to 0.37)</td></tr>
<tr><td>Head circumference (cm)</td><td>0.05 (-0.09 to 0.20)</td></tr>
</table>
Restricted to observations with creatinine ≥20 mg/dL</td></tr>
<tr><td colspan="2">Preterm birth (<37 wks) and gestational age</td></tr>
<tr><td>Ferguson et al. (2014b); Ferguson et al. (2014a) (United States; Boston)
Population: 130 cases, 352 controls from pregnancy cohort (study of predictors of pre-eclampsia, enrolled during first trimester, 2006-2008); controls randomly selected from among those delivering ≥37 wks of gestation; mean age 33 yrs
Outcome: Preterm birth (<37 wks of gestation; gestation estimated from first trimester ultrasound); additional analysis of subgroup with spontaneous preterm labor or preterm premature rupture of membranes ("spontaneous preterm," n = 57)</td><td>OR (95% CI) for preterm birth per unit increase in ln-transformed MnBP (adjusted for average specific gravity, maternal age, race/ethnicity, education level, and insurance provider) (Ferguson et al., 2014b):
<table>
<tr><td>All preterm</td><td>1.27 (0.99, 1.63)</td></tr>
<tr><td>Spontaneous preterm</td><td>1.49 (1.08, 2.06)</td></tr>
</table>
[Results weaker than those seen with DEHP metabolites]

OR (95% CI) for preterm birth per unit increase in ln-transformed MnBP at each study visit (adjusted for urine specific gravity, maternal age, race/ethnicity, education level, and insurance provider) (Ferguson et al., 2014a):</td></tr>
</table>

Reference and study design	Results
Exposure: Maternal urine sample, one to three samples collected at median 9.7, 17.9, or 26.0 wks gestation; geometric mean of all visits used in analyses MnBP in urine, SG-adjusted (µg/L): Geometric mean / 75th percentile Controls 15.9 / 22.5 All cases 18.9 / 26.0 **Analysis:** Logistic regression (ln-transformed metabolites), considering average specific gravity, maternal age, race/ethnicity, education level, health insurance provider, BMI at first study visit, smoking status, alcohol use, parity, use of assisted-reproductive technology, and sex of infant as potential covariates; additional analyses conducted for subgroup with preterm labor or premature rupture of membranes ("spontaneous preterm," n = 57) Ferguson et al. (2014a) provides the analysis based on individual sample results for each of the 4 visits	Visit 1 0.97 (0.62, 1.50) Visit 2 1.23 (0.79, 1.93) Visit 3 1.15 (0.77, 1.72) Visit 4 0.94 (0.40, 2.22)
Huang et al. (2014b) (China) **Population:** 207 women delivering at 1 hospital in Chongqing between 2011 and 2012; aged 18-35 and with no history of tobacco or alcohol use; mean age 28 yrs **Outcome:** Preterm birth (<37 wks gestation; gestational age estimated from last menstrual period) **Exposure:** Cord blood sample DBP in cord blood (µg/L): Median / 75th percentile / 95th percentile All samples 36.21 / 72.03 / 265.40 **Analysis:** Logistic and linear regression, adjusting for variables shown in results column	OR (95% CI) for preterm delivery comparing ln-DBP above and below the median (adjusted for maternal age, BMI, frequency of prenatal exam, and pregnancy history), with additional stratification by history of intravenous infusions Total sample (n = 207) 3.35 (2.05, 5.50) No intravenous infusions (n = 154) 2.38 (1.01, 5.61) Intravenous infusions (n = 53) 3.60 (1.82, 7.12) [History of intravenous infusions present in 26% of total and 55% of preterm birth group] Regression coefficient (95% CI) for change in gestational age (wks) per unit increase in ln-transformed DBP (µg/L) (adjusted for maternal age, BMI, frequency of prenatal examination, history of intravenous infusions therapy, and pregnancy history): -0.55 (-0.81, -0.30)

Reference and study design	Results
Weinberger et al. (2014) (USA, New Jersey) **Population:** 72 pregnant women >18 yrs old and expecting singleton birth, seen at High Risk Obstetric Clinic of Robert Wood Johnson University Hospital; time period not reported **Outcome:** Gestational age in medical record as determined by sonographic dating or date of implantation **Exposure:** Maternal urine sample, collected at last obstetric visit prior to delivery. MBP concentration in urine was not reported. **Analysis:** Linear regression, considering parity, race, maternal education, maternal race, parental employment, fast food consumption maternal age, and birth country as potential covariates.	Change in gestation length in days (95% CI) with interquartile change in MBP concentration (adjusted for parity and maternal race) All infants (n = 72) -2.1 (-5.2, 1.1) Males (n = 40) -2.8 (-6.8, 1.2) Females (n = 32) -0.5 (-6.2, 5.1) Interquartile range for MBP in urine = 77.8 ng/mL $p > 0.1$ for all groups
Suzuki et al. (2010) (Japan) **Population:** 149 infants from birth cohort, 2005-2008 **Outcome:** Standard clinical measurements at birth **Exposure:** Maternal urine sample, gestation wks 9-40 (mean ± SD = 29 ± 8 wks) MnBP in urine: Median / 75th percentile Unadjusted (ng/mL) 48.1 / 96.5 Cr-adjusted (mg/g Cr) 52.2 / 91.3 **Analysis:** Pearson's correlation analysis	Pearson's correlation coefficient between MnBP (mg/g Cr) and birth outcome Birth outcome / MnBP (mg/g Cr) Gestational age (wks) -0.135 $p > 0.05$ for all correlations
Huang et al. (2009) (Taiwan) **Population:** Birth cohort study; 65 infants (32 girls, 33 boys) **Outcome:** Standard clinical measurements at birth **Exposure:** Maternal urine and amniotic fluid MBP in urine (ng/mL): Median / 90th percentile Females 78.0 / 309[a] Males 79.6 / 232.6 MBP in amniotic fluid (ng/mL): Median / 90th percentile Females 85.5 / 134.6 Males 81.3 / 127.8 **Analysis:** Stratified into low and high exposure groups by median MBP concentration in amniotic fluid; AGD compared between the two exposure groups using Wilcoxon rank-sum test; Spearman correlation analysis for association between MBP and continuous variables	Clinical measurement at birth by sex and concentration of MBP in amniotic fluid Exposure group / Median MBP in exposure group (ng/mL) / Gestational age (wks) Boys Low (n = 16) 63.8 / 39.1 High (n = 17) 98.7 / 38.9 Girls Low (n = 15) 67 / 38.1 High (n = 16) 104 / 38.7 Spearman correlation coefficient between MBP in amniotic fluid (ng/mL) and clinical measurement at birth in female infants (n = 29) Gestational age (wks) 0.18

<table>
<tr><th>Reference and study design</th><th>Results</th></tr>
<tr><td>Meeker et al. (2009b) (Mexico)
Population: 30 cases, 30 controls (term births) from pregnancy cohort, 2001-2003.
Outcome: Preterm birth (<37 wks of gestation), determined using maternal recall of last menstrual period
Exposure: Maternal urine sample, third trimester
MnBP in urine, among term births
Median / 75th percentile
Unadjusted: 33.4 / 74
SG-adjusted (µg/L): 52.4 / 101
Cr-adjusted (µg/g Cr): 63.1 / 176
Analysis: Logistic regression, considering maternal age, pre-pregnancy BMI, parity, education, marital status, infant's sex, and gestational age at urine sample as potential covariates</td><td>OR (95% CI) for preterm birth by MnBP above compared with below the median (adjusted for marital status, maternal education, and infant sex and gestational age at time of urine sample)
Cr-unadjusted (µg/L): 10.7 (2.4, 47.4)
SG-adjusted (µg/L): 4.5 (1.2, 16.6)
Cr-adjusted (µg/g Cr): 5.4 (1.5, 19.3)</td></tr>
<tr><td>Wolff et al. (2008) (United States, New York City)
Population: 382 singleton live births without medical complications from birth cohort (Mt. Sinai Children's Environmental Health study), 1998-2002
Outcome: Standard clinical measurements at birth
Exposure: Maternal urine sample, third trimester
MnBP in urine (ng/mL):
Median / 75th percentile
Unadjusted: 36 / 75
Analysis: Linear regression, adjusting for variables shown in results column</td><td>Regression coefficient (95% CI) for change in gestational age with unit increase in ln-MnBP (ng/mL) (adjusted for race/ethnicity, infant sex, gestational age at delivery, ln-creatinine, prenatal smoking, pre-pregnancy BMI, maternal education, and marital status)
Gestational age (wks): 0.10 (-0.06, 0.26)
Restricted to observations with creatinine ≥20 mg/dL</td></tr>
<tr><td colspan="2">*Early pregnancy loss*</td></tr>
<tr><td>Toft et al. (2012) (Denmark)
Population: 48 women with pregnancy loss, 80 with pregnancies ending in a live birth from cohort of couples planning first pregnancy, 1992-1994
Outcome: Any pregnancy loss (n = 48), early (subclinical) embryonal loss (pregnancy identified by elevation in human chorionic gonadotropin; n = 32) or clinically-identified pregnancy loss (n = 16)
Exposure: Urine samples (one conception cycle, one preconception cycle)
MBP in urine (ng/mL), among live births:
Mean / Maximum
Live birth: 226 / 1,005
Analysis: Logistic regression, adjusting for variables shown in results column</td><td>OR (95% CI) for any pregnancy loss by tertile MBP (ng/mL) (adjusted for age, BMI, smoking, alcohol and caffeine intake, and MBP in the other cycle)
MBP tertile / Preconception / Conception cycle
1 (low): 1.0 (referent) / 1.0 (referent)
2: 0.70 (0.27, 1.84) / 1.12 (0.41, 3.02)
3 (high): 0.79 (0.32, 2.00) / 1.12 (0.43, 2.95)
OR (95% CI) for types of pregnancy loss by tertile MBP (ng/mL) in the conception cycle (adjusted for age, BMI, smoking, alcohol and caffeine intake, and MBP in the preconception cycle)
MBP tertile / Subclinical / Clinically-identified
1 (low): 1.0 (referent) / 1.0 (referent)
2: 1.25 (0.38, 4.1) / 0.87 (0.21, 3.57)
3 (high): 1.64 (0.52, 5.2) / 0.51 (0.12, 2.21)</td></tr>
</table>

3.2.9. Immune Effects in Humans

Table 3-9. Evidence pertaining to DBP and allergy/immune effects in humans

<table>
<tr><th>Reference and study design</th><th colspan="4">Results</th></tr>
<tr><td rowspan="19">Ait Bamai et al. (2014) (Japan)[a]
Population: Children (n = 122, ages <15 yrs) and adults (n = 374, ages ≥15 yrs) living in 148 detached dwellings in which at least 25 mg of dust was collected; 2006 follow-up of 2003 baseline survey
Outcome: Allergic condition assessed by self-administered questionnaire (positive response to: in the past 2 yrs have you been seen at a hospital for allergic rhinitis, allergic conjunctivitis, or atopic dermatitis?); parents completed questionnaires for children <6 yrs old)
Exposure: Dust samples
DBP in dust (μg/g dust) (percentile):
Median 75th
Floor dust (n = 148) 19.3 51.2
Multisurface dust 20.6 40.8
(n = 120)
Analysis: Generalized linear mixed effects model, considering gender, age strata (<15, ≥15 yrs, smoking status (personal and environmental tobacco smoke), furry pets in home, signs of dampness, Der 1 [not defined by authors], other phthalates dust, airborne fungi, formaldehyde, total VOC, and building characteristics as potential covariates</td><td colspan="4">OR (95% CI) for allergic condition by tertile of DBP in floor dust (μg/g dust) (adjusted for gender, age strata, smoking status, dampness index, furry pets inside the home, Der 1, and sum of other phthalates)</td></tr>
<tr><td>DBP tertile</td><td>Full sample</td><td>Children</td><td>Adults</td></tr>
<tr><td colspan="4">Allergic rhinitis</td></tr>
<tr><td>1 (low)</td><td>1.0 (referent)</td><td>1.0 (referent)</td><td>1.0 (referent)</td></tr>
<tr><td>2</td><td>1.17 (0.55, 2.51)</td><td>1.34 (0.39, 4.61)</td><td>1.02 (0.5, 2.11)</td></tr>
<tr><td>3 (high)</td><td>1.00 (0.44, 2.26)</td><td>1.16 (0.34, 3.93)</td><td>0.87 (0.38, 1.99)</td></tr>
<tr><td>(trend p)</td><td>(1.0)</td><td>(0.81)</td><td>(0.73)</td></tr>
<tr><td colspan="4">Allergic conjunctivitis</td></tr>
<tr><td>1 (low)</td><td>1.0 (referent)</td><td>1.0 (referent)</td><td>1.0 (referent)</td></tr>
<tr><td>2</td><td>1.67 (0.56, 4.98)</td><td>1.77 (0.33, 9.46)</td><td>1.58 (0.53, 4.65)</td></tr>
<tr><td>3 (high)</td><td>1.13 (0.37, 3.44)</td><td>2.09 (0.45, 9.64)</td><td>0.61 (0.16, 2.35)</td></tr>
<tr><td>(trend p)</td><td>(0.84)</td><td>(0.34)</td><td>(0.47)</td></tr>
<tr><td colspan="4">Atopic dermatitis</td></tr>
<tr><td>1 (low)</td><td>1.0 (referent)</td><td>1.0 (referent)</td><td>1.0 (referent)</td></tr>
<tr><td>2</td><td>1.47 (0.62, 3.47)</td><td>1.64 (0.43, 6.34)</td><td>1.32 (0.47, 3.71)</td></tr>
<tr><td>3 (high)</td><td>1.19 (0.46, 3.07)</td><td>1.27 (0.33, 4.82)</td><td>1.12 (0.35, 3.61)</td></tr>
<tr><td>(trend p)</td><td>(0.71)</td><td>(0.72)</td><td>(0.85)</td></tr>
<tr><td colspan="4">p-value for age interaction > 0.1 for all endpoints</td></tr>
<tr><td colspan="4">Analyses using multisurface dust measures also presented; results similar to those using floor dust measures.</td></tr>
</table>

<table>
<tr><th>Reference and study design</th><th colspan="4">Results</th></tr>
<tr><td rowspan="16">Callesen et al. (2014b)
Callesen et al. (2014a) (Denmark)[a]
Population: 81 rhinoconjunctivitis cases, 88 atopic dermatitis cases, 242 healthy controls group from population-based survey (Indoor Environment and Children's Health); ages 3-5 yrs
Outcome: Clinical exam and parent interview; allergic rhinoconjunctivitis: recurrence of at least two or more nasal symptoms (pruritus, runny nose, sneezing spells >20, nasal stenosis/ mouth breathing) and ocular symptoms (itching, conjunctival injection, or watery secretion in both eyes) when exposed to allergens; atopic dermatitis: presence of at least 3 of 4 major features and 3 of 23 minor features; 70% of rhinoconjunctivitis and 50% of atopic dermatitis cases were IgE positive based on 20 allergen tests
Exposure: DBP concentrations in dust samples from bedroom and day care centers (Callesen et al., 2014b); MnBP in urine samples from subset of</td><td colspan="4">Median DBP in dust (μg/g), by case-control status assessed by clinical examination, from Callesen et al. (2014b):</td></tr>
<tr><td></td><td></td><td colspan="2">Cases</td></tr>
<tr><td></td><td>Controls
(n = 242)</td><td>Rhinoconjunctivitis
(n = 81)</td><td>Atopic dermatitis
(n = 88)</td></tr>
<tr><td>Home</td><td>15.1</td><td>14.1</td><td>14.7</td></tr>
<tr><td>Day care</td><td>35.1</td><td>39.8</td><td>39.6</td></tr>
<tr><td>Area-weighted</td><td>21.7</td><td>22.3</td><td>23.1</td></tr>
<tr><td colspan="4">Similar results when based on case status defined by parent-questionnaire data (n = 56 rhinoconjunctivitis, n = 83 atopic dermatitis)</td></tr>
<tr><td colspan="4">OR (95% CI) for rhinoconjunctivitis or atopic dermatitis (number of cases and controls revised after reclassification of some cases and controls during clinical examination and elimination of participants with missing data on covariates) by quartile of MBP in urine (ng/mL) (adjusted for sex, breastfeeding <3 mo, smoking in the home, single allergic predisposition, and social class), from Callesen et al. (2014a)</td></tr>
<tr><td colspan="2">MnBP quartile</td><td>Rhinoconjunctivitis
(71 cases, 216 controls)</td><td>Atopic dermatitis
(76 cases, 216 controls)</td></tr>
<tr><td colspan="2">1 (low)</td><td>1.0 (referent)</td><td>1.0 (referent)</td></tr>
<tr><td colspan="2">2</td><td>1.80 (0.82, 3.96)</td><td>0.71 (0.39, 1.87)</td></tr>
<tr><td colspan="2">3</td><td>0.95 (0.42, 2.18)</td><td>0.97 (0.47, 2.19)</td></tr>
<tr><td colspan="2">4 (high)</td><td>1.36 (0.64, 2.89)</td><td>0.62 (0.60, 2.39)</td></tr>
</table>

Reference and study design	Results
population (76 with rhino-conjunctivitis, 81 with atopic dermatitis, and 222 controls) (Callesen et al., 2014a) DBP in dust among controls (μg/g) Median Home 15.1 Day Care 35.1 Weighted* average 21.7 (*weighted by assumed hours in each environment) MnBP in urine (ng/mL) of controls: Median 95th percentile Unadjusted 84.7 256.8 **Analysis:** Mann-Whitney U-test for concentration comparisons between groups; logistic regression for ORs, considering sex, breastfeeding <3 mo, antibiotic use, single allergic predisposition, visible mold, visible moisture, window condensation, cat or dog in the home, pet avoidance, changed cleaning habits, smoking in the home, and social class as potential covariates	
Wang et al. (2014) (Taiwan) **Population:** 218 children from birth cohort, born 2004-2005; follow-up at age 2 (n = 218) and age 5 (n = 191) **Outcome:** Atopic dermatitis based on ISAAC (International Study of Asthma and Allergies in Children) questionnaire (three questions—itchy rash coming and going for at least 6 mo; if yes, itchy rash in last 12 mo; ever diagnosed with atopic dermatitis by a doctor?); total serum IgE **Exposure:** Maternal urine sample, third trimester; urine samples in children (ages 2 and 5 yrs) Cr-adjusted MBP in urine (μg/g Cr): Geometric mean (SE) At 3rd trimester 64.62 (1.06) Age 2 152.92 (1.05) Age 5 57.29 (1.05) **Analysis:** Linear regression and logistic regression of log transformed data, considering sex, gestational age, parity, maternal age, education and occupation, diets and supplements	OR (95% CI) for atopic dermatitis by quartile of MBP (μg/g Cr) (adjusted for gender, gestational age, maternal education, maternal history of atopy, and prenatal environmental tobacco smoke exposure) MBP quartile (μg/g Cr) / Age 2 yrs / Age 5 yrs 1 (<98.0851) / 1.0 (referent) / 1.0 (referent) 2 (98.0851-158.8043) / 0.71 (0.27-1.85) / 0.62 (0.23-1.66) 3 (158.8043-237.9412) / 1.09 (0.44-2.73) / 0.86 (0.33-2.21) 4 (>237.9412) / 0.75 (0.29-1.93) / 0.80 (0.31-2.05) Regression coefficient (*p*-value) for log-serum total IgE at 2 yrs of age according to log-urine phthalate metabolite concentrations at age 2 (adjusted for gestational age, maternal education, maternal history of atopy, and prenatal environmental tobacco smoke exposure) All children (n = 218) 0.049 (0.71) Boys (n = 114) 0.161 (0.46) Girls (n = 104) -0.033 (0.84)

Reference and study design	Results
during pregnancy, family income, parental atopy, duration of breast feeding, tobacco smoke exposure, incense and carpets in home, and fungi on house walls as potential covariates	

Reference and study design	Results
Hoppin et al. (2013a)[a] (United States, NHANES) **Population:** 2,325 participants in population-based survey (NHANES), 2005-2006; ages ≥6 yrs **Outcome:** Self-administered questionnaire current allergy symptoms (hay fever, allergy, itchy rash, rhinitis) in past year; allergic sensitization as measured by serum IgE (19 allergen specific IgEs, ≥0.35kU/L) **Exposure:** Urine sample collected same day as serum sample; data reported in Hoppin et al. (2013b); Supplemental Material MnBP in urine (µg/L) (percentile) Median / 75th / 95th Children: 31.56 / 57.63 / 134.95 Adults: 18.58 / 36.85 / 101.08 **Analysis:** Logistic regression, adjusting for variables shown in results column and sampling weights; separate analyses for children (ages 6-17 yrs) and adults (>17 yrs)	Prevalence and OR (95% CI) for allergy symptoms and allergic sensitization per unit change in log-transformed urinary MnBP level (adjusted for age, race/ethnicity, gender, BMI, creatinine, and cotinine) Children (n = 779) Hay fever (n = 23) — 3.6% — 0.07 (0.03, 0.17) Rhinitis (n = 188) — 27.6% — 0.83 (0.46, 1.52) IgE sensitization (any) — 46.1% — 1.14 (0.68, 1.93) Adults (n = 1,546) Hay fever (n = 88) — 7.4% — 1.23 (0.54, 2.79) Rhinitis (n = 498) — 35.4% — 1.34 (0.83, 2.17) IgE sensitization (any) — 44.0% — 1.14 (0.74, 1.74) Authors reported that adjustment for poverty income ratio did not alter ORs.
Hsu et al. (2012)[a] (Taiwan) **Population:** 59 cases (48 with allergic rhinitis, 36 with eczema), 42 controls, ages 3-9 yrs, recruited through kindergartens and day care centers, 2005-2006. **Outcome:** Allergic rhinitis or eczema; initial case/control status determined through parent report of history; final status determined by clinical examination **Exposure:** Settled dust samples from child's major and minor activity rooms; urine samples collected at clinical examination DBP in dust Median / 75th percentile Dust (µg/g): 20.2 / 39.80 MnBP in urine Median / 75th percentile Unadjusted (µg/L): 57.9 / 103.7 Cr-adjusted (µg/g Cr): 54.4 / 107.3 **Analysis:** Logistic regression adjusting for variables shown in the results column	OR (95% CI) for allergic rhinitis or eczema by quartile of exposure (adjusted for age, sex, presence of fever, medication use, parents' smoking status, parents' allergy history, parents' education, and month of sampling) DBP quartile, dust (µg/g dust) — Rhinitis — Eczema 1 (5.49-13.34) — 1.0 (referent) — 1.0 (referent) 2 (13.35-20.23) — 2.54 (0.49, 13.23) — 3.92 (0.41, 37.90) 3 (20.24-39.80) — 1.46 (0.30, 7.07) — 3.99 (0.47, 33.78) 4 (39.81-684.64) — 1.68 (0.31, 9.20) — 3.43 (0.34, 34.20) (trend *p*) — >0.10 — >0.10 MnBP quartile, urine (µg/g Cr) — Rhinitis — Eczema 1 (17.28-36.34) — 1.0 (referent) — 1.0 (referent) 2 (36.35-54.43) — 1.25 (0.33, 4.74) — 1.94 (0.43, 8.73) 3 (54.44-107.25) — 0.63 (0.16, 2.38) — 1.70 (0.38, 7.49) 4 (107.26-445.56) — 0.40 (0.09, 1.76) — 0.43 (0.07, 2.51) (trend *p*) — >0.10 — >0.10 OR for all cases (at least one among asthma, rhinitis, or eczema) not significantly elevated in highest quartile DBP in dust (OR = 2.02, 95% CI = 0.37, 10.94; trend *p* >0.10)

Reference and study design	Results
Kanazawa et al. (2010) (Japan) **Population:** 134 residents (41 dwellings), including 33 reporting at least one symptom and 101 with no reported symptoms **Outcome:** Self-reported "sick house syndrome" symptoms (fatigue; feeling heavy-headed; headache; nausea/ dizziness; difficulty concentrating; itching, burning or irritation of the eyes; irritated, stuffy, or runny nose; hoarse, dry throat; cough; dry or flushed facial skin; scaling/itching of the scalp or ears; and dry, itching or red-skinned hands) **Exposure:** Air and dust sample in dwellings DBP in room air (ng/m^3): Median / Range Total concentration 200 79.6-740 DBP in dust (mg/kg): Median / Range Multi-surface 22.3 5.1-549 Floor 19.8 1.8-1,476 **Analysis:** Logistic regression, adjusting for variables shown in the results column	OR (95% CI) for mucosal symptoms per 10-fold increase in DBP concentration (adjusted for age, gender, history of allergy, and time spent at home; similar results with additional adjustment for moldy odor and for condensation) Air (ng/m^3) 0.5 (0.1-3.6) Multi-surface dust (mg/kg) 0.3 (0.1-1.0) Floor dust (mg/kg) 0.5 (0.2-1.2)
Sun et al. (2009) (China) **Population:** Cases of rhinitis (n = 225) or eczema (n = 61) and controls (n = 187 and 115 for rhinitis and eczema analysis, respectively), all students of Tianjin University who had participated in a cross-sectional study of allergic symptoms and environmental factors; 2006-2007 **Outcome:** Self-reported symptoms from questionnaire: rhinitis = in past 12 mo, had a problem with sneezing, or a runny, or a blocked nose when not having a cold or the flu, or sneezing, or a runny, or a blocked nose, or itchy-watery eyes after contact with furred animals or after contact with pollen; eczema = in past 12 mo, had an itchy	Median concentration DBP in dust (μg/g dust) Cases / Control / (*p*-value) Rhinitis 23.23 26.92 0.39 Eczema 31.15 21.76 0.24 Mann-Whitney test; similar results for t-test of log-transformed DBP

<table>
<tr><th>Reference and study design</th><th>Results</th></tr>
<tr><td>rash; controls responded no to rhinitis (n=187) or eczema (n=115) questions
Exposure: Surface dust sample in dorm rooms
DBP in dust (µg/g):
Median 75th percentile
28.56 48.82
Analysis: Logistic regression for OR, considering age, gender, passive smoking, smoking, pet raising, atopy, and building age as potential covariates; Mann-Whitney U-test for comparison between DBP concentrations of cases and controls; t-test for comparisons between log transformed concentrations</td><td></td></tr>
<tr><td><u>Kolarik et al. (2008)</u> (Bulgaria)
Population: 102 cases, 82 controls from population-based survey (ALLHOME study), 2004-2005; ages 2-7 yrs
Outcome: Cases: positive response to wheezing during the last 12 mo, rhinitis during the last 12 mo, when not having a cold, or itching rash eczema in the last 12 mo; controls: negative response to all three questions and other questions on history of wheezing, asthma, allergy symptoms or diagnosis in past
Exposure: Surface dust samples from children's bedrooms
DBP in dust (mg/g):
Geometric mean
All homes 7.86
Analysis: Dust concentrations compared between case and control homes overall, and between cases with specific symptoms in the preceding 12 mo and controls, using Mann-Whitney U-test (untransformed data) and Dunnett test (log-transformed data)</td><td>Concentration DBP in dust (mg/g dust)
<table>
<tr><th></th><th>Median</th><th>Mean</th><th>p-value for Dunnett test</th></tr>
<tr><td>Controls</td><td>9.87</td><td>12.04</td><td></td></tr>
<tr><td>All cases</td><td>9.61</td><td>12.15</td><td>(0.58)</td></tr>
<tr><td>Rhinitis</td><td>8.63</td><td>10.69</td><td>(0.96)</td></tr>
<tr><td>Eczema</td><td>9.61</td><td>13.30</td><td>(0.89)</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Reference and study design</th><th>Results</th></tr>
<tr><td>Bornehag et al. (2004) (Sweden)

Population: 198 cases, 202 controls from population-based cohort (Dampness in Buildings and Health cohort) (n = 10,852), 2001-2002; ages 2-7 yrs

Outcome: Rhinitis, wheezing, or eczema (cases report at least two incidents of rhinitis or eczema in the preceding year, and at follow-up 1.5 yrs later)

Exposure: Surface dust samples from children’s bedrooms

DBP in dust (mg/g):
Median
All homes 0.150

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</td><td>Concentration in dust (mg/g dust)
<table>
<tr><th></th><th>Median, all homes (n = 346)</th><th>Geometric mean (95% CI), homes with phthalate > detection limit (n = 158)</th></tr>
<tr><td>Controls</td><td>0.149</td><td>0.178 (0.157, 0.201)</td></tr>
<tr><td>Cases (all)</td><td>0.150</td><td>0.171 (0.152, 0.193)</td></tr>
</table>
p > 0.6 in both tests.</td></tr>
</table>

[a]Additional results for this study presented in asthma table (Table 3-10).

Table 3-10. Evidence pertaining to DBP and asthma/wheezing and hypersensitivity in humans

<table>
<tr><th>Reference and study design</th><th colspan="4">Results</th></tr>
<tr><td rowspan="8">Ait Bamai et al. (2014) (Japan)[a]
Population: Children (n = 122, ages <15 yrs) and adults (n = 374, ages ≥15 yrs) living in 148 detached dwellings in which at least 25 mg of dust was collected; 2006 follow-up of 2003 baseline survey
Outcome: Bronchial asthma assessed by self-administered questionnaire (positive response to: in the past 2 yrs have you been seen at a hospital for bronchial asthma?); parents completed questionnaires for inhabitants <6 yrs old
Exposure: Dust samples
DBP in dust (μg/g dust) (percentile):
Median 75th
Floor dust (n = 148) 19.3 31.2
Multi-surface dust (n = 120) 20.6 40.8
Analysis: Generalized linear mixed effects model, considering gender, age strata (<15, ≥15 yrs), smoking status (personal and environmental tobacco smoke), furry pets in home, signs of dampness, Der 1 (not defined by authors), other phthalates dust, airborne fungi, formaldehyde, total VOC, and building characteristic as potential covariates</td><td colspan="4">OR (95% CI) for bronchial asthma by tertile of DBP in floor dust (μg/g dust) (adjusted for gender, age strata, smoking status, dampness index, furry pets inside the home, Der 1, and sum of other phthalate dusts)</td></tr>
<tr><td>DBP tertile</td><td>Full sample</td><td>Children</td><td>Adults</td></tr>
<tr><td>1 (low)</td><td>1.0 (referent)</td><td>1.0 (referent)</td><td>1.0 (referent)</td></tr>
<tr><td>2</td><td>2.05 (0.52, 8.16)</td><td>1.29 (0.28, 5.85)</td><td>3.27 (0.35, 30.26)</td></tr>
<tr><td>3 (high)</td><td>4.54 (1.23, 16.79)</td><td>3.50 (0.68, 18.07)</td><td>5.88 (0.61, 56.74)</td></tr>
<tr><td>(trend p)</td><td>(0.02)</td><td>(0.13)</td><td>(0.13)</td></tr>
<tr><td colspan="4">p-value for age interaction = 0.84</td></tr>
<tr><td colspan="4">Analyses using multisurface dust measures also presented; results similar to those using floor dust measures.</td></tr>
<tr><td rowspan="9">Callesen et al. (2014b)
Callesen et al. (2014a)[a] (Denmark)
Population: 72 asthma cases, 242 healthy controls group from population-based survey (Indoor Environment and Children’s Health); ages 3-5 yrs; 2008
Outcome: Clinical exam and parent interview; asthma: recurrence of at least two of the three symptoms: cough, wheeze, and shortness of breath within the previous 12 mo (symptoms other than those
triggered by respiratory infections); and doctor diagnosis of asthma in combination with ongoing treatment; 47% of asthma cases were IgE positive based on 20 allergen tests
Exposure: DBP concentrations in dust samples from bedroom and day care centers; (Callesen et al., 2014b); MBP in</td><td colspan="4">Median DBP in dust (μg/g), by case-control status assessed by clinical examination</td></tr>
<tr><td></td><td colspan="2">Controls (n = 242)</td><td>Asthma (n = 72)</td></tr>
<tr><td>Home</td><td colspan="2">15.1</td><td>10.0</td></tr>
<tr><td>Day care</td><td colspan="2">35.1</td><td>37.5</td></tr>
<tr><td>Area-weighted</td><td colspan="2">21.7</td><td>17.4</td></tr>
<tr><td colspan="4">Similar results when based on case status defined by parent-questionnaire data (n = 110 asthma cases)</td></tr>
<tr><td colspan="4">OR (95% CI) for bronchial asthma (60 cases, 216 controls after reclassification of some cases and controls during clinical examination and elimination of participants with missing data on covariates) by quartile of MnBP (urine sample), adjusting for sex, breastfeeding <3 mo, smoking in the home, and single allergic predisposition (Callesen et al., 2014a)</td></tr>
<tr><td>1 (low)</td><td colspan="3">1.0 (referent)</td></tr>
<tr><td>2</td><td colspan="3">0.68 (0.31, 1.49)</td></tr>
</table>

Reference and study design	Results
urine samples from subset of population (68 with asthma and 222 controls) (Callesen et al., 2014a) DBP in dust among controls (µg/g): Median Home 15.1 Day care 25.1 Time-weighted 21.7 (weighted by assumed time spent in each environment) MnBP in urine (ng/mL) of controls: Median 95th percentile Unadjusted 84.7 256.8 **Analysis:** Mann-Whitney U-test for concentration comparisons between groups; logistic regression for ORs, considering sex, breastfeeding <3 mo, antibiotic use, single allergic predisposition, visible mold, visible moisture, window condensation, cat or dog in the home, pet avoidance, changed cleaning habits, smoking in the home, and social class as potential covariates	3 0.77 (0.35, 1.69) 4 (high) 0.60 (0.26, 1.36)
Bertelsen et al. (2013) (Norway) **Population:** 623 children from birth cohort (Environment and Childhood Asthma study), born 1992-1993; children with current asthma over-sampled (follow-up 2001-2004); ages 10 yrs **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) **Exposure:** First morning urine sample (child's), collected at study examination MnBP in urine (µg/L) (percentile): Median 75th 95th Unadjusted 138.0 209.0 377.2 SG-adjusted 141.0 215.2 378.9 **Analysis:** Logistic regression, adjusting for variables shown in the results column	OR (95% CI) for current asthma by quartile of MnBP (µg/L) (adjusted for urine specific gravity, sex, parental asthma, and household income) 1: ≤93.6 (referent) 1 (referent) 2: >93.6-138 1.2 (0.65, 2.0) 3: >138-209 1.1 (0.62, 2.0) 4: >209 0.96 (0.51, 1.8) Increase in odds of current asthma per log_{10} IQR MBP (95% CI) = 0.85 (0.64-1.1)

Reference and study design	Results
Hoppin et al. (2013a)[a] (United States, NHANES) **Population:** 2,325 participants in population-based survey (NHANES), 2005-2006; ages ≥6 yrs **Outcome:** Self-administered questionnaire (asthma, wheeze in past year) **Exposure:** Urine sample collected same day as serum sample; data reported in Hoppin et al. (2013b); Supplemental Material MnBP in urine (µg/L) (percentile) Median / 75th. / 95th. Children 31.56 / 57.63 / 134.95 Adults 18.58 / 36.85 / 101.08 **Analysis:** Logistic regression, adjusting for variables shown in results column and sampling weights; separate analyses for children (ages 6-17 yrs) and adults (>17 yrs)	Prevalence and OR (95% CI) for asthma symptoms per unit change in log-transformed urinary MnBP level (adjusted for age, race/ethnicity, gender, BMI, creatinine, and cotinine) Children (n = 779) Asthma (n = 65) 8.4% 0.63 (0.20, 2.02) Wheeze (n = 80) 10.7% 0.45 (0.20, 0.98) Adults (n = 1,546) Asthma (n = 116) 7.4% 1.75 (0.67, 4.56) Wheeze (n = 219) 16.6% 1.36 (0.74, 2.53) Authors reported that adjustment for poverty income ratio did not alter ORs
Hsu et al. (2012)[a] (Taiwan) **Population:** 9 cases, 42 controls, ages 3-9 yrs, recruited through kindergartens and day care centers, 2005-2006. **Outcome:** Initial case/control status determined through parent report of history; final status determined by clinical examination. **Exposure:** Settled dust samples from child's major and minor activity rooms; urine samples collected at clinical examination Median / 75th percentile DBP in dust (µg/g) 20.2 / 39.80 MnBP in urine: Unadjusted (µg/L) 57.9 / 103.7 Cr-adjusted (µg/g Cr) 54.4 / 107.3 **Analysis:** Logistic regression adjusting for variables shown in the results column	OR (95% CI) for asthma by quartile of exposure (adjusted for age, sex, presence of fever, medication use, parents' smoking status, parents' allergy history, parents' education, month of sampling) DBP quartile, dust (µg/g dust) — Asthma 1 (5.49-13.34) — 1.0 (referent) 2 (13.35-20.23) — 2.83 (0.55, 14.72) 3 (20.24-39.80) — 2.16 (0.48, 9.78) 4 (39.81-685) — 2.02 (0.37, 10.94) (trend *p*) — (>0.05) MnBP quartile, urine (µg/g Cr) — Asthma 1 (17.28-36.34) — 1.0 (referent) 2 (36.35-54.43) — 1.25 (0.34, 4.60) 3 (54.44-107.25) — 0.92 (0.26, 3.21) 4 (107.26-445.56) — 0.43 (0.11, 1.72) (trend *p*) — (>0.05)

Reference and study design	Results
Sun et al. (2009) (China) **Population:** 88 cases of wheezing, 320 controls*, all students of Tianjin University who had participated in a cross-sectional study of allergic symptoms and environmental factors 2006-2007 **Outcome:** Self-reported symptoms from questionnaire. Asthma/wheezing = in past 12 mo, have you had wheezing or whistling in the chest; have you had dry cough at night for more than 2 wks, apart from a cough associated with a cold or chest infection **Exposure:** Dorm room surface dust sample DBP in dust (µg/g): Median: 28.56; 75th percentile: 48.82 **Analysis:** Logistic regression for OR, considering age, gender, passive smoking, smoking, pet raising, atopy, and building age as potential covariates; Mann-Whitney U-test for comparison between DBP concentrations of cases and controls; t-test for comparisons between log transformed concentrations	OR for asthma comparing DBP in dust (µg/g dust) above and below the median (adjusted for age, gender, smoking, atopy, and building age) reportedly did not reach statistical significance (quantitative results not reported) Median concentration DBP in dust (µg/g dust) (Cases / Control / *p*-value) Wheezing: 26.25 / 24.90 / 0.62 Mann-Whitney test; similar results for t-test of log-transformed DBP
Kolarik et al. (2008)[a] (Bulgaria) Nested case-control study; n = 102 cases, 82 controls; ages 2-7 yrs (ALLHOME cohort, n = 4,479), 2004-2005. **Outcome:** Cases: positive response to wheezing during the last 12 mo, rhinitis during the last 12 mo, when not having a cold, or itching rash eczema in the last 12 mo; controls: negative response to all three questions and other questions on history of wheezing, asthma, allergy symptoms or diagnosis in past **Exposure:** Surface dust samples from children's bedrooms DBP in dust (mg/g) Geometric mean All homes: 7.86 **Analysis:** Dust concentrations compared between case and control homes overall, and between cases with specific symptoms in the preceding 12 mo and controls, using Mann-Whitney U-test (untransformed data) and Dunnett test (log-transformed data)	Concentration DBP in dust (mg/g dust) (Median / Mean / *p*-value for Dunnett test) Controls: 9.87 / 12.04 / All cases: 9.61 / 12.15 / 0.58 Wheezing: 11.17 / 12.79 / 0.41

Reference and study design	Results
[a]Additional results for this study presented in allergy/immune table (Table 3-9).	

3.2.10. Thyroid Effects in Humans

Table 3-11. Evidence pertaining to DBP and thyroid effects in humans

Reference and study design	Results
Dirtu et al. (2013) (Belgium) **Population:** 152 overweight or obese adults from weight loss cohort (ENDORUP) seen at weight management clinic, 43 age- and sex-matched controls from hospital staff and other volunteers, enrolled 2009-2012; among obese/overweight group, 65 received bariatric surgery and 87 received standard diet and lifestyle counseling; follow-up 3, 6, and 12 mo **Outcome:** Serum thyroid hormone levels (details of blood collection were not reported) **Exposure:** Urine sample (24-hr) MnBP in urine (ng/mL): Median / 75th percentile / 90th percentile Controls: 37 / 67 / 88 Obese (at baseline): 38 / 55 / 89 **Analysis:** Linear regression, adjusting for variables shown in results column	Regression coefficient (*p*-value) for change in hormone level with unit change in ln-MnBP (adjusted for age, weight loss, and sex, or stratified by sex) (0.0 = no effect) Full sample / Men / Women Overweight/obese group Free T_4: -0.07 (0.42) / -0.10 (0.52) / -0.07 (0.52) TSH: 0.09 (0.29) / 0.11 (0.50) / 0.10 (0.36) Referent group Free T_4: 0.13 (0.44) / 0.22 (0.55) / 0.07 (0.74) TSH: 0.38 (0.02) / -0.11 (0.76) / 0.50 (0.01)
Brucker-Davis et al. (2011) (France) **Population:** 41 healthy newborn boys from prospective study of cryptorchidism (Brucker-Davis et al., 2008b). [MBP analysis was added later in the study, so sample size is less than total of 86 participants.] **Outcome:** Thyroid hormone levels in cord blood **Exposure:** Cord blood sample at birth and maternal milk sample 3-5 d postpartum Phthalate in cord blood (ng/mL): Median / Range MBP (n = 41): 2.9 / 0.1-14.3 Phthalate in milk (ng/g fat): Median / Range MBP (n = 39): 10.6 / 2.2-114 **Analysis:** Spearman correlation analysis **Related references:** Brucker-Davis et al. (2010) Brucker-Davis et al. (2008b) (same cohort).	Spearman correlation coefficient (*p*-value) between free T3 in cord blood (pmol/L) in maternal milk (ng/g fat) 0.272 (0.03) No significant association was reported between free T4 or TSH and DBP in maternal milk (data not shown). No significant associations were reported between free T3, free T4, or TSH and MBP in cord blood or maternal milk (data not shown).

Reference and study design	Results
Meeker and Ferguson (2011) (United States, NHANES) **Population:** 1,346 adults age ≥20 yrs and 329 adolescents age 12-19 yrs, participants in 2007-2008 NHANES **Outcome:** Serum thyroid hormone levels **Exposure:** Urine sample Cr-adjusted MnBP in urine (μg/g Cr) (percentile): Median / 75th / 95th Adults: 17.1 / 28.1 / 69.9 Adolescents: 21.9 / 35.9 / 72.5 **Analysis:** Linear regression adjusting for variables shown in results column	Regression coefficient (95% CI) for change in hormone level with unit increase in ln-MnBP (adjusted for age, sex, race, BMI, ln-serum cotinine, ln-urinary creatinine, and ln-urinary iodine, and weighted for sampling strategy) (Adults; Adolescents) Total T_3 (ng/dL): 1.03 (-1.66, 3.71); 2.42 (-3.17, 8.02) Ln-Free T_3 (pg/mL): -0.0019 (-0.0082, 0.0044); 0.014 (-0.0059, 0.034) Total T_4 (μg/mL): 0.018 (-0.12, 0.15); -0.044 (-0.35, 0.26) Ln-Free T_4 (ng/dL): 0.0056 (-0.013, 0.024); -0.021 (-0.047, 0.0056) Ln-TSH (μIU/mL): -0.015 (-0.077, 0.047); -0.041 (-0.17, 0.086) Ln-Tg (ng/mL): -0.021 (-0.095, 0.053); -0.087 (-0.22, 0.050)
Boas et al. (2010) (Denmark) **Population:** 758 children from birth cohort study, born 1997-2001; examined 2006-2007, ages 4-9 yrs **Outcome:** Serum thyroid hormone levels (nonfasting sample) **Exposure:** Urine sample (child's), collected same day as serum samples Unadjusted MBP + MIBP in urine (μg/L): Median / 75th percentile Boys: 130 / 207 Girls: 121 / 216 Cr-adjusted MBP + MIBP in urine (μg/g Cr): Median / 75th percentile Boys: 191 / 276 Girls: 227 / 312 **Analysis:** Linear regression, adjusting for variables shown in the results column	Regression coefficient (*p*-value) for change in hormone level with unit change in ln-MBP+MIBP (adjusted for sex and age) (0.0 = no effect) (Unadjusted; Cr-adjusted) T_3: -0.09 (0.005); -0.01 (0.87) Free T_3: -0.21 (0.002); 0.03 (0.79) T_4: -2.18 (0.24); -1.64 (0.55) Free T_4: -0.04 (0.82); -0.19 (0.48) TSH: 0.00 (0.83); 0.05 (0.092) IGF-1: -0.01 (0.67); 0.02 (0.34) IGFBP-3: -0.02 (0.02); -0.01 (0.43) Similar patterns seen in analyses stratified by gender. Units for hormone analyses were not reported in the publication.

Reference and study design	Results
Huang et al. (2007) (Taiwan) **Population:** 76 pregnant women undergoing amniocentesis due to age >35 yrs or abnormal α-fetoprotein or β-hCG test, 2005-2006 **Outcome:** Serum thyroid hormone levels collected during 2nd trimester **Exposure:** Urine sample, collected same day as serum samples MBP in urine: Median / 75th percentile / 95th percentile Unadjusted (ng/mL): 81.8 / 131 / 368 Cr-adjusted (µg/g Cr): 195 / 339 / 839 **Analysis:** Spearman correlation analysis; linear regression, adjusting for variables shown in results column	Spearman correlation coefficient between hormone level and MBP Unadjusted MBP (ng/mL) / Cr-adjusted MBP (µg/g Cr) T_3 (ng/dL): -0.234 / -0.212* T_4 (µg/dL): -0.248* / -0.292* Free T_4 (ng/dL): -0.368* / -0.191* TSH (µIU/mL): 0.079 / -0.020 *$p < 0.05$ Adjusted regression coefficient (p-value) for change in ln-T_4 with change in ln-MBP (adjusted for age, BMI, gestational age, and other phthalate metabolites [MEP, MEHP, MEHP, MMP]) T_4 (nmol/L): -0.112 (0.003) Free T_4 (pmol/L): -0.110 (<0.001)
Meeker et al. (2007) (United States, Boston) **Population:** 408 male partners from subfertility clinic, 2000-2004; mean (± SD) age 36 (± 5.3) yrs **Outcome:** Serum thyroid hormone levels **Exposure:** Urine sample, collected same day as serum samples MBP in urine (ng/mL): Median / 75th percentile / 95th percentile SG-adjusted: 17.0 / 30.4 / 65.1 **Analysis:** Linear regression, considering age, BMI, smoking status, race, previous examination for infertility, prior impregnation of partner, timing of blood and urine samples, and time of day as potential covariates	Regression coefficient (95% CI) for change in hormone level per IQR change in SG-adjusted MBP (ng/mL, after back-transformation from ln-MBP) (adjusted for age, BMI, current smoking, and time of blood sample) Untransformed hormone levels (0.0 = no effect) Total T_3 (ng/mL): -0.005 (-0.024, 0.012) Free T_4 (ng/dL): 0.003 (-0.023, 0.028) Ln-transformed hormone levels (1.0 = no effect) TSH (µIU/mL): 1.02 (0.96, 1.09)
Congenital hypothyroidism	
Jung et al. (2013) (Korea) **Population:** 39 infants with congenital hypothyroidism and their mothers, 20 unaffected infants and their mothers, recruited from hospital; time period not reported. **Outcome:** Congenital hypothyroidism **Exposure:** Plasma sample Phthalate in plasma (infant controls) (ng/mL): Mean ± SD DBP: 54.96 ± 17.82 MnBP: 60.34 ± 28.25 **Analysis:** Not described in the publication	DBP or MnBP in plasma (ng/mL), mean ± SD Controls / Cases Infants DBP: 54.96 ± 17.82 / 51.11 ± 27.57 MnBP: 60.34 ± 28.25 / 56.48 ± 29.23 Mothers DBP: 29.94 ± 22.07 / 36.30 ± 19.27 MnBP: 19.87 ± 15.16 / 27.38 ± 15.75 $p > 0.1$ for comparison between case and control infants.

3.2.11. Pulmonary Function in Humans

Table 3-12. Evidence pertaining to DBP and pulmonary function in humans

<table>
<tr><th>Reference and study design</th><th colspan="4">Results</th></tr>
<tr><td rowspan="7">Cakmak et al. (2014) (Canada)
Population: 3,147 participants* in population-based survey (Canadian Health Measures Survey), ages 6-49 yrs
Outcome: Pulmonary function based on FVC and FEV_1 (expressed as percent of values predicted based on age, height, and sex)
Exposure: Urine sample collected at same time as pulmonary function testing
MnBP in urine (µg/g Cr), all participants:
Geometric mean (95%CI)
Cr-adjusted 30.65 (29.8-31.52)
Analysis: Linear regression, generalized linear mixed models (weighted based on sampling weights), considering BMI, ethnicity, education, income, passive smoking, current smoking, and ambient conditions on day of lung function measures (temperature, relative humidity, barometric temperature, nitrogen dioxide, ozone, and fine particulates ($PM_{2.5}$) as potential covariates; stratified by age (6-16, 17-49 yrs) and sex
*Study reports number of participants inconsistently; Table 3 reports 3,071 participants, while the Methods section and all other data tables report 3,147 participants.</td><td colspan="4">Change in pulmonary function (95% CI) per interquartile range increase in Cr-adjusted urinary MnBP (adjusted for age, sex, smoking, fasting, income education, and $PM_{2.5}$)</td></tr>
<tr><td></td><td>FEV_1</td><td>FVC</td><td>FEV_1/ FVC</td></tr>
<tr><td>All participants (n = 3,071)</td><td>-0.8 (-1.4, -0.3)</td><td>-0.9 (-1.5, -0.3)</td><td>-0.1 (-0.7, 0.5)</td></tr>
<tr><td>Children, 6-16 yrs (n = 1,642)</td><td>-0.5 (-1.3, 0.3)</td><td>-0.9 (-1.6, -0.1)</td><td>0.9 (-0.7, 2.6)</td></tr>
<tr><td>Adults, ≥17 yrs (n = 1,505)</td><td>-0.8 (-1.7, 0.2)</td><td>-0.6 (-1.5, 0.2)</td><td>-0.3 (-1.0, 0.4)</td></tr>
<tr><td>Male (n = 1,555)</td><td>-1.1 (-2.0, 0.2)</td><td>-1.0 (-1.8, -0.2)</td><td>-0.2 (-0.8, 0.4)</td></tr>
<tr><td>Female (n = 1,592)</td><td>-1.0 (-2.0, 0.1)</td><td>-0.9 (-1.6, -0.2)</td><td>-0.3 (-1.0, 0.4)</td></tr>
<tr><td>Kolena et al. (2014) (Slovakia)
Population: 30 adult workers (20 men and 10 women) involved in driving waste trucks (men) or sorting and processing waste substances for recycling; mean age 46 yrs
Outcome: Pulmonary function measured by PEF percent of predicted value; FEV_1/FVC; FEV_1 percent of predicted value; and FVC percent of predicted value.
Exposure: Urine samples collected at same time as spirometry measures
MnBP in urine (ng/mL) (percentile):
Median 75th 95th
Unadjusted 67.13 92.84 130.04
Analysis: Linear regression, considering smoking history and anthropometric characteristics as potential covariates.</td><td colspan="4">No significant association between pulmonary function measures (PEF percent of predicted value; FEV_1/FVC; FEV_1 percent of predicted value; and FVC percent of predicted value) and MnBP in urine (data not shown).</td></tr>
<tr><td>Park et al. (2013) (Korea)</td><td colspan="4">Regression coefficient (β) for change in pulmonary function with change in ln-MnBP (Cr-adjusted) (adjusted for age, sex,</td></tr>
</table>

Reference and study design	Results
Population: 418 persons >60 yrs old enrolled in the Korean Elderly Environmental Panel, evaluated 2008-2009 **Outcome:** FVC, FEV_1, and FEF between 25 and 75% of FVC during three medical examinations **Exposure:** Urine (collected at same time as three exams) MnBP in urine (µg/L) (percentile): Median / 75th / 95th Unadjusted 38.9 / 65.38 / 162.7 **Analysis:** Concentrations in urine averaged across 3 samples for each individual; best of 3 pulmonary function measures used in analysis. Linear regression adjusting for variables shown in results column. Additional analysis conducted on groups stratified by genetic polymorphisms in CAT, SOD2, and MPO	months since previous visit, BMI, Cr-adjusted cotinine, mean temperature and mean dew point). — β (SE) / *p*-value FEV_1 (L): 0.001 (0.013) / 0.93 FVC (L): 0.007 (0.016) / 0.65 FEV_1/FVC: -0.212 (0.308) / 0.49 FEF (L/second): -0.025 (0.027) / 0.35 Stratification by haplotype did not reveal any significant associations with MBP ($p > 0.1$ for all subgroups).
Hoppin et al. (2004) (United States, NHANES) **Population:** 240 participants in population-based survey (NHANES III), 1988-1994; ages 20-60 yrs **Outcome:** FVC, FEV1, PEF, MMEF **Exposure:** Urine sample, collected at time of pulmonary function testing Mean (SD) MBP in urine: — Men / Women Unadjusted (ng/mL): 40 (2.9) / 43 (3.9) Cr-adjusted (ng/g Cr): 30 (2.5) / 45 (3.1) **Analysis:** Linear regression, stratified by sex and adjusted for variables shown in results column	Regression coefficient (SE) for change in pulmonary function measure per interquartile range increase in MBP (31.53 ng/g creatinine) (adjusted for age, age squared, height, BMI, smoking, and race) β (SE): Men / Women FVC: -131 (63)* / 34 (45) FEV1: -112 (51)* / 42 (39) PEF: -367 (181)* / -68 (111) MMEF: -139 (127) / 72 (85) *$p < 0.05$

3.2.12. Neurodevelopmental Effects in Humans

Table 3-13. Evidence pertaining to DBP and neurodevelopmental effects in humans

Reference and study design	Results
Neurobehavioral measures in school-aged children	
Chopra et al. (2014) (United States, NHANES) **Population:** 1,493 participants in population-based survey (NHANES), 2001-2004, ages 6-15 yrs **Exposure:** Urine sample collected same day as NHANES exam MBP in urine (μg/g Cr): Median / 75th percentile / 90th percentile Cr-adjusted: 30.3 / 50.9 / 84.3 Sum DBP metabolites (MBP + MIBP) Median / 75th percentile / 90th percentile Cr-adjusted: 36.3 / 62.0 / 97.8 **Outcome:** Attention deficit disorder or learning disorder as reported by parent **Analysis:** Logistic regression, considering age, sex, race, household income, low birth weight, health insurance coverage, routine source of healthcare, mental health professional use in past year, child blood lead level, maternal age at birth, and maternal smoking during pregnancy as potential covariates	Geometric mean (95% CI) Cr-adjusted DBP metabolites (MIBP + MBP)in urine (μg/g Cr) by diagnosis Neither condition (n = 1,262): 35.9 (33.4, 38.6) Attention deficit disorder only (n = 56): 31.7 (24.3, 41.3) Learning disorder only (n = 116): 33.3 (27.5, 40.5) Both condition (n = 56): 49.3 (36.4, 66.8) (trend p = 0.28) OR (95% CI) per 10-fold increase in Cr-adjusted log-transformed DBP metabolites (MIBP + MBP) (adjusted for sex, age, race, household income, log-transformed blood lead, and maternal smoking during pregnancy) Attention deficit disorder only (n = 112): 1.8 (0.6, 4.8) Learning disorder only (n = 173): 1.3 (0.6, 2.9) Both conditions (n = 56): 3.3 (0.9, 12.7) Authors reported no interaction between child's blood lead and phthalate concentration (quantitative results not reported).
Kobrosly et al. (2014) (United States; Minnesota, Missouri, California, Iowa) **Population:** 153 children (n = 76 girls, n = 77 boys) from birth cohort study (Study for Future Families), born 2000-2005, ages 6-10 yrs in 2010 follow-up **Outcome:** Child Behavior Checklist completed by parent **Exposure:** Maternal urine sample, 3rd trimester (mean 26.6 wks) MnBP in urine (ng/mL): Geometric mean (95% CI) Unadjusted: 13.6 (11.5, 16.1) **Analysis:** Linear regression, considering sex, age, mother's education, urinary creatinine, family stress measure, and race/ethnicity as potential covariates	Regression coefficient (95% CI) for change in raw score on child behavior checklist per unit increase in ln-transformed MnBP (adjusted for sex, age, mother's education and urinary creatinine, and family stress score). Boys / Girls Anxiety/depression: 0.01 (-0.25, 0.26) / -0.14 (-0.40, 0.12) Withdrawn: 0.02 (-0.19, 0.23) / -0.06 (-0.27, 0.15) Somatic complaints: -0.07 (-0.28, 0.13) / -0.13 (-0.34, 0.08) Social problems*: 0.02 (-0.19, 0.24) / -0.10 (-0.32, 0.11) Thought problems: -0.01 (-0.23, 0.20) / -0.03 (-0.25, 0.19)

Reference and study design	Results
	Attention problems: 0.12 (-0.12, 0.37); -0.01 (-0.26, 0.25) Rule-breaking behavior: 0.14 (-0.05, 0.34); 0.02 (-0.19, 0.22) Aggressive behavior: 0.12 (-0.15, 0.39); -0.07 (-0.34, 0.21) Internalizing behavior: -0.01 (-0.30, 0.29); -0.16 (-0.46, 0.14) Externalizing behavior: 0.17 (-0.12, 0.45); -0.02 (-0.31, 0.27) Total problems: 0.12 (-0.29, 0.53); -0.14 (-0.55, 0.28) All *p*-values > 0.05
Park et al. (2014) (South Korea) **Population:** 277 children (150 males and 127 females) aged 8-11 yrs **Outcome:** Anxiety as assessed by Trait Anxiety Inventory for Children (TAIC; 20 self-rating questions) administered to children **Exposure:** Urine sample MnBP in urine (µg/g Cr): Mean ± SD Cr-adjusted 46.6 ± 21.6 **Analysis:** Pearson correlation analysis	Pearson correlation coefficient (*p*-value) between anxiety score and Cr-adjusted urine MnBP (µg/g Cr) All children -0.071 (0.239) Male -0.099 (0.229) Female -0.030 (0.740)
Miodovnik et al. (2011) (United States, New York City) **Population:** 137 children from birth cohort (Mt Sinai Children's Environmental Health study), born 1998-2002, follow-up at ages 7-9 yrs **Outcome:** Social functioning based on maternal reporting on Social Responsiveness Scale (SRS) (5 domains) **Exposure:** **M**aternal urine sample, 25-40 wks gestation Phthalates in urine (µg/L): Median; 75th percentile MnBP 33; 87 [See Engel et al. (2008) for data pertaining to individual metabolite levels in the Mt. Sinai Children's Environmental Health cohort.] **Analysis:** Generalized linear regression model, considering maternal age, IQ, marital status, education, and urinary creatinine, and child's sex, race, and age as potential covariates	Regression coefficient (95% CI) for change in social functioning score per unit increase in ln-MnBP (µg/L) (adjusted for child race, sex, caretaker marital status, urinary creatinine) MBP Total SRS 1.37 (-0.43, 3.17) Cognition 1.24 (-0.62, 3.10) Communication 1.85 (-0.08, 3.78) Mannerisms 1.30 (-0.60, 3.21) Motivation 0.28 (-1.36, 1.92) Awareness 0.63 (-1.01, 2.26)
Engel et al. (2010) (United States, New York City) **Population:** 177 children from original birth cohort studied by Engel et al. (2009) 54% boys, three follow-up exams at ages 4.5-5.5, 6-6.5, and 7-9 yrs	Regression coefficient for change in behavioral score (BASC-PRS) per unit increase in ln-phthalate level (µM/L) in boys (adjusted for race, educational level and marital status of the primary caretaker, and urinary creatinine)

Reference and study design	Results
Outcome: Behavior assessed by maternal reporting on Behavior Rating Inventory of Executive Function (BRIEF) and Behavior Assessment System for Children—Parent Rating *Scales* (BASC-PRS) **Exposure:** Maternal urine sample, 25-40 wks gestation Median / 75th percentile MnBP: 33 / 87 [See Engel et al. (2008) for data pertaining to individual metabolite levels in the Mt. Sinai Children's Environmental Health cohort.] **Analysis:** Generalized linear regression model, adjusting for variables shown in results column; other variables (not specified) were considered	MBP / LMW Clinical scales (higher score = more problem behaviors) Aggression: 1.28* / 1.24* Anxiety: -0.04 / 0.78 Attention problems: 0.92 / 1.29* Atypicality: 0.83 / 0.95 Conduct problems: 0.92 / 2.40* Depression: 0.78 / 1.18* Hyperactivity/ impulsivity: 1.34 / 1.03 Somatization: 0.84 / 0.36 Withdrawal: -0.10 / 0.46 Adaptive scales (lower score = more problem behaviors) Adaptability: -0.92 / -1.08* Leadership: -0.54 / -0.88 Social skills: -0.75 / -1.04 Composite scales (higher score = more problem behaviors) Externalizing problems: 1.36* / 1.75* Internalizing problems: 0.66 / 0.99 Adaptive skills: -1.18 / -0.98 Behavioral Symptom Index: 1.23 / 1.55* Regression coefficient for change in behavioral score (BRIEF scores; higher score = worse executive functioning) per unit increase in ln-phthalate level (µM/L) in boys and girls (adjusted for race, sex, educational level and marital status of the primary caretaker, and urinary creatinine) MBP / Low MW Emotional control: 0.79 / 1.33* Behavioral regulation index: 0.67 / 1.13 Initiate: 0.77 / 0.81 Working memory: 1.53* / 1.03 Plan/organize: 1.31 / 1.02 Metacognition index: 1.09 / 1.05 Global executive composite score: 0.98 / 1.23* *$p \leq 0.05$ Study authors reported there were few significant associations between phthalate concentration and

Reference and study design	Results
	behavior among girls (quantitative results not reported).
Kim et al. (2009) (Korea) **Population:** 261, 3rd-5th grade children recruited from four cities in Korea, 2007; mean age = 9.7 yrs **Outcome:** Attention deficit—hyperactivity disorder (ADHD) symptoms measured by teacher rating scale and continuous performance tests **Exposure:** Urine sample (child's) collected at same time as assessment MnBP in urine (µg/L) Mean ± SD Unadjusted 46.7 ± 21.4 **Analysis:** Linear regression adjusting for variables shown in results column	Regression coefficient (*p*-value) for change in ADHD symptoms per unit increase in ln-MnBP (µg/L) (adjusted for child's IQ, age, gender, parental education, and socioeconomic status). ADHD Teacher rating scale: Inattention -2.09 (0.19) Hyperactivity -0.41 (0.78) Total -2.49 (0.39) Continuous performance test: Omission (inattention) 15.84 (0.03) Commission (impulsivity) 18.31 (0.03) Reaction time -2.92 (0.61) SD of Reaction time 18.12 (0.30)
Neurobehavioral and developmental measures in infants and preschool-aged children	
Braun et al. (2014) (United States) **Population:** 175 children from birth cohort in Ohio (Health Outcomes and Measures of the Environment [HOME] cohort, recruited during pregnancy, 2003-2006). Follow-up at ages 4-5 yrs **Outcome:** Autistic behaviors based on Social Responsiveness Scale completed by mother; 65 item scale, higher score = more autistic behaviors **Exposure:** Maternal urine samples, 16-26 wks gestation MnBP in urine (µg/g Cr) (percentile): Median 75th 95th Cr-adjusted 26 37 75 **Analysis:** Semi-Bayesian hierarchical regression model	Regression coefficient (95% CI) for change in total score per unit increase in log-transformed Cr-adjusted MnBP (adjusted for maternal demographic and perinatal factors, depressive symptoms, caregiving environment, and serum cotinine) -0.4 (-2.2, 1.4) Adjusting for 40+ other chemicals (phthalates, polychlorinated biphenyls, brominated flame retardants, and perfluronated compounds): -1.2 (-3.4, 0.9) Similar results using several other approaches to this modeling.
Téllez-Rojo et al. (2013) (Mexico) **Population:** 135 children from birth cohort (Early Life Exposure in Mexico to Environmental Toxicants cohort; mothers recruited during first trimester, 1997-2003) **Outcome:** Mental and psychomotor development based on Bayley Scales of Infant Development-II (assessed by trained examiner, videotaped for quality control assessment) tested at 24, 30, and 36 mo of age. **Exposure:** Maternal urine sample, 3rd trimester MnBP in urine (ng/mL): Geometric mean (95% CI) SG-adjusted 85.61 (71.55, 102.42) **Analysis:** Linear regression for longitudinal data, stratified by sex and adjusted for variables shown in results column **Related reference**: Ettinger et al. (2009)	Regression coefficient (95% CI) for change in neurodevelopment score per unit increase in maternal ln-MnBP (adjusted for birthweight, breastfeeding practices, weight-for-age, child's age, mother's age, mother's education, and laboratory) Total sample (n = 135) / Boys (n = 64) / Girls (n = 71) MDI 0.30 (-1.04, 1.65) / 0.54 (-1.28, 2.37) / -0.15 (-2.16, 1.84) PDI 0.49 (-0.66, 1.64) / 0.86 (-0.54, 2.27) / 0.52 (-1.68, 2.73)

Reference and study design	Results
Whyatt et al. (2012) (United States, New York City) **Population:** 297 children from birth cohort (Columbia Center for Children's Environmental Health), born 1999-2006; 3-yr follow-up, mean age 36 mo (range 27-42 mo) **Outcome:** Mental, psychomotor and behavioral development at 3 yrs based on Bayley Scales of Infant Development-II (assessed by trained examiners) and Child Behavior Checklist (completed by parent) **Exposure:** Maternal urine sample, 3rd trimester MnBP in urine (ng/mL) Geometric mean (95% CI) Unadjusted 38.0 (33.9, 42.6) **Analysis:** Linear and logistic regression adjusting for variables shown in results column; Wald test used to detect sex differences	Regression coefficient (95% CI) for change in neurodevelopment score per unit increase in maternal ln-MnBP (adjusted for specific gravity, race/ethnicity, maternal marital status and prenatal alcohol consumption, child's gestational age and sex, and quality of care-taking environment) | | Boys (n = 140) | Girls (n = 157) | | MDI | 0.30 (-1.99, 2.59) | -2.67 (-4.70, -0.65) | | PDI | -3.08 (-5.82, -0.33) | -2.41 (-4.91, 0.08) | Adjusted OR (95% CI) for risk of mental or psychomotor delay (score ≤85) per ln-unit increase in maternal ln-MBP (each model adjusted for one or more of the following: specific gravity, race/ethnicity, maternal marital status and prenatal alcohol consumption, child's gestational age and sex, and quality of care-taking environment) | | Boys (n = 140) | Girls (n = 157) | | MDI | 0.68 (0.43, 1.07) | 1.44 (0.84, 2.47) | | PDI | 1.58 (0.95, 2.61) | 1.57 (0.84, 2.94) | Regression coefficient (95% CI) for change in neurobehavior per unit increase in maternal ln-MBP (adjusted for specific gravity; ethnicity; maternal IQ, demoralization, hardship, satisfaction during pregnancy and prenatal exposure to PAH and BPA; and child's sex and age at testing) | | Boys (n = 129) | Girls (n = 148) | | Emotionally reactive | 0.71 (0.22, 1.19) | -0.02 (-0.50, 0.45) | | Anxious/ depressed | 0.17 (-0.40, 0.75) | 0.41 (-0.11, 0.94) | | Somatic complaints | 0.77 (0.21, 1.33) | 0.43 (-0.06, 0.91) | | Withdrawn behavior | 0.56 (0.09, 1.03) | 0.47 (-0.03, 0.98) | | Internalizing behavior | 2.21 (0.66, 3.76) | 1.29 (-0.15, 2.72) | Effect modification by gender observed for emotionally reactive behavior (*p*-value of 0.03). OR (95% CI) for child's score in the borderline or clinical range (compared to normal) per unit increase in maternal ln-MBP (adjusted for specific gravity, maternal demoralization and satisfaction

Reference and study design	Results
	during pregnancy, and child's sex and age at testing) | | Borderline | Clinical | Somatic complaints: 1.32 (0.84, 2.08) | 1.37 (0.73, 2.56) Withdrawn behavior: 0.60 (0.31, 1.16) | 2.23 (1.27, 3.92) Internalizing behavior: 1.31 (0.82, 2.10) | 1.44 (0.92, 2.25
[Kim et al. (2011)](#) (Korea) **Population:** Prospective cohort study, n = 460 infants enrolled in Mothers and Children's Environmental Health Study from three cities in Korea, 2006-2009 **Outcome:** Mental and Psychomotor development at 6 mo of age based on Bayley Scales of Infant Development-II administered by trained examiners **Exposure:** Maternal urine sample, third trimester MnBP in urine (μg/L): Median 75th percentile Unadjusted 16.6 41.1 **Analysis:** Linear regression adjusting for variables shown in results column	Regression coefficient (95% CI) for change in neurodevelopment score per unit increase in ln-MnBP (μg/g Cr) (adjusted for birth weight, sex, maternal age, maternal education, family income, breastfeeding, residential area, and maternal intelligence in subgroup). All children (n = 417) | Subgroup (n = 227)[a] MDI: -0.54 (-1.18, 0.10) | -0.64 (-1.51, 0.23) PDI: -0.79 (-1.60, 0.03) | -1.07 (-2.10, -0.03) [a]Subgroup for whom maternal intelligence measures were available. Regression coefficient (95% CI) stratified by sex (same adjustments as above). Males (n = 211) | Females (n = 206) Mental Delay Index: -0.93[b] | -0.21 (-1.17, 0.75) Psychomotor Delay Index: -1.25 (-2.40, -0.11) | -0.42 (-1.63, 0.78) [b]Study reports erroneous 95% CI, but indicates that the result was significant at $p = 0.04$ No significant interaction between sex and MBP for MDI ($p = 0.30$) or PDI ($p = 0.30$).
Intellectual function in infants and school-aged children	
[Cho et al. (2010)](#) (Korea) **Population:** 621 3rd and 4th grade children from five cities in Korea, 2008; mean age = 9.0 yrs **Outcome:** Cognitive function based on Korean Wechsler Intelligence Scale for Children administered by 23 trained examiners	Regression coefficient (95% CI) for change in cognitive function per unit-increase in ln-MnBP (μg/g Cr) (adjusted for age, gender, birth weight, breastfeeding history, residential area, paternal education, socioeconomic status, and maternal IQ) Full-scale IQ: 0.4 (-1.4, 2.1) Verbal IQ: -0.1 (-0.8, 0.6)

Reference and study design	Results	
Exposure: Urine sample (child's) MnBP in urine (μg/L): Median 75th percentile Unadjusted 50.5 93.5 **Analysis:** Linear regression adjusting for variables shown in results column	Vocabulary	-0.3 (-0.7, 0.2) 0.1 (-0.4, 0.4)

1 Abbreviations: MDI = Mental Delay Index; PDI = Psycho-motor Delay Index

3.2.13. Obesity Effects in Humans

Table 3-14. Evidence pertaining to DBP and obesity in humans

Reference and study design	Results
Buser et al. (2014) (United States, NHANES) **Population:** Participants in population-based survey (NHANES), 2007-2010, ages ≥6 yrs [sample size not reported] **Outcome:** BMI measured at exam; divided into obese (BMI z-score ≥95th percentile in children, BMI ≥30 in adults) and overweight (BMI z-score 85th-95th percentiles in children, BMI 25-29.9 in adults) **Exposure:** Urine sample, collected at same time as exam Unadjusted MnBP in urine (ng/mL) Geometric mean (SE): Ages 6-19 yrs 23.00 (0.93) Ages ≥20 yrs 15.21 (0.56) **Analysis:** Logistic regression, considering age, race/ethnicity, sex, urinary creatinine, poverty income ratio, calorie intake, and serum cotinine as potential covariates in analyses of ages 6-19 yrs; or age, race/ethnicity, sex, education, diabetes, alcohol consumption, cigarette smoking, calorie intake, vigorous recreational activities, urinary creatinine, and serum cotinine as potential covariates in analyses of ages ≥20 yrs)	OR (95% CI) in children (6-19 yrs of age) for obesity or overweight comparing highest quartile urinary MnBP (>47.54 ng/mL) with lowest quartile (≤12.05 ng/mL) (adjusted for age, race/ethnicity, calorie intake, serum cotinine, urinary creatinine, and income level) Obese / Overweight All: 1.62 (0.54, 4.93) / 0.95 (0.51, 1.75) Boys: 3.15 (0.90, 11.01) / 1.49 (0.62, 11.01) Girls: 0.55 (0.15, 2.05) / 0.64 (0.27, 1.53) OR (95% CI) in adults (≥20 yrs of age) for obesity or overweight comparing highest quartile urinary MnBP (>31.59 ng/mL) with lowest quartile (<7.69 ng/mL) (adjusted for age, gender, race/ethnicity, calorie intake, recreational activity, serum cotinine, education level, smoking status, alcohol intake, and diabetes) Obese / Overweight All: 0.89 (0.65, 1.23) / 0.91 (0.63, 1.30) Men: 0.75 (0.42, 1.36) / 0.87 (0.50, 1.53) Women: 0.97 (0.54, 1.75) / 0.92 (0.56, 1.51)
Song et al. (2014) (United States) **Population:** 977 Controls from nested case-control study of incident diabetes in Nurses Health Study (NHS, n = 393, mean age 65.6 yrs, followed until 2010) and Nurses Health Study II (NHS II, n = 577, mean age 45.6 yrs, followed until 2009) **Outcome:** Change in body weight based on self-reported data from biennial questionnaires; self-reported body weights in these cohorts of registered nurses was highly accurate: a correlation coefficient of 0.96 was observed between self-reported weight and measured weights among 184 NHS participants **Exposure:** Urine sample collected at beginning of follow-up period (collected 2000-2001 for NHS; 1995-2000 for NHS II) Sum MBP + MIBP in urine (nmol/L): Median by quartile Unadjusted 67, 140, 249, 481 **Analysis:** Logistic regression, mixed-effect	Annual rate of weight change (95% CI) by quartile urinary sum MBP + MIBP (adjusted for cohort origin, age at sample collection, menopausal status, smoking status, physical activity, alcohol use, alternative healthy eating index score, caloric intake, baseline body weight, and urinary creatinine levels): Sum MBP + MIBP quartile (median concentration, nmol/L) / Annual rate of weight change in kg/yr (95% CI) 1 (67): 0.0 (referent) 2 (140): 0.19 (0.03, 0.34) 3 (249): 0.21 (0.06, 0.37) 4 (481): 0.34 (0.18, 0.50) (trend $p < 0.001$)

Reference and study design	Results
models for prospective annual weight change rate by quartile sum MBP + MIBP using product terms between concentrations and year after baseline; adjusting for variables shown in results column	
Dirtu et al. (2013) (Belgium) **Population:** 152 overweight or obese adults from weight loss cohort (ENDORUP) seen at weight management clinic, 43 age- and sex-matched controls from hospital staff and other volunteers, enrolled 2009-2012; among obese/overweight group, 65 received bariatric surgery and 87 received standard diet and lifestyle counseling; follow-up 3, 6, and 12 mo **Outcome:** Waist circumference measured at each follow-up visit **Exposure:** Urine sample (24-hr sample) MnBP, in urine (ng/mL) Median / 75th percentile / 90th percentile Controls: 37 / 67 / 88 Obese: 38 / 55 / 89 (at baseline) **Analysis:** Linear regression, adjusting for variables shown in results column; treatment of repeated urinary phthalate measures was not specified	Regression coefficient (*p*-value) for change in waist circumference with unit change in ln-MnBP (adjusted for age, weight loss, and sex, or stratified by sex) (0.0 = no effect) Full sample / Men / Women Overweight/ obese group: 0.12 (0.14) / 0.06 (0.69) / 0.10 (0.39) Referent group: -0.22 (0.16) / 0.15 (0.60) / -0.14 (0.45)
Hart et al. (2013) (Australia) **Population:** 121 girls from birth cohort study (Western Australian Pregnancy Cohort), whose mothers were recruited at 18 wks of gestation between 1989 and 1991; follow-up at ages 14-16 yrs **Outcome:** Offspring BMI (height and weight measured at clinic visit on d 2-5 of menstrual cycle) **Exposure:** Maternal serum samples (n = 123) collected at 18 and 34-36 wks of gestation (combined aliquot from both time periods) MnBP in serum (ng/mL): Median / 90th percentile Unadjusted: 2.46 / 10.99 **Analysis:** Correlation between log-transformed MBP and BMI	Authors reported no association between adolescent BMI (either as absolute value or as age- and gender-adjusted z-score) and MnBP in maternal serum (r = -0.10-0.04, *p* = 0.345-0.931).

<table>
<tr><th>Reference and study design</th><th>Results</th></tr>
<tr><td>

Trasande et al. (2013a) (United States, NHANES)

Population: 2,884 participants in population-based survey (NHANES), 2003-2008; 6-19 yrs old

Outcome: BMI z-score, obesity (BMI z-score ≥95th percentile), and overweight (BMI z-score ≥85th percentile) (measured)

Exposure: Urine sample, collected at same time as BMI measurement

ΣLMW phthalates in urine (µM):

	Geometric mean
Not obese	0.701
Obese	0.855

ΣLMW phthalates = sum of MEP, MBP, and MIBP (individual metabolite concentrations not reported but are available in the NHANES database)

Analysis: Logistic regression for overweight and obese classification; linear regression of BMI z-score as continuous variable; adjusted for variables shown in results column

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Full sample results, no association with ln-LMW phthalates: OR or regression coefficient (95% CI) per one unit increase in ∑LMW phthalates (µM) (adjusted for urinary creatinine, sex, poverty-income ratio, parental education, serum cotinine, age, and race/ethnicity, caloric intake, and television watching)

Overweight	OR (95% CI)	1.01 (0.90, 1.13)
Obese	OR (95% CI)	1.02 (0.90, 1.17)
BMI z-score	β (95% CI)	0.03 (-0.03, 0.09)

Interaction by ethnicity, with associations seen between ln-LMW phthalates and each of the obesity measures in blacks, but not in whites or Hispanics. Using same adjustment factors as above, the associations with ln-MnBP are:

	∑LMW phthalates			MnBP
	Hispanic	White	Black	Black
Over-weight OR (95% CI)	0.88 (0.72, 1.08)	0.97 (0.78, 1.22)	1.21 (1.05, 1.39)	1.11 (0.93, 1.33)
Obese OR (95% CI)	0.97 (0.83, 1.14)	0.94 (0.69, 1.29)	1.22 (1.07, 1.39)	1.21 (1.00, 1.45)
BMI z-score β (95% CI)	-0.04 (-0.15, 0.06)	0.02 (-0.08, 0.12)	0.09 (0.003, 0.18)	0.08 (-0.02, 0.18)

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Wang et al. (2013) (China)

Population: 259 primary and middle school students, 8-15 yrs old, stratified sample from six schools, selected based on sex and BMI

Outcome: BMI, waist circumference (measured)

Exposure: First morning urine sample, collected at same time as BMI measurement

MnBP in urine (ng/mL):

Geometric mean (SD)

47.5 (1.1

Analysis: Linear regression, sampling weights applied to adjust for sampling strategy; adjusted for variables shown in the results column

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Regression coefficient (95% CI) for change in BMI or waist circumference per unit increase in SG-adjusted lnMnBP phthalates (adjusted for age and sex in Model 1; DEHP, MCHP, MMP, and MEP in Model 2)

	Model 1	Model 2
BMI	0.028 (0.001, 0.055)	0.008 (-0.027, 0.048)
Waist circumference	0.015 (-0.007, 0.037)	-0.003 (-0.031, 0.025)

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</table>

Reference and study design	Results
Kasper-Sonnenberg et al. (2012) (Germany) **Population:** 104 mothers (and children) enrolled in birth cohort study, children born between 2000 and 2002, follow-up in 2007-2009; mean age 39.2 yrs (mothers), 6.8 yrs (children) **Outcome:** BMI based on questionnaire (mothers) and measurements (children) **Exposure:** Urine sample (first morning), collected on same day as exam Cr-adjusted MnBP and OH-MnBP in urine (µg/g Cr): Geometric mean (95% CI) Children MnBP 46.9 (40.8, 53.9) OH-MnBP 6.8 (5.6, 8.3) ∑DBP 55.4 (48.2, 63.8) Adults MnBP 27.5 (24.8, 30.5) OH-MnBP 1.7 (1.2, 2.3) ∑DBP 30.4 (27.3, 33.8) **Analysis:** Spearman's rank correlation analysis	Spearman correlation coefficient between ∑DBP and BMI in: Children -0.191 ($p > 0.05$) Mothers -0.199 ($p \leq 0.05$)
Teitelbaum et al. (2012) (United States, New York City) **Population:** 387 children (80 boys, 307 girls) in child development cohort (Growing Up Healthy Study), 2004-2008; Hispanic and black), 6-8 yrs at enrollment **Outcome:** BMI and waist circumference measured 1 yr after enrollment; normal weight = BMI <85th percentile (n = 2,284); overweight = BMI ≥85th percentile (n = 578) **Exposure:** Urine sample, collected at enrollment Cr-adjusted phthalates in urine (µg/g Cr), median: MBP ∑Low MWP Boys 74.0 253.2 Girls 62.7 294 Low molecular weight phthalate metabolites included MEP, MnBP, and MiBP. **Analysis:** Linear regression, considering sex, age at baseline, sedentary hours, metabolic equivalent hours, caloric intake, race, ethnicity, season of urine collection, family income, and parent education as potential covariates; restricted to children with creatinine ≥10 mg/dL	Regression coefficient (95% CI) for change in body metric per unit change in ln-MnBP (µg/g Cr) (adjusted for creatinine, age, sex, sedentary hours, metabolic equivalent hours, Hispanic ethnicity, caloric intake, season, and parental education level) BMI (kg/m^2) Full sample 0.19 (-0.31, 0.69) Girls 0.19 (-0.38, -0.76) Boys -0.12 (-1.34, -1.10) Waist circumference (cm) Full sample 0.54 (-0.80, 1.89) Girls 0.51 (-0.98, 20) Boys -0.16 (-3.49, 3.17)

<table>
<tr><th>Reference and study design</th><th>Results</th></tr>
<tr><td>

Svensson et al. (2011) (Mexico)
Population: 182 women; healthy controls without diabetes from case-control study of breast cancer, 2007-2008; mean age 54 yrs
Outcome: BMI, waist circumference, and waist:height ratio
Exposure: First morning urine sample collected at time of clinical evaluation
Cr-adjusted MnBP in urine (µg/g Cr):
Geometric mean (SD)
No diabetes 82.5 (2.6)
Analysis: Spearman correlation coefficient
Related references: Lopez-Carrillo et al. (2010)

</td><td>

Spearman correlation coefficient between anthropometric measure and ln-MnBP in urine (µg/g Cr)

<table>
<tr><td>BMI (kg/m^2)</td><td>0.0249</td></tr>
<tr><td>Waist circumference (cm)</td><td>-0.0478</td></tr>
<tr><td>Waist/height ratio</td><td>-0.0020</td></tr>
</table>

($p > 0.05$ for all parameters)

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Hatch et al. (2008) (United States, NHANES)
Population: 4,369 (2,251 males, 2,118 females) participants in population-based survey (NHANES), 1999-2002; ages 6-80 yrs
Outcome: BMI, waist circumference (measured)
Exposure: Urine sample, collected at time of obesity measurement
MBP in urine (µg/g Cr):
Range of geometric means in different age-sex groups = 15-48
Analysis: Linear regression, adjusting for variables shown in results column; separate analyses by sex-age group (ages 6-11, 12-19, 20-59, 60-80 yrs)

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Regression coefficient (95% CI) for change in body metric per quartile increase in unadjusted MBP (µg/L), by age (age, creatinine, height, race/ethnicity, socioeconomic status, fat intake, dairy intake, fruit and vegetable intake, physical activity, TV/video and computer use, and smoking status, and for women, menopausal status, parity)

<table>
<tr><th>MBP Quartile</th><th>6-11 yrs β</th><th>12-19 yrs β</th><th>20-59 yrs β</th><th>60-80 yrs β</th></tr>
<tr><td colspan="5">Waist circumference, males</td></tr>
<tr><td>1 (low)</td><td>1.0 (referent)</td><td>1.0 (referent)</td><td>1.0 (referent)</td><td>1.0 (referent)</td></tr>
<tr><td>2</td><td>1.24 (-1.72, 4.19)</td><td>0.83 (-2.78, 4.43)</td><td>1.86 (-1.05, 4.77)</td><td>-0.65 (-4.09, 2.80)</td></tr>
<tr><td>3</td><td>-1.28 (-5.74, 3.18)</td><td>-0.70 (-4.02, 2.62)</td><td>3.67 (1.27, 6.07)</td><td>-2.60 (-5.27, 0.07)</td></tr>
<tr><td>4 (high)</td><td>1.25 (-1.91, 4.40)</td><td>-1.47 (-5.41, 2.48)</td><td>2.91 (0.22, 5.60)</td><td>-2.60 (-6.05, 0.85)</td></tr>
<tr><td>(trend *p*)</td><td>(0.86)</td><td>(0.31)</td><td>(0.01)</td><td>(0.08)</td></tr>
<tr><td colspan="5">Waist circumference, females</td></tr>
<tr><td>1 (low)</td><td>1.0 (referent)</td><td>1.0 (referent)</td><td>1.0 (referent)</td><td>1.0 (referent)</td></tr>
<tr><td>2</td><td>0.63 (-2.39, 3.64)</td><td>1.08 (-2.05, 4.22)</td><td>-0.61 (-2.87, 1.65)</td><td>-1.85 (-6.19, 2.50)</td></tr>
<tr><td>3</td><td>0.69 (-2.74, 4.12)</td><td>0.38 (-3.46, 4.23)</td><td>-0.06 (-3.33, 3.21)</td><td>-3.94 (-7.47, -0.41)</td></tr>
<tr><td>4 (high)</td><td>0.37 (-2.67, 3.40)</td><td>-0.47 (-4.71, 3.77)</td><td>-2.60 (-6.15, 0.95)</td><td>-5.67 (-9.31, -2.03)</td></tr>
<tr><td>(trend *p*)</td><td>(0.84)</td><td>(0.31)</td><td>(0.24)</td><td>(0.01)</td></tr>
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Reference and study design	Results				
	BMI, males				
	1 (low)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
	2	0.77 (-0.37, 1.90)	0.09 (-1.32, 1.49)	0.66 (-0.48, 1.79)	-0.36 (-1.79, 1.07)
	3	-0.24 (-1.91, 1.42)	-0.53 (-1.77, 0.70)	1.22 (0.35, 2.09)	-1.44 (-2.61, -0.28)
	4 (high)	0.80 (-0.42, 2.03)	-0.87 (-2.54, 0.79)	0.65 (-0.39, 1.69)	-1.12 (-2.49, 0.24)
	(trend *p*)	(0.56)	(0.2)	(0.11)	(0.04)
	BMI, females				
	1 (low)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
	2	0.35 (-0.75, 1.45)	0.37 (-1.20, 1.93)	-0.68 (-1.78, 0.41)	-0.87 (-2.70, 0.96)
	3	0.43 (-0.90, 1.77)	0.17 (-1.60, 1.94)	0.04 (-1.82, 1.90)	-1.26 (-2.70, 0.18)
	4 (high)	0.07 (-1.12, 1.27)	-0.17 (-2.24, 1.90)	-1.43 (-3.37, 0.52)	-2.69 (-4.54, -0.84)
	(trend *p*)	(0.55)	(0.2)	(0.29)	(0.01)
Stahlhut et al. (2007) (United States, NHANES) **Population:** 1,451 men in population-based survey (NHANES), 1999-2002; ages >18 yrs; excluded if taking insulin, oral hypoglycemic agents, or sex hormone agonists/antagonists **Outcome:** Waist circumference (measured) **Exposure:** Urine sample, collected at time of obesity measurement MBP and MIBP in urine (µg/g Cr): Median Cr-adjusted 21.2 **Analysis:** Linear regression, adjusting for variables shown in results column	Regression coefficient per unit increase in ln-MBP+MIBP (adjusted for age, age-squared, race/ethnicity, fat intake, calorie intake, physical activity level, smoking exposure based on cotinine, urinary creatinine, glomerular filtration rate, serum ALT, and GGT) B ± SE (*p*-value) Waist circumference (n = 1,292) 0.79 ± 0.47 (0.11) Increase in waist circumference began in 3rd quartile of exposure (data shown graphically).				

3.2.14. Diabetes Effects in Humans

Table 3-15. Evidence pertaining to DBP and diabetes in humans

<table>
<tr><th>Reference and study design</th><th>Results</th></tr>
<tr><td colspan="2">Diabetes diagnosis</td></tr>
<tr><td>
Sun et al. (2014) (United States)
Population: 971 incident diabetes cases and 970 controls from among participants in Nurses Health Study (NHS, 394 cases and 393 controls, mean age 65.6 yrs, 2000-2008) and Nurses Health Study II (NHS II, 577 cases and 577 controls, mean age 45.6 yrs, 1996-2007)
Outcome: Incident type 2 diabetes assessed in biennial follow-up questionnaires. Confirmed based on: (a) self-report of elevated fasting glucose ≥7.0 mmol/L, random plasma glucose ≥11.1 mmol/L, or plasma glucose ≥11.1 mmol/L and at least one symptom (excessive thirst, polyuria, weight loss, or hunger); (b) no symptoms but elevated glucose on two separate occasions; or (c) treatment with insulin or oral hypoglycemic medication
Exposure: Urine sample, collected at beginning of follow-up period (2000-2002 for NHS; 1996-2001 for NHSII)
MnBP + MIBP in urine (nmol/L):
Median by quartile
NHS 47.1, 88.7, 152.0, 334.2
NHS II 107.0, 199.5, 300.3, 591.5
MnBP in urine (μg/L):
Median by quartile
NHS II 13.9, 26.3, 39.4, 78.1
Analysis: Conditional logistic regression, adjusting for variables shown in results column
</td><td>
OR (95% CI), highest compared with lowest quartile metabolite(s), adjusting for matching factors including age at sample collection, race, fasting status, time of sample collection, menopausal status, use of hormone replacement therapy (NHSII only), urinary creatinine levels, BMI, smoking status, postmenopausal hormone use (NHS only), oral contraceptive (NHS II only), physical activity, alcohol use, family history of diabetes, history of hypercholesterolemia or hypertension, and alternative healthy eating index score
<table>
<tr><th>MnBP + MIBP Quartile</th><th>NHS nmol/L</th><th>NHS OR (95% CI)</th><th>NHSII nmol/L</th><th>NHSII OR (95% CI)</th></tr>
<tr><td>1</td><td>47.1</td><td>1.0 (referent)</td><td>107.0</td><td>1.0 (referent)</td></tr>
<tr><td>2</td><td>88.7</td><td>1.26 (0.75, 2.12)</td><td>199.5</td><td>1.38 (0.81, 2.35)</td></tr>
<tr><td>3</td><td>152.0</td><td>1.01 (0.59, 1.73)</td><td>300.3</td><td>1.17 (0.66, 2.10)</td></tr>
<tr><td>4</td><td>334.2</td><td>0.91 (0.50, 1.68)</td><td>591.5</td><td>3.16 (1.68, 5.95)</td></tr>
<tr><td>(trend p)</td><td></td><td>(0.51)</td><td></td><td>(0.0002)</td></tr>
</table>
<table>
<tr><th>MnBP Quartile</th><th>NHSII μg/L</th><th>NHSII OR (95% CI)</th></tr>
<tr><td>1</td><td>13.9</td><td>1.0 (referent)</td></tr>
<tr><td>2</td><td>26.3</td><td>1.53 (0.90, 2.61)</td></tr>
<tr><td>3</td><td>39.4</td><td>1.18 (0.67, 2.09)</td></tr>
<tr><td>4</td><td>78.1</td><td>3.16 (1.69, 5.92)</td></tr>
<tr><td>(trend p)</td><td></td><td>(0.0003)</td></tr>
</table>
</td></tr>
<tr><td>
James-Todd et al. (2012) (United States, NHANES)
Population: 215 cases, 1,235 controls from population-based survey (NHANES), 2001-2008; women ages 20-79 yrs
Outcome: Positive response to, “Other than during pregnancy, have you ever been told by a doctor or health professional that you have diabetes or sugar diabetes?”
</td><td>
OR (95% CI) for diabetes by quartile of MnBP (adjusted for urinary creatinine, age, race/ethnicity, education, poverty status, fasting time, total caloric intake, total fat intake, smoking status, and physical activity; little change with additional adjustment for BMI and waist circumference)
<table>
<tr><th>MBP quartile</th><th></th></tr>
<tr><td>1 (low)</td><td>1.0 (referent)</td></tr>
<tr><td>2</td><td>1.29 (0.78-2.13)</td></tr>
<tr><td>3</td><td>1.71 (1.04-2.81)</td></tr>
</table>
</td></tr>
</table>

Reference and study design	Results
Exposure: Urine sample, collected at time of survey MnBP in urine (units not reported): Geometric mean Unadjusted 17.7 (based on larger sample of 2,350 women)	4 (high) 1.06 (0.61-1.85)
Svensson et al. (2011) (Mexico) **Population:** 221 women with diabetes, 182 healthy without diabetes from case-control study of breast cancer, 2007-2008; mean age 54 yrs **Outcome:** Self-reported diabetes **Exposure:** First morning urine samples MnBP in urine (µg/g creatinine): Geometric mean (SD) No diabetes 82.5 (2.6) Diabetes 82.3 (2.7) **Analysis:** Logistic regression, adjusted for variables shown in the results column (age and waist-height ratio not found to be potential confounders)	OR (95% CI) per unit increase in ln-MnBP (adjusted for creatinine and education): 1. 10 (0.75, 1.61)
Markers of insulin resistance	
Huang et al. (2014a) (United States, NHANES) **Population:** 3,083 participants in population-based survey (NHANES), 2001-2008; ages 12-<80 yrs; self-reported non-diabetic, non-pregnant participants **Outcome:** Fasting blood glucose; fasting insulin; Homeostasis Model Assessment of insulin resistance (HOMA) **Exposure:** Urine sample at time of clinical exam Cr-adjusted MnBP in urine (µg/g Cr): Median 75th percentile Men 13.6 22.3 Women 22.3 35.9 **Analysis:** Logistic regression, adjusting for variables shown in the results column	Median change (95% CI) in biomarker for diabetes by quartile of MnBP (adjusted for age, gender, race/ethnicity, fasting time, urinary creatinine, total caloric intake, triglycerides, education, poverty, and smoking status) MBP Quartile / Fasting glucose / Fasting insulin / HOMA-IR 1 (low): referent / referent / referent 2: 0.95 (-0.22, 2.13) / 1.15 (0.52, 1.78) / 0.28 (0.11, 0.44) 3: 1.70 (0.51, 2.89) / 1.41 (0.72, 2.09) / 0.28 (0.11, 0.46) 4 (high): 1.91 (0.51, 3.31) / 1.11 (0.31, 1.92) / 0.34 (0.15, 0.54) (trend *p*): (0.0193) / (0.0918) / (0.0059)
Kim et al. (2013) (South Korea) **Population:** 560 adults ≥60 yrs (146 men and 414 women), mean age 70.7 yrs, 2008 to 2010 **Outcome:** Insulin resistance as measured by fasting serum glucose and insulin levels and calculated HOMA-IR	Regression coefficient (95% CI) between insulin resistance biomarkers and log-transformed, creatinine-adjusted MnBP in urine (adjusting for age, sex, BMI, educational attainment, exercise, cotinine level, air pollutant and meteorological factors, and total caloric and fat intakes) Fasting serum glucose 0.06 (-0.04, 0.17) Fasting serum insulin 0.38 (-0.30, 1.07) HOMA-IR 0.16 (-0.09, 0.40)

Reference and study design	Results
Exposure: Urine samples collected over 3-5 visits MnBP in urine (µg/mL) (percentile): Median 75th 95th 56.57 97.18 201.72 **Analysis:** Linear regression mixed-effect model, adjusting for variables shown in the results column.	Models with fewer adjustments also showed no association.
Trasande et al. (2013c) (United States, NHANES) **Population:** 760 participants in the 2003-2008 NHANES, 12-19 yrs old **Outcome:** Homeostatic model assessment of insulin resistance (HOMA-IR), calculated as fasting glucose (mmol/L) multiplied by fasting insulin (µU/mL divided by 22.5 **Exposure:** Urine sample, collected at same time as insulin resistance measurements. ΣLMW phthalates in urine (µM): Median 75th percentile Unadjusted 0.83 1.89 ΣLMW phthalates = sum of MEP, MBP, and MIBP Urinary concentration of MBP alone not reported. **Analysis:** HOMA-IR assessed as continuous or categorical variable; categorical analysis used cut point of 4.39, reflecting >2 SD above the mean HOMA-IR for normal weight adolescents with normal fasting glucose in NHANES 1999-2002. Linear and logistic regression analyses, adjusting for variables shown in results column. HOMA-IR and urinary phthalate measures natural-log transformed for analysis.	OR (95% CI) for insulin resistance and ln-urinary metabolite concentration (µM), adjusted for urinary creatinine, BMI category, continuous age, race/ethnicity, caregiver education, poverty-income ratio, gender, serum cotinine, and caloric intake. Ln-MBP 1.55 (1.11, 2.16) Ln-ΣLMW 0.92 (0.71, 1.19) Regression coefficient (95% CI) for increase in ln-HOMA-IR per unit increase in ln-urinary metabolite concentration (µM), adjusted for urinary creatinine, BMI category, continuous age, race/ethnicity, caregiver education, poverty-income ratio, gender, serum cotinine, and caloric intake. Ln-MBP 0.13 (0.01, 0.26) Ln-ΣLMW -0.07 (-0.18, 0.04)
James-Todd et al. (2012) (United States, NHANES) **Population:** 2,092 women without history of diabetes with various measures of insulin resistance from population-based survey (NHANES), 2001-2008; women age 20-79 yrs **Outcome:** Among women without history of diabetes, fasting blood glucose (FBG) (n = 985), homeostasis model assessment-estimated insulin resistance (HOMA) (n = 971), glycosolated hemoglobin A1c (n = 2,092)	Among women without diabetes, difference (from first quartile) in median value (95% CI) of glucose and insulin parameters by quartile of MBP (Model 1 adjusted for urine creatinine, age, race/ethnicity, education level, poverty status, fasting time, total caloric intake, total fat intake, smoking status, and physical activity; Model 2 also adjusted for BMI and waist circumference) MnBP Quartile — Model 1 — Model 2 Fasting glucose (mg/dL) 1 (low) (referent) (referent) 2 -0.35 (-2.07, 1.38) -0.62 (-2.62, 1.38) 3 -0.19 (-2.22, 1.83) 0.19 (-2.05, 2.43) 4 (high) -0.03 (-2.35, 2.30) -0.05 (-2.47,2.36)

Reference and study design	Results
Exposure: Urine sample, collected at time of survey MnBP in urine (units not reported): Geometric mean Unadjusted 17.7 (based on larger sample of 2,350 women) **Analysis:** Logistic regression, adjusting for variables shown in the results column	Ln (HOMA) 1 (low) — (referent) — (referent) 2 — 0.09 (-0.06, 0.25) — 0.04 (-0.08, 0.16) 3 — 0.09 (-0.06, 0.24) — 0.11 (-0.01, 0.23) 4 (high) — 0.14 (-0.04, 0.31) — 0.10 (-0.04, 0.24) A1c (%) 1 (low) — (referent) — (referent) 2 — 0.01 (-0.04, 0.06) — 0.00 (-0.04, 0.04) 3 — -0.02 (-0.08, 0.03) — -0.03 (-0.08, 0.02) 4 (high) — -0.03 (-0.09, 0.02) — -0.02 (-0.07, 0.03)
Hong et al. (2009) (South Korea) **Population:** 960 adults (446 men and 514 women) not being treated with hypoglycemic agents or insulin, 2005 **Outcome:** Insulin resistance as measured by fasting serum glucose and insulin levels and calculated HOMA-IR **Exposure:** Urine sample MBP in urine (ng/mL) (percentile): Median — 75^{th} — 90^{th} Cr-corrected 35.91 — 64.62 — 107.25 **Analysis:** Analysis of these endpoints was not detailed.	No significant association was observed between insulin resistance biomarkers (fasting serum insulin, fasting serum glucose, and HOMA-IR) and MBP in urine (comparing insulin resistance biomarkers in urine MBP >90^{th} percentile to urine MBP ≤90^{th} percentile groups) (data not shown).
Stahlhut et al. (2007) (United States, NHANES) **Population:** 1,451 men in population-based survey (NHANES), 1999-2002; ages >18 yrs; excluded if taking insulin, oral hypoglycemic agents, or sex hormone agonists/antagonists **Outcome:** Homeostasis model assessment-estimated insulin resistance (HOMA) **Exposure:** Urine sample, collected at time of obesity measurement MBP in urine: Median Cr-adjusted (μg/g Cr) 21.2 **Analysis:** Linear regression, adjusting for variables shown in results column	Regression coefficient per unit increase in ln-MBP (adjusted for age, age-squared, race/ethnicity, fat intake, calorie intake, physical activity level, smoking exposure based on cotinine, urinary creatinine, glomerular filtration rate, serum ALT, and GGT) Outcome — Model 1 β ± SE (*p*-value) — Model 2 β ± SE (*p*-value) HOMA (ln) (n = 622) — 0.064 ± 0.024 (0.011) — 0.043 ± 0.023 (0.081) Increases in HOMA began in 3^{rd} quintile of exposure (data shown graphically).

3.2.15. Cardiovascular Effects in Humans

Table 3-16. Evidence pertaining to DBP and cardiovascular disease risk factors in humans

Reference and study design	Results
Shiue (2014) (United States, NHANES) **Population:** 2,489 participants in population-based survey (NHANES), 2011-2012; ages ≥20 yrs **Outcome:** High blood pressure (systolic blood pressure ≥140 mmHg and diastolic blood pressure ≥90 mmHg) **Exposure:** Urine sample collected at time of clinical exam MnBP in urine (units not given): Mean ± SD Normal BP 23.58 ± 87.67 High BP 25.47 ± 40.33 **Analysis:** Survey-weighted logistic regression, adjusting for variables shown in results column; t-test for comparison between concentrations	OR (95% CI) for high blood pressure per unit increase in log-transformed MnBP (adjusted for urinary creatinine, age, sex, ethnicity, BMI and sampling weights) 1.35 (1.13, 1.62) Mean ± SD MBP in urine (units not given) in participants with normal and high blood pressure: Normal BP (n = 2,180) 23.58 ± 87.67 High BP (n = 309) 25.47 ± 40.33 $p = 0.709$
Trasande et al. (2013b) (United States, NHANES) **Population:** 2,447 children in population-based survey (NHANES), 2003-2008; ages 8-19 yrs old **Outcome:** Systolic blood pressure (SBP) and diastolic blood pressure (DBP) z-score (based on CSC norms, sex, and age); prehypertension (BP ≥90th percentile for age/height/sex); fasting serum triglycerides (n = 906; high = ≥100 mg/dL); nonfasting high density cholesterol (HDL; n = 2,555; low = <40 mg/dL) **Exposure:** Urine sample, collected at time of BMI measurement ∑LMW phthalates in urine (µM): Geometric mean BP <90th percentile 0.817 ∑Low MWP = sum of MEP, MBP, and MIBP (individual metabolite concentrations not reported but are available in the NHANES database) **Analysis:** Logistic regression for pre-hypertension (BP ≥90th percentile) classification; linear regression for SBP and DBP z-score and triglycerides and HDL as continuous variable; all models adjusted for variables shown in results column	Changes in z-score (95% CI) per unit increase in ln-phthalates (adjusted for sex, caloric intake, television watching, poverty:income, parental education, serum cotinine, urinary creatinine, BMI, race/ethnicity, and age) MnBP SBP 0.06 (0.001, 0.12) DBP 0.02 (-0.03, 0.07) Triglycerides not reported HDL not reported OR (95% CI) for BP ≥90th percentile per unit increase in ln-phthalates MnBP BP ≥90th percentile 1.05 (0.82, 1.35) High triglycerides not reported Low HDL not reported Interactions with covariates examined in supplemental analyses; stratified analyses showed a statistically significant association between ∑low MWP and SBP.

3.2.16. Cancer Effects in Humans

Table 3-17. Evidence pertaining to DBP and cancer in humans

Reference and study design	Results
Carran and Shaw (2012) (New Zealand) **Population:** 76 female offspring born to New Zealand soldiers exposed to DBP during military service in Malaya from 1948-1960 **Outcome:** Breast cancer. Assessed via questionnaire sent to the veterans in 2009 (age 70-> 80 yrs), followed up with personal interview. Low response rate: of 252 veterans contacted, 85 responded, of whom 71 reported DBP exposure; 58 of these had children (n=155; 79 male, 76 female) after return to New Zealand following military service. **Exposure:** Exposure to DBP self-reported via questionnaire (DBP used as insect repellant and Acaricide; applied through painting of seams of clothes before military operations in jungle areas of Malaysia). Authors performed dose reconstruction experiments using DBP-treated clothing; estimated daily exposure 64 mg/kg-day. **Analysis:** Incidence in daughters of exposed compared to U.S. general population incidence rate (date[s] not reported) for women age <39 yrs (New Zealand incidences not available)	Breast cancer frequency General population / Daughters of Exposed cohort 0.48% / 4.0% (3/76)* *$p < 0.05$.
Lopez-Carrillo et al. (2010) (Mexico) **Population:** 233 incident cases, 221 population controls matched by age and residency, ≥18 yrs of age, >1 yr in study area, 2007-2008; mean age 53 yrs; participation rates: 94.8% of cases and 99.5% of controls **Outcome:** Histologically-confirmed breast cancer **Exposure:** Urine sample (for cases, urine collected on average 2 mo after diagnosis, but before treatment) MnBP in urine, controls: Geometric mean Cr-adjusted (μg/g Cr) 82.47 **Analysis:** Logistic regression, adjusting for variables shown in results column	Geometric mean (95% CI) MnBP in urine (μg/g Cr), by menopausal status — / Controls / Cases Full sample ($p < 0.05$) / 82.47 (72.67, 93.60) / 62.98 (56.06, 70.76) Pre-menopause ($p < 0.05$) / 81.61 (65.61, 101.51) / 57.56 (47.63, 69.55) Post-menopause ($p < 0.05$) / 82.91 (70.85, 97.03) / 66.52 (57.33, 77.18) OR (95% CI) for breast cancer, by tertile of MnBP (adjusted for current age, age at menarche, parity, menopausal status, and other phthalate metabolites) MnBP tertile (μg/g Cr) / Full sample 1 (6.21-52.55) / 1.0 (referent) 2 (52.55-113.69) / 1.08 (0.66, 1.78) 3 (113.70-1,746.03) / 0.85 (0.47, 1.57) (trend p) / (0.51)

3.3. EXPERIMENTAL STUDIES

3.3.1. Male Reproductive Effects

Table 3-18. Evidence pertaining to male reproductive toxicity following oral exposure to DBP: alterations in testes weight in animals

Reference and study design	Results						
Changes in testis weight and volume after gestational exposure							
Mylchreest et al. (2000) Rat (Sprague-Dawley); assessed in male offspring from 11-20 litters/group 0, 0.5, 5, 50, 100, 500 mg/kg-day Gavage GDs 12-21	*response relative to control*						
	Doses	0	0.5	5	50	100	500
	Absolute right testis weight in adults						
	PND 110	0%	2%	-0.3%	3.3%	0.2%	-7.6%
	Note: Mean testis weight was significantly decreased at 500 when enlarged (> 3 g) testes were excluded. Malformed reproductive organs were also excluded from analysis in the 500 mg/kg-day group.						
Lee et al. (2004) Rat (Sprague-Dawley); 6-8 dams/group; assessed in 8-10 male offspring/group (including ≥1 male/litter) 0, 20, 200, 2,000, 10,000 ppm Diet (0, 2-3, 14-29, 148-291, 712-1,372) mg/kg-day Diet GD 15-PND 21	*response relative to control*						
	Doses	0	2-3	14-29	148-291	712-1,372	
	Relative testis weight						
	PND 21	0%	-5%	-7%	-7%	-19*%	
	PND 77	0%	1%	-3%	6%	-8%	
	PND 140	0%	-7%	-13%	0%	NA	
	Note: Study authors indicated that a sufficient number of male animals could not be obtained in the highest dose group at PNW 20. Doses represent a range estimated by the study authors for three different time periods (GDs 15-20, PNDs 2-10, and PNDs 10-21).						
Ahmad et al. (2014) Rat (Strain not specified); assessed in male offspring; sample size not reported 0, 2, 10, 50 mg/kg-day Gavage GD 14 to Parturition	*response relative to control*						
	Doses	0	2	10	50		
	Absolute testis weight						
	PND 75	0%	0%	-1%	-3*%		
Mahood et al. (2007) Rat (Wistar); assessed in males from 4-16 litters/group (28-98 male offspring/group) 0, 4, 20, 100, 500 mg/kg-day Gavage GDs 13-20 or 13-21	*response relative to control*						
	Doses	0	4	20	100	500	
	Absolute testis weight[a]						
	GD 21	0%	4%	-2%	-13%	-30*%	
	Adult (PND 90)	0%	-8%	-2%	-1%	-47*%	
	Note: Male offspring analyzed at GD 21 were exposed from GDs 13-20; male offspring analyzed at PND 90 were exposed from GDs 13-21.						
	response relative to control						

Reference and study design	Results				
Monsanto (1984) Rat (CD); 20 breeding pairs/group [females exposed only], F1: 9-10 males per group 0, 5, 50, 500 mg/kg-day Diet F0: 14 days before mating and continued through weaning [PND 21] F1, group A: continued basal diet to PND 70 F1, group B: Received same dose as F0 to PND 70	Doses	0	5	50	500
	Absolute testis weight				
	F1, group A	0%	-6%	-4%	-2%
	F1, group B	0%	3%	3%	-8%
	Relative testis weight				
	F1, group A	0%	-5%	2%	0%
	F1, group B	0%	5%	4%	-3%
Shirai et al. (2013) Rat (Sprague-Dawley); 4 males/group, 20 litters/ group 0, 10, 30, 50, 100 mg/kg-day Gavage PNDs 12-21	*response relative to control*				
	Doses	0	10	30	50	100
	Relative testis weight[a]					
	PND 35	0%	0%	-3%	2%	1%
	PND 49	0%	2%	1%	2%	3%
	PND 63	0%	2%	0%	2%	-18*%
	PND 98	0%	-2%	4%	0%	-31*%
	PND 119	0%	1%	3%	2%	-38*%
Salazar et al. (2004) Rat (Long Evans); 15 dams/group; assessed in 6 male offspring/group 0, 610, 2,500 ppm Diet (0, 12, 50 mg/kg-day)[b] Diet 2.5 months before mating to PND 14	*response relative to control*				
	Doses	0	12	50	
	Relative testis weight				
	PND 1[b]	0%	-21*%	-21*%	
Zhang et al. (2004b) Rat (Sprague-Dawley); 14-16 dams/group; assessed in 20 male offspring/group 0, 50, 250, 500 mg/kg-day Gavage GD 1-PND 21	*response relative to control*				
	Doses	0	50	250	500
	Absolute testis weight in adults, right testis weight				
	PND 70	0%	2%	-6%	-11%
Johnson et al. (2008) Rat (Long Evans); 3-7 litters/group; assessed in 1-12 male pups/litter 0, 50, 100, 200 mg/kg-day Gavage GDs 12-21	*response relative to control*				
	Doses	0	50	100	200
	Absolute testis weight				
	PND 21	0%	0.1%	10%	3%
	response relative to control				

<table>
<tr><th>Reference and study design</th><th colspan="5">Results</th></tr>
<tr><td rowspan="3"><u>NTP (1991)</u>
Rat (Sprague Dawley); 20-40 males/generation/group
0, 66, 320, or 651 mg/kg-day
Diet
Multigenerational study
Note: study authors did not specify date of necropsy for F1 animals.</td><td>Doses</td><td>0</td><td>66</td><td>320</td><td>651</td></tr>
<tr><td colspan="5">Absolute testis weight in adult F1 rats</td></tr>
<tr><td></td><td>0%</td><td>0%</td><td>2%</td><td>-39%</td></tr>
<tr><td rowspan="4"><u>Mylchreest et al. (1999a)</u>
Rat (Sprague-Dawley); 9-10 litters/group; (52-62 male offspring/group)
0, 100, 250, 500 mg/kg-day
Gavage
GDs 12-21</td><td colspan="5">response relative to control</td></tr>
<tr><td>Doses</td><td>0</td><td>100</td><td>250</td><td>500</td></tr>
<tr><td colspan="5">Absolute testis weight in adults, right testis weight</td></tr>
<tr><td>3-month old</td><td>0%</td><td>2%</td><td>-1%</td><td>-14*%</td></tr>
<tr><td rowspan="4"><u>Macleod et al. (2010)</u>
Rat (Wistar); ≥3 litters/group; assessed in 6-21 male offspring/group
0, 100, 500 mg/kg-day
Gavage
GDs 13-21</td><td colspan="5">response relative to control</td></tr>
<tr><td>Doses</td><td>0</td><td colspan="2">100</td><td>500</td></tr>
<tr><td colspan="5">Absolute testis weight</td></tr>
<tr><td>PND 25[b]</td><td>0%</td><td colspan="2">-2%</td><td>-24*%</td></tr>
<tr><td rowspan="4"><u>Drake et al. (2009)</u>
Rat (Wistar); 13-15 litters/group; assessed in 32-45 male offspring/group
0, 100, 500 mg/kg-day
Gavage
GDs 15-21</td><td colspan="5">response relative to control</td></tr>
<tr><td>Doses</td><td>0</td><td colspan="2">100</td><td>500</td></tr>
<tr><td colspan="5">Absolute testis weight in adults</td></tr>
<tr><td>>12 wks[b]</td><td>0%</td><td colspan="2">-5%</td><td>-28*%</td></tr>
<tr><td rowspan="4"><u>Martino-Andrade et al. (2009)</u>
Rat (Wistar); 4-8 group
0, 100, 500 mg/kg-day
Gavage
GDs 13-21</td><td colspan="5">response relative to control</td></tr>
<tr><td>Doses</td><td>0</td><td colspan="2">100</td><td>500</td></tr>
<tr><td colspan="5">Absolute testis weight in adults</td></tr>
<tr><td>PND 90</td><td>0%</td><td colspan="2">-0.6%</td><td>2%</td></tr>
</table>

<table>
<tr><th>Reference and study design</th><th colspan="8">Results</th></tr>
<tr><td rowspan="4">NTP (1995)
Mouse (B6C3F1); 20 females/group; 10 offspring/sex/group
0, 1,250, 2,500, 5,000, 7,500, 10,000 ppm or 20,000 (dams [gestation/lactation]:0, 244, 488, 975, 1,463, 1,950, 3,900 mg/kg-day[c]; pups [post-weaning]: 0, 199, 437, 750, 1,286, 3,804 mg/kg-day in males
Diet
Dams: GD 1-PND 28; Pups: PNDs 29-56</td><td colspan="8">response relative to control</td></tr>
<tr><td>Doses</td><td>0</td><td>199</td><td>437</td><td>750</td><td>1,286</td><td>3,804</td><td></td></tr>
<tr><td colspan="8">Absolute right testis weight</td></tr>
<tr><td>PND 56</td><td>0%</td><td>2%</td><td>3%</td><td>-1%</td><td>0%</td><td>-12%</td><td></td></tr>
<tr><td colspan="9">Changes in testis weight and volume after pubertal and/or adult exposure</td></tr>
<tr><td rowspan="4">Bao et al. (2011)
Rat (Sprague-Dawley); 5-week-old males, 20/group
0, 0.1, 1.0, 10, 100, 500 mg/kg-day
Gavage
30 days</td><td colspan="8">response relative to control</td></tr>
<tr><td>Doses</td><td>0</td><td>0.1</td><td>1.0</td><td>10</td><td>100</td><td>500</td><td></td></tr>
<tr><td colspan="8">Absolute testis weight after pubertal exposure</td></tr>
<tr><td></td><td>0%</td><td>-3%</td><td>-2%</td><td>-4%</td><td>-2%</td><td>-25*%</td><td></td></tr>
<tr><td rowspan="10">Moody et al. (2013)
Mouse (C57Bl/6J); 8-20 four day old males/group, 2-9 litters/ group
0, 1, 10, 100, 500 mg/kg-day from PNDs 4-7 or PNDs 4-21; 0, 1, 10, 50, 100, 250, 500 mg/kg-day from PNDs 4-14
Gavage
PNDs 4-7, PNDs 4-14, or PNDs 4-21</td><td colspan="8">response relative to control</td></tr>
<tr><td>Doses</td><td>0</td><td>1</td><td>10</td><td>50</td><td>100</td><td>250</td><td>500</td></tr>
<tr><td colspan="8">Relative testis weight (PND 7)</td></tr>
<tr><td>Individual</td><td>0%</td><td>7%</td><td>-4%</td><td>-</td><td>-12%</td><td>-</td><td>-23*%</td></tr>
<tr><td>Litter Means</td><td>0%</td><td>3%</td><td>-11%</td><td>-</td><td>-69*%</td><td>-</td><td>-44%</td></tr>
<tr><td colspan="8">Relative testis weight (PND 14)</td></tr>
<tr><td>Individual</td><td>0%</td><td>-5%</td><td>-10%</td><td>-13*%</td><td>-17*%</td><td>-34*%</td><td>-41*%</td></tr>
<tr><td>Litter Means</td><td>0%</td><td>-2%</td><td>-8%</td><td>-12%</td><td>-16%</td><td>-33%</td><td>-38%</td></tr>
<tr><td colspan="8">Relative testis weight in adults (PND 56 after exposure from PNDs 4-21)</td></tr>
<tr><td>Individual</td><td>0%</td><td>4%</td><td>8%</td><td>-</td><td>5%</td><td>-</td><td>-12*%</td></tr>
<tr><td rowspan="4">Monsanto (1984)
Rat (CD); 20 breeding pairs/group; 19-20 animals evaluated [males exposed only]
0, 5, 50, 500 mg/kg-day
Diet
105 days</td><td colspan="8">response relative to control</td></tr>
<tr><td>Doses</td><td>0</td><td>5</td><td>50</td><td>500</td><td colspan="3"></td></tr>
<tr><td colspan="8">Absolute testis weight</td></tr>
<tr><td></td><td>0%</td><td>2%</td><td>0%</td><td>1%</td><td colspan="3"></td></tr>
</table>

Reference and study design	Results				
BASF (1992) Rat (Wistar); 10/sex/group; assessed in 10 males/group 0, 30, 152, 752 mg/kg-day Diet 3 months (PNDs 42-135)	*response relative to control*				
	Doses	0	30	152	752
	Absolute testis weight in adult rats				
		0%	2%	-2%	5%
Tsutsumi et al. (2004) Rat (F344); 6-week-old males, 5/group 0, 61, 255, 1,536 mg/kg-day Diet 28 days	*response relative to control*				
	Doses	0	61	255	1,536
	Relative testis weight in adults				
		0%	2%	3%	-9%
	NOTE: Study authors noted that rats in the high-dose group were observed to rake the food, leading to food loss out of cage and probable overestimation of food consumption and dietary intake.				
Lee et al. (2008) Rat (Sprague-Dawley); 3-week-old males, 6/group 0, 100, 500 mg/kg-day Gavage 30 days	*response relative to control*				
	Doses	0	100	500	
	Absolute testis weight in pre-pubertal rats				
		0%	-6%	-62*%	

PND = postnatal day; PNW = postnatal week; NR = not reported
[a]Values reported by the study authors were estimated from published graphs using "Grab It!", a Microsoft Excel based free software application used to digitize data from image files. Publisher: datatrendsoftware.com.
[b]Details on dose estimation were not provided by the study authors.
[c]Doses calculated using U.S. EPA (1988) reference subchronic values for food intake (0.0048 kg/day) and body weight (0.0065 kg) in female B6C3F1 mice.
*Statistically increased over control as reported by study authors.

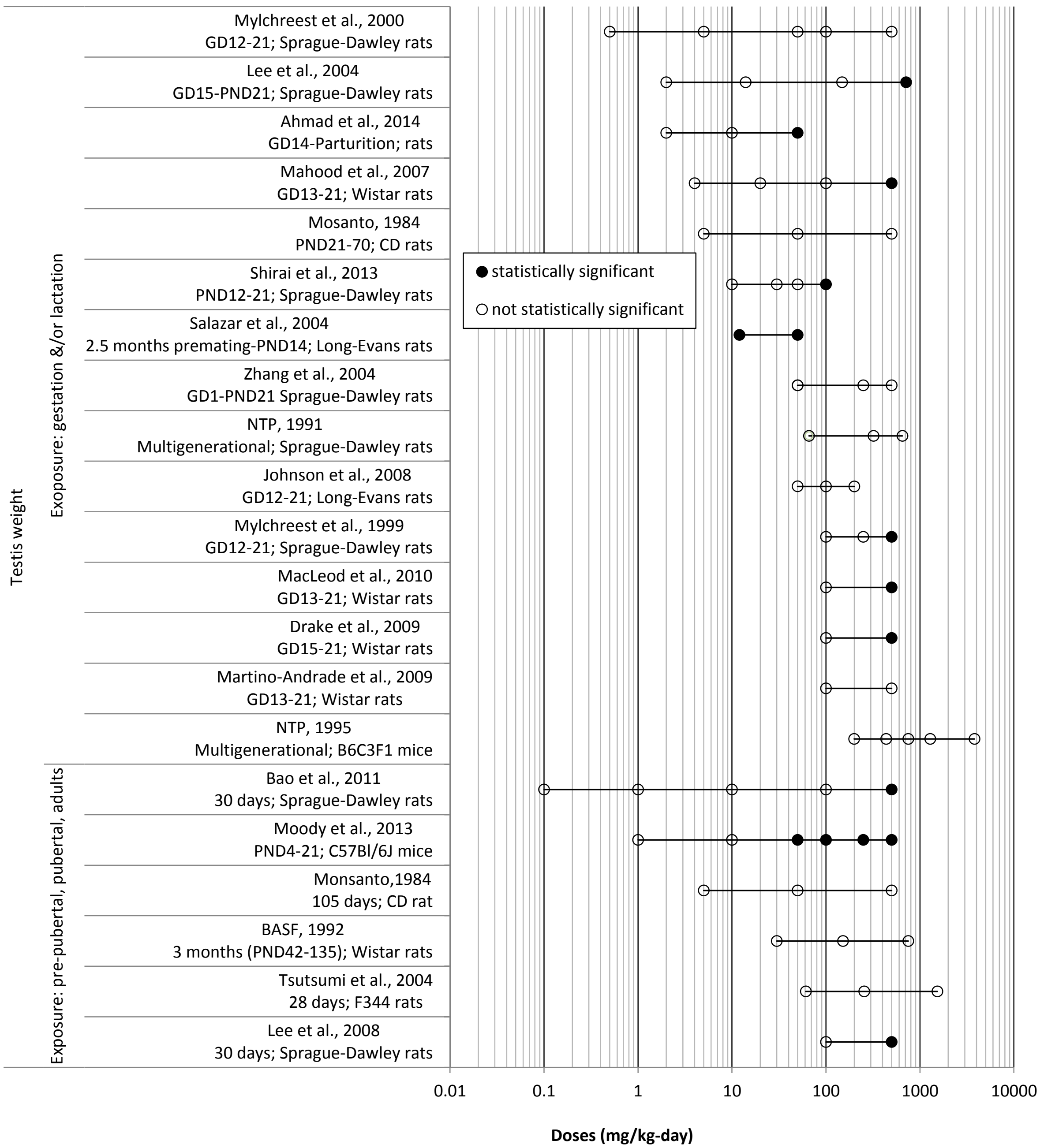


Figure 3-1. Exposure-response array of male reproductive toxicity following oral exposure to DBP: alterations in testes weights.

Table 3-19. Evidence pertaining to male reproductive toxicity following oral exposure to DBP: alterations in accessory male reproductive organ weights in animals

Reference and study design	Results						
Changes in epididymis weight after gestational exposure							
[Mylchreest et al. (2000)](#) Rat (Sprague-Dawley); assessed in male offspring from 11-20 litters/group 0, 0.5, 5, 50, 100, 500 mg/kg-day Gavage GDs 12-21	*response relative to control*						
	Doses	0	0.5	5	50	100	500
	Absolute right epididymis weight in adults						
	PND 110	0%	1%	0.2%	3%	-1%	-13*%
	Note: Malformed reproductive organs were excluded from analysis in the 500 mg/kg-day group.						
[Lee et al. (2004)](#) Rat (Sprague-Dawley); 6-8 dams/group; assessed in 8-10 male offspring/group (including ≥1 male/litter) 0, 20, 200, 2,000, 10,000 ppm Diet (0, 2-3, 14-29, 148-291, 712-1,372 mg/kg-day) Diet GD 15-PND 21	*response relative to control*						
	Doses	0	2-3	14-29	148-291	712-1,372	
	Relative epididymides weight						
	PND 21	0%	-11%	0%	-11%	-11%	
	PND 77	0%	0%	-8%	-4%	-21%	
	PND 140	0%	-8%	-12%	0%	NA	
	Note: Study authors indicated that a sufficient number of male animals could not be obtained in the high-dose group at PND 140. Doses represent a range estimated by the study authors for three different time periods (GDs 15-20, PNDs 2-10, and PNDs 10-21).						
[Ahmad et al. (2014)](#) Rat (Strain not specified); assessed in male offspring; sample size not reported 0, 2, 10, 50 mg/kg-day Gavage GD 14 to Parturition	*response relative to control*						
	Doses	0	2	10	50		
	Absolute epididymis weight						
	PND 75	0%	-2%	-4%	-12*%		
[Zhang et al. (2004b)](#) Rat (Sprague-Dawley); 14-16 dams/group; assessed in 20 male offspring/group 0, 50, 250, 500 mg/kg-day Gavage GD 1-PND 21	*response relative to control*						
	Doses	0	50	250	500		
	Absolute right epididymis weight in adults						
	PND 70	0%	-0.3%	-16*%	-29*%		

Reference and study design	Results						
Johnson et al. (2008) Rat (Long-Evans); 3-7 litters/group; assessed in 1-12 male pups/litter 0, 50, 100, 200 mg/kg-day Gavage GDs 12-21	*response relative to control*						
	Doses	0	50	100	200		
	Absolute epididymis weight						
	PND 21	0%	-8%	-12%	-24%		
NTP (1991) Rat (Sprague-Dawley); 20 breeding pairs/dose/generation; 40 control breeding pairs 0, 0.1, 0.5, 1% Diet (0, 66, 320, or 651 mg/kg-day) Multigenerational study	*response relative to control*						
	Doses	0	66	320	651		
	Absolute right cauda epididymis weight in adults						
	~PND 88	0%	3	-2	-43*		
	Absolute right epididymis weight in adults						
	~PND 88	0%	3	0	-29*		
	Note: Adult F1 males were sampled on PND 88 ± 10 days						
Mylchreest et al. (1999a) Rat (Sprague-Dawley); 9-10 litters/group; (52-62 male offspring/group) 0, 100, 250, 500 mg/kg-day Gavage GDs 12-21	*response relative to control*						
	Doses	0	100	250	500		
	Absolute right epididymis weight in adults						
	3-month old	0%	3%	-2%	-26*%		
Martino-Andrade et al. (2009) Rat (Wistar); 4-7 litters/group;(8-17 male offspring/group) 0, 100, 500 mg/kg-day Gavage GDs 13-21	*response relative to control*						
	Doses	0	100	500			
	Absolute epididymis weight in adults						
	PND 90	0%	4%	-3%			
Changes in epididymis weight after pubertal and/or adult exposure							
Bao et al. (2011) Rat (Sprague-Dawley); 5-week-old males 20/group 0, 0.1, 1.0, 10, 100, 500 mg/kg-day Gavage 30 days	*response relative to control*						
	Doses	0	0.1	1.0	10	100	500
	Absolute epididymis weight after pubertal exposure						
		0%	1%	-3%	1%	3%	-14*%

Reference and study design	Results						
Moody et al. (2013) Mouse (C57Bl/6J); 8-10 four day old males/group 0, 1, 10, 100, 500 mg/kg-day Gavage PNDs 4-21	*response relative to control*						
	Doses	0	1	10	100	500	
	Relative epididymis weight in adults						
	PND 56	0%	7%	11%	6%	21%	
Tsutsumi et al. (2004) Rat (F344); 6-week-old males, 5/group 0, 61, 255, 1,536 mg/kg-day Diet 4 weeks	*response relative to control*						
	Doses	0	61	255	1,536		
	Relative epididymis weight in adults						
		0%	3%	3%	-10%		
	Note: Study authors noted that rats in the high-dose group were observed to "rake" the food (chow), leading to food loss out of cage and probable overestimation of food consumption and dietary intake.						
Lee et al. (2008) Rat (Sprague-Dawley); 3-week-old males, 6/group 0, 100, 500 mg/kg-day Gavage 30 days	*response relative to control*						
	Doses	0	100	500			
	Absolute epididymis weight in pre-pubertal rats						
		0%	-5%	-36*%			
Zhou et al. (2011) Rat (Sprague-Dawley); 10 adult males/group 0, 100, 250, 500 mg/kg-day Gavage 2 weeks	*response relative to control*						
	Doses	0	100	250	500		
	Absolute epididymis weight in adults[a]						
		0%	1%	-4%	-17*%		
Changes in prostate weight after gestational exposure							
Mylchreest et al. (2000) Rat (Sprague-Dawley); assessed in male offspring from 11-20 litters/group 0, 0.5, 5, 50, 100, 500 mg/kg-day Gavage GDs 12-21	*response relative to control*						
	Doses	0	0.5	5	50	100	500
	Absolute prostate weight in adults *(PND 110)*						
	Ventral	0%	-4%	-1%	-5%	-3%	-17%
	Dorsolateral	0%	2%	2%	1%	-4%	-17*%
	response relative to control						
	Doses	0	2-3	14-29	148-291	712-1,372	
	Relative ventral prostate weight in adults						
	PND 77	0%	33%	42*%	25%	8%	
	PND 140	0%	-20%	-13%	-20%	NA	

Reference and study design	Results				
Lee et al. (2004) Rat (Sprague-Dawley); 6-8 dams/group; assessed in 8-10 male offspring/group (including ≥1 male/litter) 0, 20, 200, 2,000, 10,000 ppm Diet (0, 2-3, 14-29, 148-291, 712-1,372) mg/kg-day Diet GD 15-PND 21	Note: Study authors indicated that a sufficient number of male animals could not be obtained in the high-dose group at PND 140. Doses represent a range estimated by the study authors for three different time periods (GDs 15-20, PNDs 2-10, and PNDs 10-21).				
Ahmad et al. (2014) Rat (Strain not specified); assessed in male offspring; sample size not reported 0, 2, 10, 50 mg/kg-day Gavage GD 14 to Parturition	*response relative to control*				
	Doses	0	2	10	50
	Absolute prostate weight in adults				
	PND 75	0%	-1%	-2%	-15*%
Zhang et al. (2004b) Rat (Sprague-Dawley); 14-16 dams/group; assessed in 20 male offspring/group 0, 50, 250, 500 mg/kg-day Gavage GD 1-PND 21	*response relative to control*				
	Doses	0	50	250	500
	Absolute prostate weight in adults				
	PND 70	0%	-16%	-31*%	2%
NTP (1991) Rat (Sprague-Dawley); 20 breeding pairs/dose/generation; 40 control breeding pairs, 0, 0.1, 0.5, 1% Diet (0, 66, 320, or 651 mg/kg-day) Multigenerational study	*response relative to control*				
	Doses	0	66	320	651
	Absolute prostate weight in adults				
	~PND 88	0%	-2%	-12%	-26*%
	Note: Adult F1 males were sampled on PND 88 ± 10 days				
Macleod et al. (2010) Rat (Wistar); ≥3 litters/group; assessed in 6-21 male offspring/group 0, 100, 500 mg/kg-day Gavage GDs 13-21	*response relative to control*				
	Doses	0	100	500	
	Absolute ventral prostate weight				
	PND 25[a]	0%	-27*%	-20*%	
Drake et al. (2009) Rat (Wistar); 13-15/group 0, 100, 500 mg/kg-day Gavage GDs 15-21	*response relative to control*				
	Doses	0	100	500	
	Absolute ventral prostate weight in adults				
	>12 wks[a]	0%	-18%	-36*%	
Martino-Andrade et al. (2009)	*response relative to control*				
	Doses	0	100	500	

Reference and study design	Results					
Rat (Wistar); 4-7 litters/group;(8-17 male offspring/group) 0, 100, 500 mg/kg-day Gavage GDs 13-21	**Absolute prostate weight in adults**					
	PND 90	0%	-3%	-8%		
[Mylchreest et al. (1999a)](#) Rat (Sprague-Dawley); 9-10 litters/group; (52-62 male offspring/group) 0, 100, 250, 500 mg/kg-day Gavage GDs 12-21	*response relative to control*					
	Doses	0	100	250	500	
	Absolute prostate weight in adults *(3-month old)*					
	Ventral Prostate	0%	2%	-8%	-10%	
	Dorsolateral	0%	0%	0%	-5%	
Changes in prostate weight after pubertal and/or adult exposure						
[Tsutsumi et al. (2004)](#) Rat (F344); 6-week-old males, 5/group 0, 61, 255, 1,536 mg/kg-day Diet 4 weeks	*response relative to control*					
	Doses	0	61	255	1,536	
	Absolute prostate weight in adults					
	Ventral Prostate	0%	-6%	10%	-10%	
	Dorsolateral	0%	-4%	-12%	-19*%	
	Note: Study authors noted that rats in the high-dose group were observed to rake the food, leading to food loss out of cage and probable overestimation of food consumption and dietary intake.					
[Lee et al. (2008)](#) Rat (Sprague-Dawley); 3-week-old males, 6/group 0, 100, 500 mg/kg-day Gavage 30 days	*response relative to control*					
	Doses	0	100	500		
	Absolute ventral prostate weight in pre-pubertal rats					
		0%	-6%	-23*%		
Changes in seminal vesicle weight after gestational exposure						
[Mylchreest et al. (2000)](#) Rat (Sprague-Dawley); assessed in male offspring from 11-20 litters/group 0, 0.5, 5, 50, 100, 500 mg/kg-day Gavage GDs 12-21	*response relative to control*					
	Doses	0	0.5	5	50	100	500
	Absolute seminal vesicle weight in adults					
	PND 110	0%	4%	4%	3%	2%	-8%
[Lee et al. (2004)](#) Rat (Sprague-Dawley); 6-8 dams/group; assessed in 8-10 male offspring/group (including ≥1 male/litter) 0, 20, 200, 2,000, 10,000 ppm Diet (0, 2-3, 14-29, 148-291, 712-1,372 mg/kg)	*response relative to control*					
	Doses	0	2-3	14-29	148-291	712-1,372	
	Relative seminal vesicle weight					
	PND 77	0%	-3%	7%	-17%	-13%	
	PND 140	0%	-10%	-13%	-10%	NA	

Reference and study design	Results				
Diet GD 15-PND 21	Note: Study authors indicated that a sufficient number of male animals could not be obtained in the high-dose group at PND 140. Doses represent a range estimated by the study authors for three different time periods (GDs 15-20, PNDs 2-10, and PNDs 10-21).				
Ahmad et al. (2014) Rat (Strain not specified); assessed in male offspring; sample size not reported 0, 2, 10, 50 mg/kg-day Gavage GD 14 to Parturition	*response relative to control*				
	Doses	0	2	10	50
	Absolute seminal vesicle weight in adults				
	PND 75	0%	-1%	-1%	-13*%
NTP (1991) Rat (Sprague-Dawley); 20 breeding pairs/dose/generation; 40 control breeding pairs, 0, 0.1, 0.5, 1% Diet (0, 66, 320, or 651 mg/kg-day) Multigenerational study	*response relative to control*				
	Doses	0	66	320	651
	Absolute seminal vesicle weight in adults				
	~PND 88	0%	1%	-4%	-29*%
	Note: Adult F1 males were sampled on PND 88 ± 10 days				
Martino-Andrade et al. (2009) Rat (Wistar); 4-7 litters/group; (8-17 male offspring/group) 0, 100, 500 mg/kg-day Gavage GDs 13-21	*response relative to control*				
	Doses	0	100	500	
	Absolute seminal vesicle weight in adults				
	PND 90	0%	-10%	-8%	
Macleod et al. (2010) Rat (Wistar); ≥3 litters/group; assessed in 6-21 male offspring/group 0, 100, 500 mg/kg-day Gavage GDs 13-21	*response relative to control*				
	Doses	0	100	500	
	Absolute seminal vesicle weight				
	PND 25[a]	0%	-12%	-59*%	
Mylchreest et al. (1999a) Rat (Sprague-Dawley); 9-10 litters/group; (52-62 male offspring/group) 0, 100, 250, 500 mg/kg-day Gavage GDs 12-21	*response relative to control*				
	Doses	0	100	250	500
	Absolute seminal vesicle weight in adults				
	3-month old	0%	0%	-1%	-21*%
Changes in seminal vesicle weight after pubertal and/or adult exposure					
Tsutsumi et al. (2004) Rat (F344); 6-week-old males, 5/group 0, 61, 255, 1,536 mg/kg-day Diet	*response relative to control*				
	Doses	0	61	255	1,536
	Absolute seminal vesicle weight in adults				
		0%	-3%	-5%	-17*%

Reference and study design	Results						
4 weeks	Note: Study authors noted that rats in the high-dose group were observed to rake the food, leading to food loss out of cage and probable overestimation of food consumption and dietary intake.						
Lee et al. (2008) Rat (Sprague-Dawley); 3-week-old males, 6/group 0, 100, 500 mg/kg-day Gavage 30 days	*response relative to control*						
	Doses	0	100	500			
	Absolute seminal vesicle weight in pre-pubertal rats						
		0%	-8%	-47*%			
Changes in vas deferens weight after gestational exposure							
Mylchreest et al. (2000) Rat (Sprague-Dawley); assessed in male offspring from 11-20 litters/group 0, 0.5, 5, 50, 100, 500 mg/kg-day Gavage GDs 12-21	*response relative to control*						
	Doses	0	0.5	5	50	100	500
	Absolute vas deferens weight in adults						
	PND 110	0%	2%	1%	2%	1%	-7%
Mylchreest et al. (1999a) Rat (Sprague-Dawley); 9-10 litters/group; (52-62 male offspring/group) 0, 100, 250, 500 mg/kg-day Gavage GDs 12-21	*response relative to control*						
	Doses	0	100	250	500		
	Absolute vas deferens weight in adults						
	3-month old	0%	2%	13%	-8%		
Changes in levator ani weight after gestational exposure							
Mylchreest et al. (2000) Rat (Sprague-Dawley); assessed in male offspring from 11-20 litters/group 0, 0.5, 5, 50, 100, 500 mg/kg-day Gavage GDs 12-21	*response relative to control*						
	Doses	0	0.5	5	50	100	500
	Absolute levator ani weight in adults						
	PND 110	0%	0.2%	-3%	-5%	-5%	-24*%
Martino-Andrade et al. (2009) Rat (Wistar); 4-7 litters/group;(8-17 male offspring/group) 0, 100, 500 mg/kg-day Gavage GDs 13-21	*response relative to control*						
	Doses	0	100	500			
	Absolute levator ani/bulbocavernosus muscle weight in adults						
	3-month old	0%	1%	-1%			

PND = postnatal day
[a]Values reported by the study authors were estimated from published graphs using "Grab It!", a Microsoft Excel based free software application used to digitize data from image files. Publisher: datatrendsoftware.com.
*Statistically increased over control as reported by study authors.

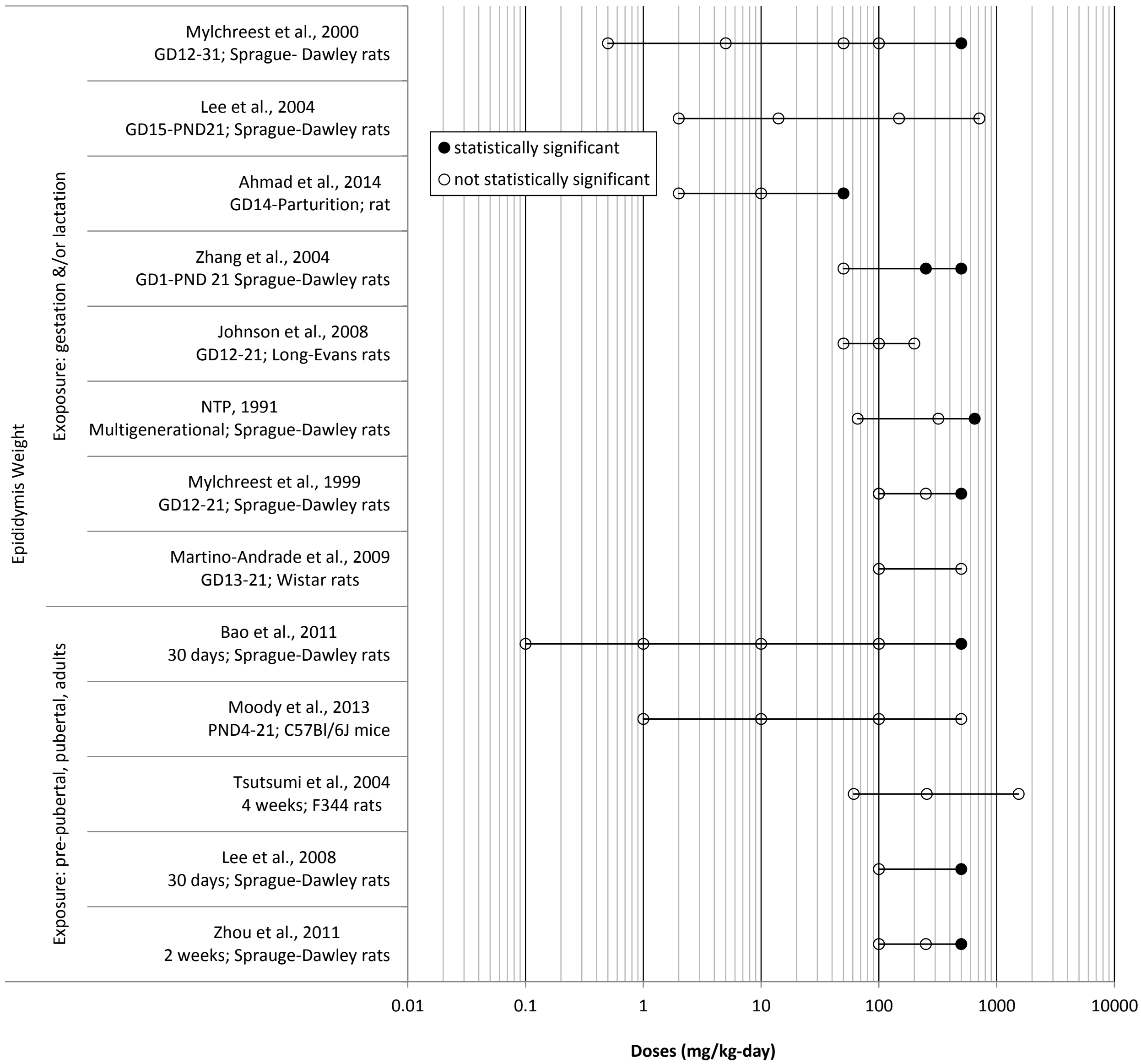


Figure 3-2. Exposure-response array of male reproductive toxicity following oral exposure to DBP: alterations in epididymis weights.

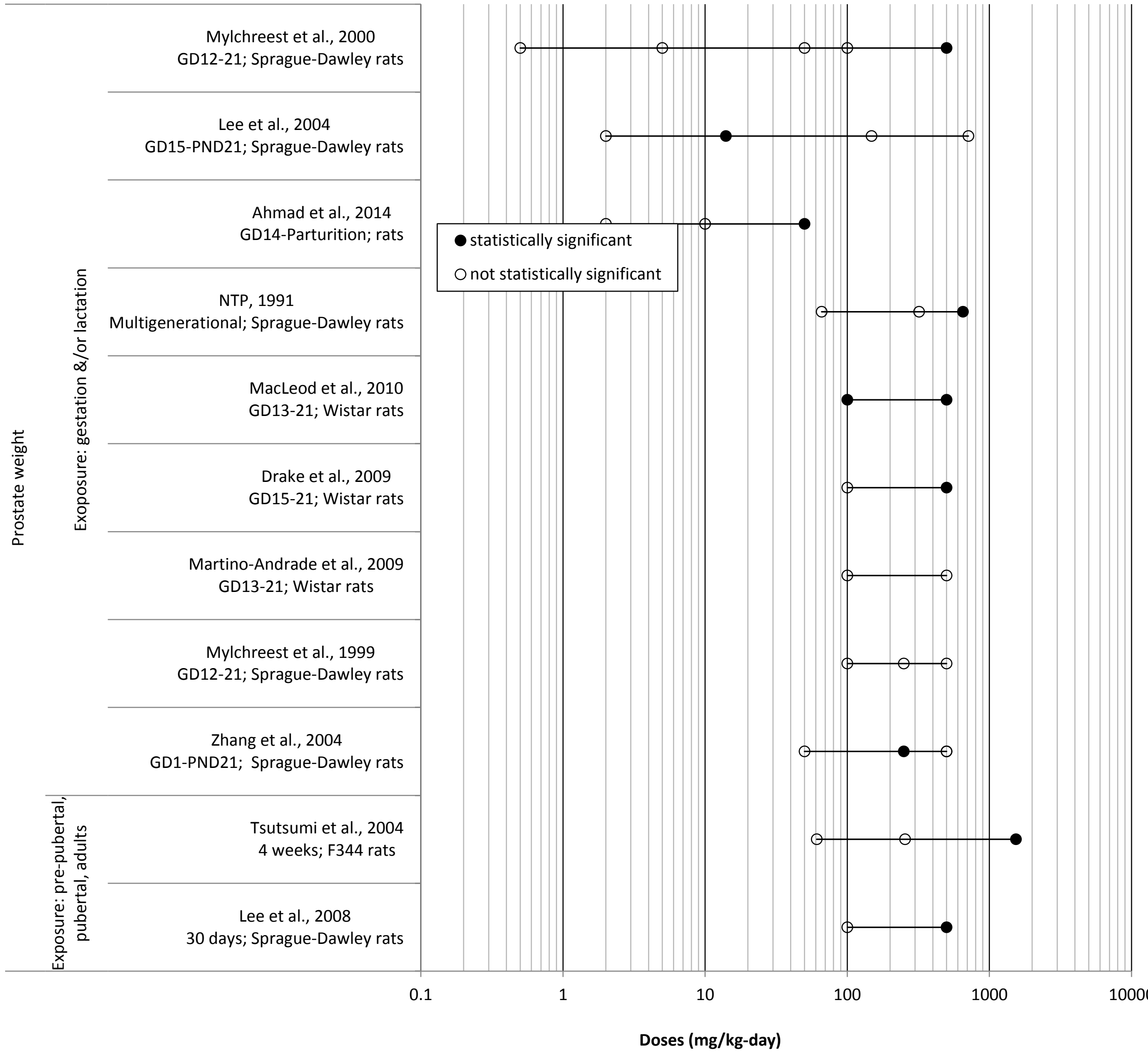


Figure 3-3. Exposure-response array of male reproductive toxicity following oral exposure to DBP: alterations in prostate weights.

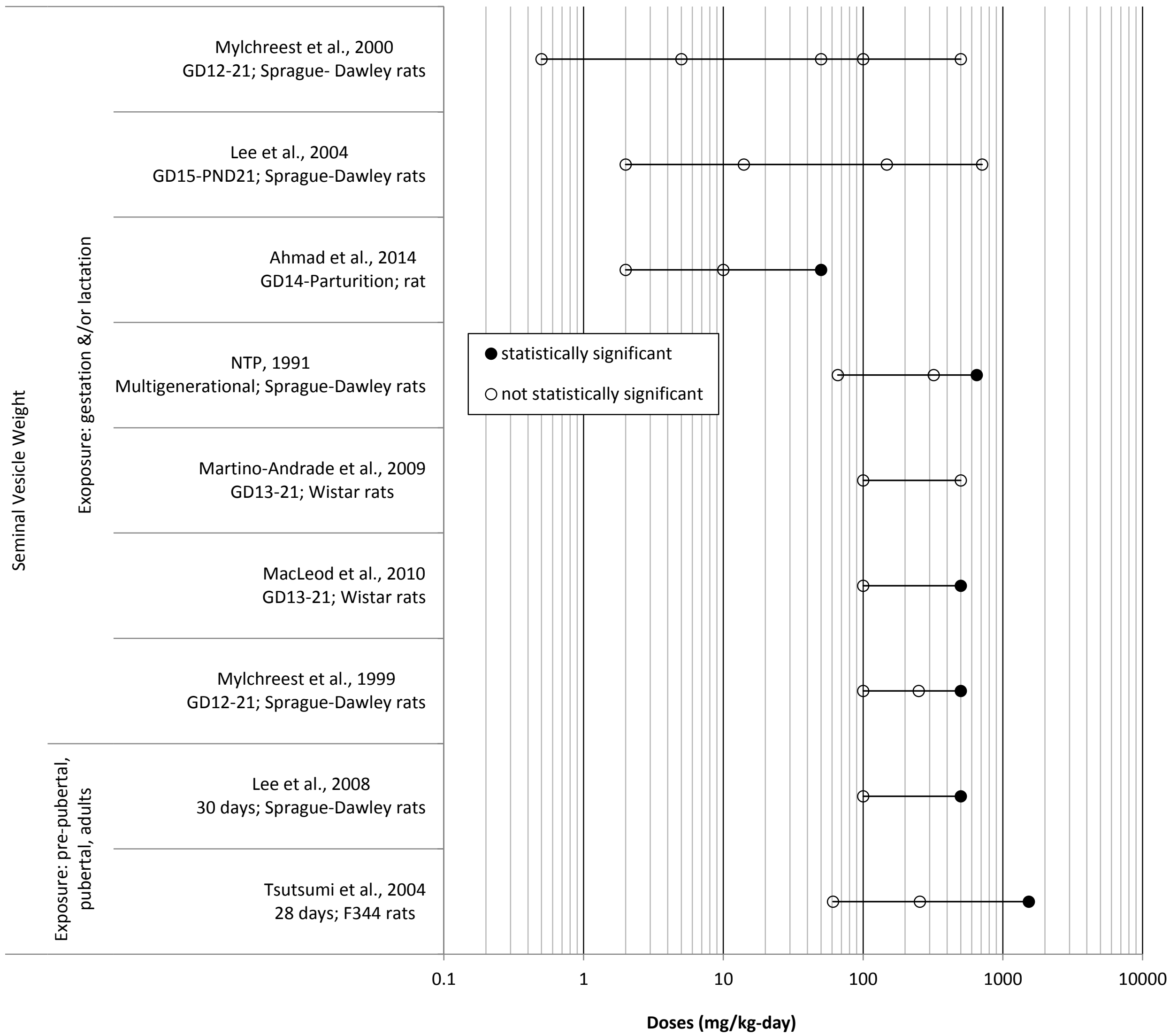


Figure 3-4. Exposure-response array of male reproductive toxicity following oral exposure to DBP: alterations in seminal vesicle weights.

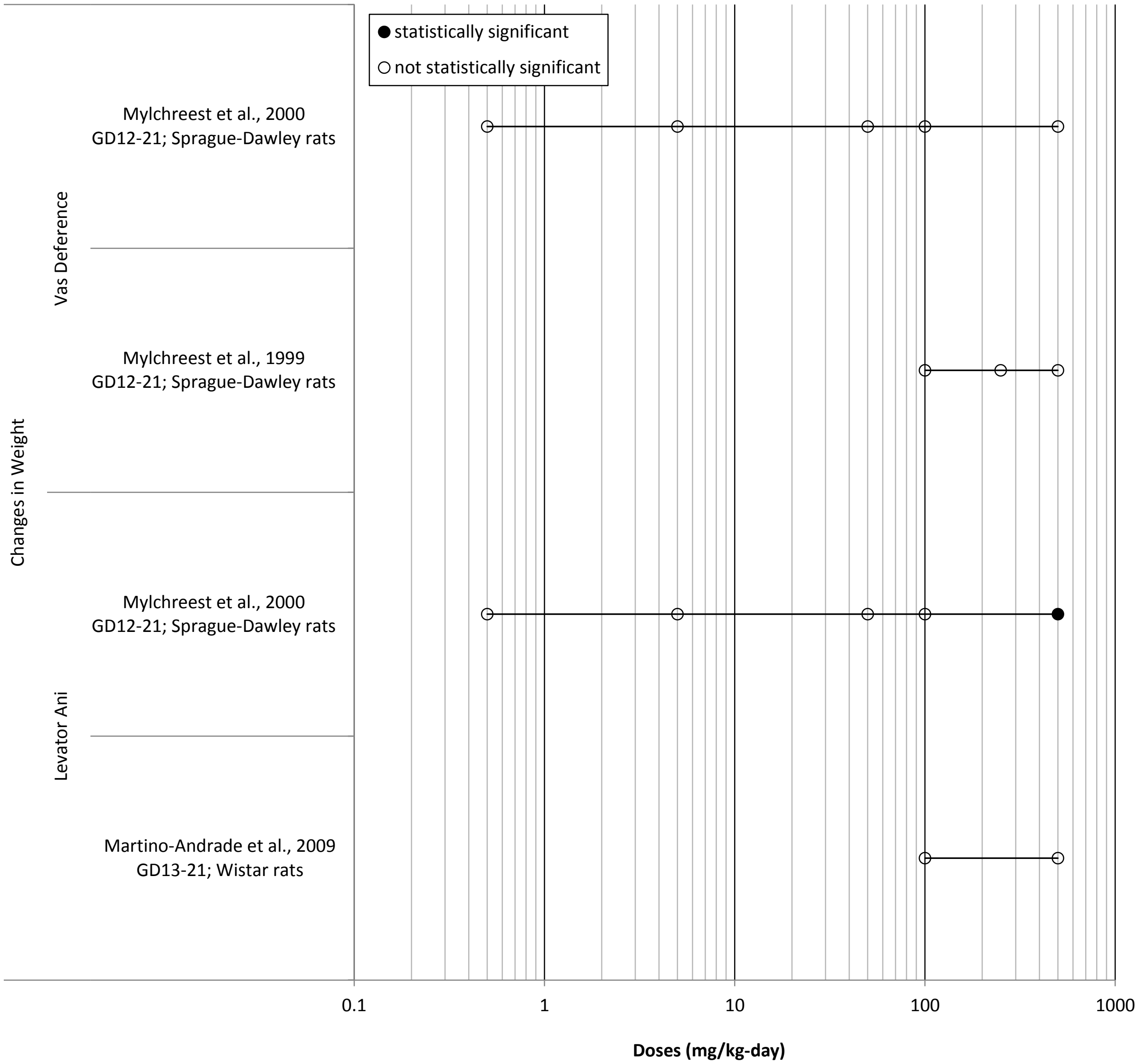


Figure 3-5. Exposure-response array of male reproductive toxicity following oral exposure to DBP: alterations in vas deference weights.

Table 3-20. Evidence pertaining to male reproductive toxicity following oral exposure to DBP: histopathological changes in animals

Reference and study design	Results							
Histopathological changes after gestational exposure								
Boekelheide et al. (2009) Rat (Sprague Dawley); 4-5 litters/treatment group; 10 litters/control group 0, 0.1, 1, 10, 30, 50, 100, 500 mg/kg-day Gavage GDs 12-20	*response relative to control*							
	Doses	0.1	1	10	30	50	100	500
	Testis volume							
	GD 21 fetuses[a]	-3%	-6%	-1%	-29%	-50*%	-51*%	-48*%
	Number of cells per testis							
	GD 21 fetuses[a]	-1%	-3%	-21%	-42*%	-46*%	-47*%	-51*%
	Number of tubular cross sections							
	GD 21 fetuses[a]	-6%	-8%	-6%	-12%	-45*%	-39*%	-47*%
	Number of MNGs							
	GD 21 fetuses[a]	-50%	0%	100%	400%	700%	6,950*%	5,750*%
Mylchreest et al. (2000) Rat (Sprague-Dawley; 11-20 litters/group; assessed in 103-140 male offspring/group 0, 0.5, 5, 50, 100, 500 mg/kg-day Gavage GDs 12-21	Doses	0	0.5	5	50	100	500	
	Seminiferous tubule degeneration in adults[b] *(PND 110)*							
	Incidence	0/134	1/118	0/103	0/120	2/140	27/58	
	Percent	0%	1%	0%	0%	1%	47%	
	Testicular interstitial cell hyperplasia in adults *(PND 110)* Increased number of Leydig cells with focal or irregular distribution							
	Incidence	0/134	0/118	0/103	0/120	0/140	14/58	
	Percent	0%	0%	0%	0%	0%	24%	
	Testicular interstitial cell adenoma in adults *(PND 110)*							
	Incidence	0/134	0/118	0/103	0/120	0/140	1/58	
	Percent	0%	0%	0%	0%	0%	2%	
Lee et al. (2004) Rat (Sprague-Dawley); 6-8 dams/group; assessed in 8-10 male offspring/group (including ≥1 male/litter) 0, 20, 200, 2,000, 10,000 ppm Diet (0, 2-3, 14-29, 148-291, 712-1,372 mg/kg-day) Diet GD 15-PND 21	Doses	0	2-3	14-29	148-291	712-1,372		
	Decreased epididymal ductular cross sections *(PND 21 pups)*							
	Incidence	0/8	0/8	0/8	5/8*5	7/8*		
	Percent	0%	0%	0%	63%	88%		
	Reduced spermatocyte development *(PND 21 pups)*							
	Incidence	0/8	4/8*	4/8*	8/8*	8/8*		
	Percent	0%	50%	50%	50%	50%		
	Aggregated foci of Leydig cells *(PND 21 pups)*							

Reference and study design	Results					
	Incidence	0/8	0/8	1/8	8/8*	8/8*
	Percent	0%	0%	13%	100%	100%
	Epididymal intraductular debris; minimal *(PND 77 adults)*					
	Incidence	1/8	0/8	0/8	0/8	4/10
	Percent	13%	0%	0%	0%	40%
	Epididymal hypoplasia *(PND 77 adults)*					
	Incidence	0/8	0/8	0/8	0/8	2/10
	Percent	0%	0%	0%	0%	20%
	Leydig cell hyperplasia *(PND 140 adults)*					
	Incidence	1/10	1/10	1/8	0/10	NA
	Percent	10%	10%	13%	0%	NA
	Flattening of surface epithelia in prostate ventral lobe *(PND 140 adults)*					
	Incidence	3/10	2/10	4/8	7/10	NA
	Percent	30%	20%	50%	70%	NA
	Note: Doses represent a range estimated by the study authors for three different time periods (GDs 15-20, PNDs 2-10, and PNDs 10-21).					
Mahood et al. (2007) Rat (Wistar); assessed in male offspring from 5-9 litters/group (GD 21 endpoints) or 5-12 adult male offspring/group (PND 90) 0, 4, 20, 100, 500 mg/kg-day Gavage GDs 13-20 or 13-21	*response relative to control*					
	Doses	0	4	20	100	500
	Number of Leydig cell clusters/testis					
	GD 21 fetuses	0%	-6%	-9%	-48*%	-53*%
	Small Leydig cell clusters/testis					
	GD 21 fetuses[a]	0%	-6%	-3%	-15*%	-42*%
	Medium Leydig cell clusters/testis					
	GD 21 fetuses[a]	0%	5%	-1%	13*%	3%
	Large Leydig cell clusters/testis					
	GD 21 fetuses[a]	0%	0%	5%	1%	38*%
	Seminiferous cords containing MNGs					
	GD 21 fetuses[a]	0%	-0.3%	4%	18*%	36*%
	SCO tubules in adult rats with scrotal testes *(PND 90)*					
	Incidence	0/9	0/11	1/5	8/12	6/9
	Percent F1	0%	0%	20%	67*%	67*%
	Note: Male offspring analyzed at PND 21 were exposed from GDs 13-20; male offspring analyzed at PND 90 were exposed from GDs 13-21. Small clusters account for ≤5% of the total LC cluster area/testis, medium clusters for 5.1-14.9%, and large clusters ≥15%.					
	Doses	0	5	50	500	

Reference and study design	Results					
Monsanto (1984) Rat (CD); 20 breeding pairs/group [females exposed only], F1: 9-10 males per group 0, 5, 50, 500 mg/kg-day Diet F0: 14 days before mating and continued through weaning [PND 21] F1, group A: continued basal diet to PND 70 F1, group B: Received same dose as F0 to PND 70	**Epididymal aspermia** F1, group A					
	Incidence	0/10	1/10	1/10	1/9	
	Percent	0%	10%	10%	11%	
	Testicular degeneration F1, group A					
	Incidence	0/10	1/10	1/10	2/9	
	Percent	0%	10%	10%	22%	
	Epididymal aspermia F1, group B					
	Incidence	0/10	0/10	0/10	3/10	
	Percent	0%	0%	0%	30%	
	Testicular degeneration F1, group B					
	Incidence	0/10	0/10	0/10	4/10	
	Percent	0%	0%	0%	40%	
Shirai et al. (2013) Rat (Sprague-Dawley); 4 males/group, 20 litters/ group 0, 10, 30, 50, 100 mg/kg-day Gavage PNDs 12-21	*response relative to control*					
	Doses	0	10	30	50	100
	Leydig cell number[a]					
	PND 35	0%	-2%	5%	0%	7%
	PND 49	0%	-5%	3%	-2%	16%
	PND 63	0%	-7%	-1%	0%	60*%
	PND 98	0%	8%	-5%	10%	127*%
	PND 119	0%	2%	7%	7%	195*%
	Smooth Endoplasmic Reticulum amount[a]					
	PND 35	0%	2%	2%	-1%	3%
	PND 49	0%	0%	2%	-1%	2%
	PND 63	0%	-2%	-4%	-4%	-70*%
	PND 98	0%	-3%	-4%	-5%	-85*%
	PND 119	0%	3%	0%	3%	-100%
Johnson et al. (2008) Rat (Long-Evans); 3-7 litters/group; assessed in 1-5 males/litter 0, 50, 100, 200 mg/kg-day Gavage GDs 12-21	*response relative to control*					
	Doses	0	50	100	200	
	Seminiferous cord diameter					
	GD 21 fetuses[a]	0%	-1%	NE	8*%	
	Percent seminiferous cords with MNGs					
	GD 21 fetuses[a]	0%	2%	NE	29*%	

Reference and study design	Results				
Martino-Andrade et al. (2009) Rat (Wistar); 7-8 litters/group; assessed in 1-2 males/litter 0, 100, 500 mg/kg-day Gavage GDs 13-21	*response relative to control*				
	Doses	0	100		500
	Seminiferous cord diameter				
	GD 21 fetuses[a]	0%	6%		28*%
	Number of MNGs				
	GD 21 fetuses[a]	0%	10%		20*%
Johnson et al. (2011) Rat (F344); 5 males/group 0, 100, 500 mg/kg-day Gavage GDs 12-20	*response relative to control*				
	Doses	0	100		500
	Percent seminiferous cords with MNGs				
	GD 20 fetuses[a]	0%	17*%		23*%
Mylchreest et al. (1999a) Rat (Sprague-Dawley); 11-20 litters/group; assessed in 45-55 male offspring/group 0, 100, 250, 500 mg/kg-day Gavage GDs 12-21	Doses	0	100	250	500
	Seminiferous tubule degeneration in adults[b] *(3-months old)*				
	Incidence	3/51	1/51	6/55	22/45
	Percent	6%	2%	11%	49%
	Testicular interstitial cell hyperplasia in adults *(3-months old)* Increased number of Leydig cells with focal or irregular distribution				
	Incidence	0/51	0/51	1/55	5/45
	Percent	0%	0%	2%	11%
	Testicular interstitial cell adenoma in adults *(3-months old)*				
	Incidence	0/51	0/51	0/55	2/45
	Percent	0%	0%	0%	4%
	Abnormal epididymis in adults *(3-months old)*				
	Incidence	2/51	0/51	2/55	14/45
	Percent	4%	0%	4%	31%
Barlow et al. (2004) Rat (Sprague-Dawley); 8-11 litters/group (35-74 male offspring/group) 0, 100, 500 mg/kg-day Gavage GDs 12-21	Doses	0	100		500
	Testicular dysgenesis (aberrant/immature seminiferous tubules) *Percent unilateral litter incidence*				
	PND 180	0%	0%		64*%
	PND 370	10%	0%		73*%
	PND 540	0%	0%		38%
	Percent bilateral litter incidence				
	PND 180	0%	0%		27%
	PND 370	0%	0%		73*%
	PND 540	0%	0%		38%

Reference and study design	Results					
	Germ cell degeneration *Percent unilateral litter incidence*					
	PND 180	20%	50%	55%		
	PND 370	10%	22%	73*%		
	PND 540	22%	60%	63%		
	Percent bilateral litter incidence					
	PND 180	0%	0%	73*%		
	PND 370	10%	22%	100*%		
	PND 540	22%	20%	88*%		
	Rete testis (sperm stasis with granulomatuous inflammation and fibrosis) *Percent unilateral litter incidence*					
	PND 180	10%	30%	55%		
	PND 370	10%	0%	82*%		
	PND 540	0%	20%	50*%		
	Percent bilateral litter incidence					
	PND 180	0%	0%	18%		
	PND 370	0%	22%	45*%		
	PND 540	0%	10%	38%		
Gaido et al. (2007) Mouse (C57Bl6); 4-6 litters/group 0, 250, 500 mg/kg-day Gavage GDs 16-18	*response relative to control*					
	Doses	0	250	500		
	Seminiferous cord diameter[b]					
		0%	11*%	17*%		
	Number of MNGs per cord cross-section[b]					
		0%	300*%	420*%		
	Number of nuclei per MNG[b]					
		0%	32*%	24*%		
Histopathological changes after pubertal and/or adult exposure						
Bao et al. (2011) Rat (Sprague-Dawley); 5-week-old males, 20/group 0, 0.1,1.0, 10, 100, 500 mg/kg-day Gavage 30 days	*response relative to control*					
	Doses	0	0.1	1.0	10	100	500
	Number of Sertoli cells/seminiferous tubule after pubertal exposure[a]					
		0%	-1%	-4%	0%	-14*%	-43*%
Moody et al. (2013) Mouse (C57Bl/6J); 4-10 four day old males/group	Doses	0	1	10	100	500
	Histological markers of Sertoli cell development *(PND 14)*					
	Tubules with centrally localized Sertoli cell nuclei					

Reference and study design	Results					
(0, 1, 10, 100, 500 mg/kg-day)	*Proportion*	9%	12%	11%	22%	24*%
Gavage	**Cross sections containing lumen**					
PNDs 4-14 or PNDs 4-21	*Proportion*	53%	50%	47%	42%	17*%
	Histological markers in seminiferous cords of spermatogenesis progression *(PND 14)*					
	Spermatogonia					
	Percent	9%	8%	10%	10%	23*%
	Preleptotene-zygote spermatocytes					
	Percent	20%	22%	25%	28%	38*%
	Pachytene spermatocytes					
	Percent	13%	9%	4*%	5*%	2*%
	Histological markers of spermatogenesis progression in adults *(PND 56 after exposure from PNDs 4-21)*					
	Absent pre-meiotic/meiotic germ cells					
	Incidence	20%	83%	17%	67%	83%
	Absent postmeiotic germ cells					
	Incidence	20%	83%	83%	33%	100%
	Absent partial spermatogenesis					
	Incidence	0%	50%	67%	100%	83%
Monsanto (1984)	Doses	0	5	50	500	
Rat (CD); 20 breeding pairs/group 19-20 animals evaluated [males exposed only]	**Chronic prostatitis**					
0, 5, 50, 500 mg/kg-day	*Incidence*	3/19	0/20	2/19	3/19	
Diet	*Percent*	16%	0%	10%	16%	
105 days	**Normal appearing testis**					
	Incidence	19/19	20/20	19/19	19/19	
	Percent	100%	100%	100%	100%	
	Normal appearing epididymis					
	Incidence	19/19	20/20	19/19	19/19	
	Percent	100%	100%	100%	100%	

NA = Not available; NE = Not examined; MNG = multinucleated gonocyte/germ cell; SCO = Sertoli cell only

[a]Values reported by the study authors were estimated from published graphs using “Grab It!”, a Microsoft Excel based free software application used to digitize data from image files. Publisher: datatrendsoftware.com.

[b]Study shows seminiferous tubule degeneration in adults (3-months old) with mild (6-20% tubules affected), moderate (21-50% affected) or severe (>50% affected) degeneration

*Statistically increased over control as reported by study authors.

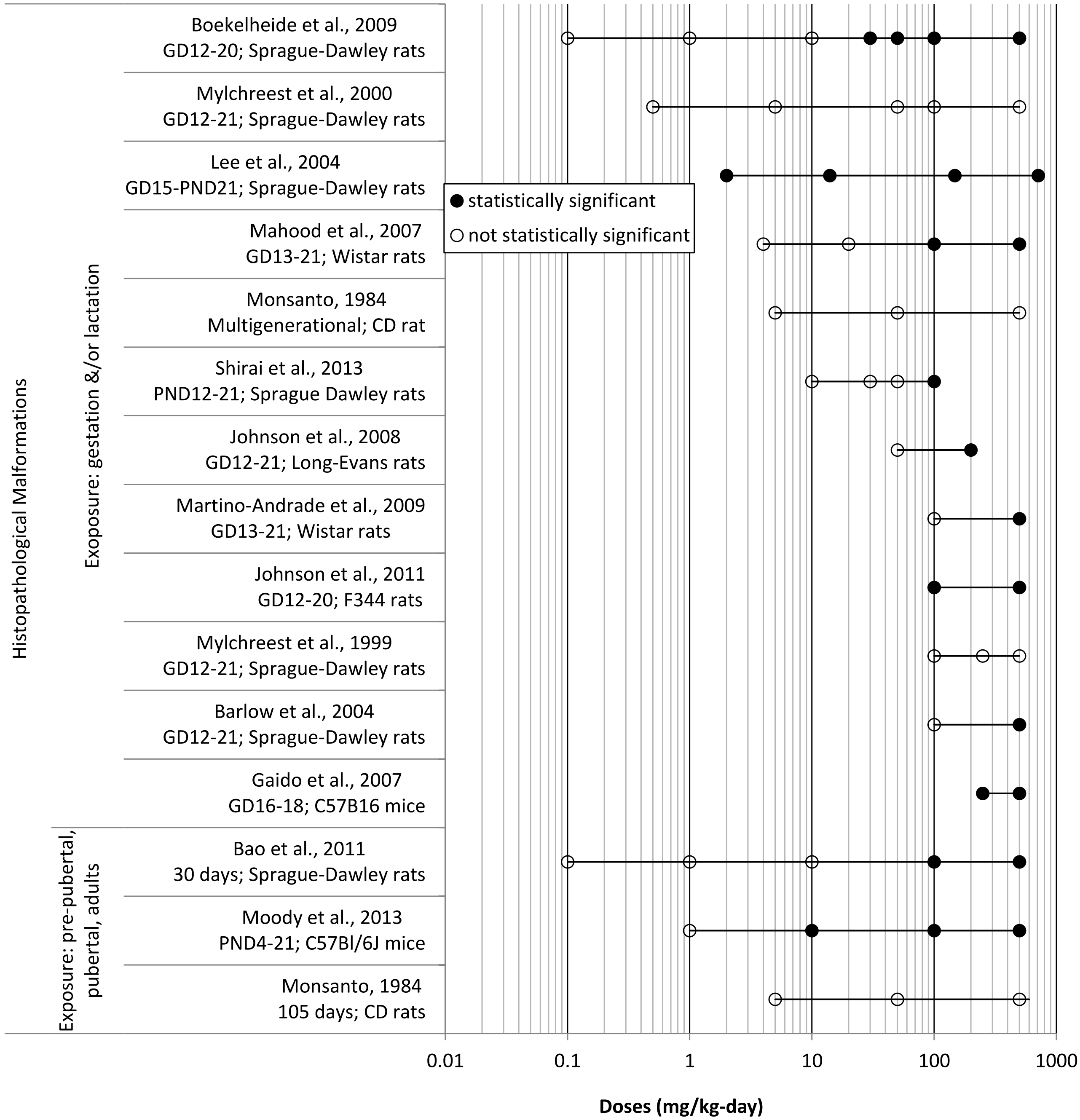


Figure 3-6. Exposure-response array of male reproductive toxicity following oral exposure to DBP: histopathological effects.

Table 3-21. Evidence pertaining to male reproductive toxicity following oral exposure to DBP: external and internal malformations in animals

Reference and study design	Results						
Hypospadias							
Mylchreest et al. (2000) Rat (Sprague-Dawley); assessed in male offspring from 11-20 litters/group 0, 0.5, 5, 50, 100, 500 mg/kg-day Gavage GDs 12-21	Doses	0	0.5	5	50	100	500
	Hypospadias in adults *(PND 110)*						
	Litter incidence	0/20	0/20	0/19	0/20	0/20	4/11
	Percent	0%	0%	0%	0%	0%	36%
Mylchreest et al. (1999a) Rat (Sprague-Dawley); assessed in male offspring from 9-10 litters/group/group 0, 100, 250, 500 mg/kg-day Gavage GDs 12-21	Doses	0	100	250	500		
	Hypospadias in adults						
	Litter incidence	0/10	0/9	0/10	4/9		
	Percent	0%	0%	0%	44%		
Drake et al. (2009) Rat (Wistar); 13-15 litters/group; assessed in 32-45 male offspring/group 0, 100, 500 mg/kg-day Gavage GDs 15-21	Doses	0	100	500			
	Adult (>12 weeks) male offspring with Hypospadias						
	Percent	0%	0%	31*%			
Barlow et al. (2004) Rat (Sprague-Dawley); 8-11 litters/group (35-74 male offspring/group) 0, 100, 500 mg/kg-day Gavage GDs 12-21	Doses	0	100	500			
	Hypospadias in adults *Percent litter incidence*						
	PND 180	0%	0%	27%			
	PND 370	0%	0%	64*%			
	PND 540	0%	0%	50*%			
Cryptorchidism, and absent/atrophied testis							
Mahood et al. (2007) Rat (Wistar); assessed in male offspring from 3-7 litters/group 0, 4, 20, 100, 500 mg/kg-day Gavage GDs 13-21	Doses	0	4	20	100	500	
	Cryptorchidism in adults *(PND 90)*						
	Total	0/28	0/11	0/18	1/20	18/20	
	Percent	0%	0%	0%	5%	90%	

Reference and study design	Results				
Monsanto (1984) Rat (CD); 20 breeding pairs/group; 129-20 animals evaluated [males exposed only] 0, 50, 500 mg/kg-day Diet 105 days	Doses	0	5	50	500
	Moderate undescended testis				
	Incidence	19/19	20/20	19/19	19/19
	Percent	21%	45%	58%	53%
Monsanto (1984) Rat (CD); 20 breeding pairs/group [females exposed only], F1: 9-10 males per group 0, 5, 50, 500 mg/kg-day Diet F0: 14 days before mating and continued through weaning [PND 21] F1, group A: continued basal diet to PND 70 F1, group B: Received same dose as F0 to PND 70	Doses	0	5	50	500
	Incidence enlarged testis F1, group A				
	Incidence	0/9	0/10	0/10	0/10
	Percent	0%	0%	0%	0%
	Incidence small unilateral or bilateral testis F1, group A				
	Incidence	0/9	0/10	0/10	1/10
	Percent	0%	0%	0%	10%
	Incidence enlarged testis F1, group B				
	Incidence	0/10	0/10	1/10	0/10
	Percent	0%	0%	10%	0%
	Incidence small unilateral or bilateral testis F1, group B				
	Incidence	0/10	0/10	0/10	2/10
	Percent	0%	0%	0%	20%
Mylchreest et al. (1999a) Rat (Sprague-Dawley); assessed in male offspring from 9-10 litters/group 0, 100, 250, 500 mg/kg-day Gavage GDs 12-21	Doses	0	100	250	500
	Cryptorchidism in adults *(PNDs 100-105)*				
	Litter incidence	0/10	0/9	1/10	3/9
	Percent	0%	0%	10%	33%
Drake et al. (2009) Rat (Wistar); 13-15 litters/group; assessed in 32-45 male offspring/group 0, 100, 500 mg/kg-day Gavage GDs 15-21	Doses	0	100	500	
	Adult male offspring with Cryptorchidism *(>84 days)*				
	Percent	0%	0%	53*%	

Reference and study design	Results					
Barlow et al. (2004) Rat (Sprague-Dawley); 8-11 litters/group (35-74 male offspring/group) 0, 100, 500 mg/kg-day Gavage GDs 12-21	Doses	0	100	500		
	Absent, atrophied, enlarged testis (unilateral) *Percent litter incidence*					
	PND 180	20%	60%	36%		
	PND 370	10%	22%	82*%		
	PND 540	11%	30%	75*%		
	Absent, atrophied, enlarged testis (bilateral) *Percent litter incidence*					
	PND 180	0%	0%	82*%		
	PND 370	0%	22%	100*%		
	PND 540	11%	10%	88*%		
Malformed, absent or partially developed prostate, epididymis and/or seminal vesicle						

Reference and study design	Doses	0	0.5	5	50	100	500
Mylchreest et al. (2000) Rat (Sprague-Dawley); assessed in male offspring from 11-20 litters/group 0, 0.5, 5, 50, 100, 500 mg/kg-day Gavage GDs 12-21	**Absent/partially developed epididymis in adults** *(PND 110)*						
	Litter incidence	0/20	0/20	0/19	0/20	0/20	9/11
	Percent	0%	0%	0%	0%	0%	82%
	Absent ventral prostate in adults *(PND 110)*						
	Litter incidence	0/20	0/20	0/19	0/20	0/20	1/11
	Percent	0%	0%	0%	0%	0%	9%
	Partially developed seminal vesicle in adults *(PND 110)*						
	Litter incidence	0/20	0/20	0/19	0/20	0/20	4/11
	Percent	0%	0%	0%	0%	0%	36%
	Absent/partially developed vas deferens in adults *(PND 110)*						
	Litter incidence	0/20	0/20	0/19	0/20	0/20	9/11
	Percent	0%	0%	0%	0%	0%	82%

Reference and study design	Results				
Mylchreest et al. (1999a) Rat (Sprague-Dawley); assessed in male offspring from 9-10 litters/group 0, 100, 250, 500 mg/kg-day Gavage GDs 12-21	Doses	0	100	250	500
	Absent/partially developed epididymis in adults				
	Litter incidence	0/10	0/9	4/10	8/9
	Percent	0%	0%	40%	89%
	Absent prostate in adults				
	Litter incidence	0/10	0/9	0/10	1/9
	Percent	0%	0%	0%	11%
	Absent seminal vesicle in adults				
	Litter incidence	0/10	0/9	0/10	0/9
	Percent	0%	0%	0%	0%

Reference and study design	Results			
Barlow et al. (2004) Rat (Sprague-Dawley); 8-11 litters/group (35-74 male offspring/group) 0, 100, 500 mg/kg-day Gavage GDs 12-21	Doses	0	100	500
	Partially developed epididymis (unilateral) *Percent litter incidence*			
	PND 180	10%	40%	64*%
	PND 370	10%	11%	55*%
	PND 540	11%	30%	63%
	Partially developed epididymis (bilateral)			
	PND 180	0%	0%	82*%
	PND 370	0%	11%	100*%
	PND 540	11%	10%	88*%
	Absent/small prostate			
	PND 180	0%	0%	82*%
	PND 370	20%	22%	100*%
	PND 540	89%	70%	100%
	Absent/malformed seminal vesicles			
	PND 180	0%	0%	91*%
	PND 370	0%	0%	91*%
	PND 540	56%	70%	100%
	Absent vas deferens (unilateral)			
	PND 180	0%	0%	82*%
	PND 370	0%	0%	82*%
	PND 540	0%	0%	50*%
	Absent vas deferens (bilateral)			
	PND 180	0%	0%	45*%
	PND 370	0%	0%	45*%

Reference and study design	Results				
	PND 540	0%	0%	50*%	
Malformations after pubertal and/or adult exposure					
Monsanto (1984) Rat (CD); 19-20 breeding pairs/group [males exposed only] 0, 5, 50, 500 mg/kg-day Diet 105 days	Doses	0	5	50	500
	Normal appearing testis				
	Incidence	19/19	20/20	19/19	19/19
	Percent	100%	100%	100%	100%

*Statistical significance as reported by study authors.

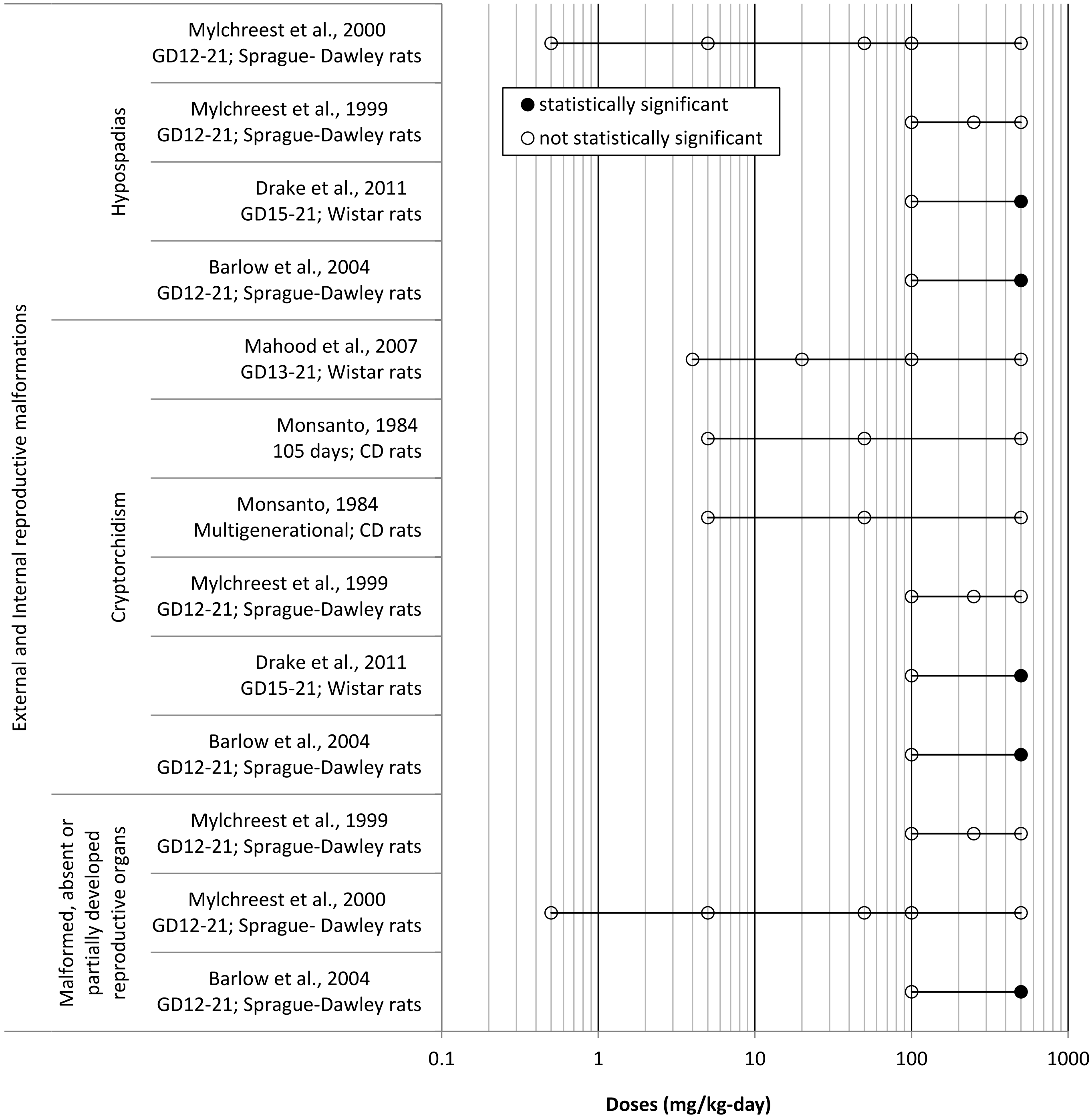


Figure 3-7. Exposure-response array of male reproductive toxicity following oral exposure to DBP: external and internal reproductive malformations in animals.

Table 3-22. Evidence pertaining to male reproductive toxicity following oral exposure to DBP: alterations in male reproductive puberty effects and indicators of reproductive development.

Reference and study design	Results					
Changes in anogenital distance						
Mylchreest et al. (2000) Rat (Sprague-Dawley); 11-20 dams/ group; AGD assessed in males from 11-20 litters/group 0, 0.5, 5, 50, 100, 500 mg/kg-day Gavage GDs 12-21	*response relative to control*					
	Doses	0	0.5	5	50	100	500
	Male AGD (litter means)[a]					
	PND 1	0%	-0.3%	-1%	-3%	-3%	-12*%
Lee et al. (2004) Rat (Sprague-Dawley); 6-8 dams/ group; AGD assessed in males from 6-8 litters/group 0, 20, 200, 2,000, 10,000 ppm Diet (0, 2-3, 14-29, 148-291, 712-1,372 mg/kg-day) Diet GDs 15-20	*response relative to control*					
	Doses	0	2-3	14-29	148-291	712-1,372	
	Male AGD (litter means)					
	PND 2	0%	5%	3%	3%	-19*%	
Lee et al. (2006b) Rat (Wistar); number of treated dams not reported; AGD assessed in 16-47 males/group 0, 20, 200, 2,000, 10,000 ppm Diet (0, 2, 21, 205, 1,025 mg/kg-day)[b] Diet GD 15-PND 21	*response relative to control*					
	Doses	0	2	21	205	1,025	
	Male AGD[a]					
	PND 1	0%	-2%	-5*%	-6*%	-8*%	
	Male AGD/body weight[a]					
		0%	-1%	-3%	-4%	-3%	
Zhang et al. (2004b) Rat (Sprague-Dawley); 20 dams/group; AGD assessed in 14-16 litters/group 0, 50, 250, 500 mg/kg-day Gavage GD 1-PND 21	*response relative to control*					
	Doses	0	50	250	500		
	Male AGD (litter means)[a]					
	PND 4	0%	3%	-10*%	-24*%		
	Male AGD/body weight[a]					
		0%	4%	-3*%	-11*%		
Mylchreest et al. (1999a) Rat (Sprague-Dawley); 10 dams/ group; AGD assessed in males from 9-10 litters/group 0, 100, 250, 500 mg/kg-day Gavage GDs 12-21	*response relative to control*					
	Doses	0	100	250	500		
	Male AGD (litter means)[a]					
	PND 1	0%	-4%	-9*%	-24*%		

Reference and study design	Results			
Barlow et al. (2004)	*response relative to control*			
Rat (Sprague-Dawley); 10-11 dams/ group; AGD assessed in males from 10-11 litter/group/time-point	Doses	0	100	500
0, 100, 500 mg/kg-day	**Male AGD (litter means)[a]**			
Gavage	*PND 1*	0%	-2%	-14*%
GDs 12-21	*PND 180*	0%	-2%	-9*%
	Note: Body weight was used as a covariate for analysis.			
Johnson et al. (2011)	*response relative to control*			
Rat (F344); 5-6 dams/group; AGD assessed in males from 5-6 litters/ group	Doses	0	100	500
0, 100, 500 mg/kg-day	**Male AGD (litter means)[a]**			
Gavage	*GD 20*	0%	-3%	-18*%
GDs 12-20				
Drake et al. (2009)	*response relative to control*			
Rat (Wistar); 13-15 dams/group; 32-45 male offspring/group	Doses	0	100	500
0, 100, 500 mg/kg-day	**Male AGD in adult offspring**			
Gavage	*>12 weeks of age[a]*	0%	-7%	-17*%
GDs 13-21				
Macleod et al. (2010)	*response relative to control*			
Rat (Wistar); number of treated dams not reported; AGD assessed in 6-21 male offspring/group	Doses	0	100	500
0, 100, 500 mg/kg-day	**Male AGD**			
Gavage	*PND 25[a]*	0%	-2%	-25*%
GDs 13-21				
Martino-Andrade et al. (2009)	*response relative to control*			
Rat (Wistar); 7-9 dams/group; AGD assessed in 7-9 litters/group (27-37 male fetuses/group)	Doses	0	100	500
0, 100, 500 mg/kg-day	**Male AGD (litter means)**			
Gavage	*GD 21*	0%	-9%	-12*%
GDs 13-21	**Male AGD/body weight$^{1/3}$**			
	GD 21	0%	-8*%	-12*%
Heger et al. (2012)	*response relative to control*			
Mouse (CD-1); 5 dams/group	Doses		0	500
0, 500 mg/kg-day	**Male AGD (litter means)[b]**			
Gavage	*PND 3*		0%	-2%
GDs 14-18				
DBP-induced changes in AGD in exposed sexually immature animals				

Reference and study design	Results							
Moody et al. (2013) Mouse (C57Bl/6J); 3-10 four day old males/group 0, 5, 10, 50, 100, 250, 500 mg/kg-day from PNDs 4-14; 0, 1, 10, 100, 500 mg/kg-day from PNDs 4-14 Gavage PNDs 4-14, PNDs 4-21	*response relative to control*							
	Doses	0	1	10	50	100	250	500
	AGD measurements *(PND 14)*							
		0%	-12%	-13%	-17*%	-14*%	-13%	-29*%
	AGD - relative to body weight							
		0%	-7%	-4%	-12%	-5%	-13%	-22*%
	AGD - relative to trunk length							
		0%	-12*%	-13*%	-15*%	-13*%	-13*%	-27*%
	AGD measurements in Adults *(PND 56 after exposure from PNDs 4-21)*							
		0%	-17*%	-14*%	-	-14*%	-	-18*%
	AGD - relative to body weight							
		0%	-21*%	-9%	-	-7%	-	-17*%
	AGD - relative to trunk length							
		0%	-22*%	-14*%	-	-14*%	-	-16*%
Nipple retention								
Mylchreest et al. (2000) Rat (Sprague-Dawley); 11-20 dams/group; nipple retention assessed in males from 11-20 litters/group 0, 0.5, 5, 50, 100, 500 mg/kg-day Gavage GDs 12-21	*response relative to control*							
	Doses	0	0.5	5	50	100	500	
	Presence of nipples in males *(PND 14)*							
	Litter incidence	5/19	5/20	8/19	10/20	16/20*	11/11*	
	Percent	26%	25%	42%	50%	80*%	100*%	
	Note: Body weight was used as a covariate for analysis.							
Lee et al. (2004) Rat (Sprague-Dawley); 6-8 litters/ group; nipple retention assessed in males from 6-8 litters/ group (29-36 male offspring/group) 0, 20, 200, 2,000, 10,000 ppm Diet (0, 2-3, 14-29, 148-291, 712-1,372) mg/kg-day Diet GD 15-PND 21	*response relative to control*							
	Doses	0	2-3	14-29	148-291	712-1,372		
	Percent of male pups with nipple retention *(PND 14)*							
		0%	4%	13%	15%	100*%		
	Note: The litter was the unit of statistical comparison.							
Mylchreest et al. (1999a) Rat (Sprague-Dawley); 10 dams/ group; nipple retention assessed in males from 9-10 litters/group (54-62 male offspring/group)	Doses	0	100	250	500			
	Presence of nipples in males *PND 14*							
	Litter incidence	0/10	0/9	5/10	8/9			
	Percent	0%	0%	50%	89%			

Reference and study design	Results					
0, 100, 250, 500 mg/kg-day Gavage GDs 12-21	Note: Statistical analysis was not performed by study authors.					
Barlow et al. (2004) Rat (Sprague-Dawley); 10-11 dams/ group; nipple retention was assessed in males from 10-11 litters/group/ time-point 0, 100, 500 mg/kg-day Gavage GDs 12-21	*response relative to control*					
	Doses	0	100	500		
	Areolae (PND 13) or nipples (PND 180) per male (litter means)[a] *Fold change relative to controls*					
	PND 13	0%	57*%	438*%		
	PND 180	0%	79%	7,476*%		
Martino-Andrade et al. (2009) Rat (Wistar); 4-7 dams/group; nipple retention evaluated in 4-7 litters/ group (8-31 male offspring/group) 0, 100, 500 mg/kg-day Gavage GDs 13-21	Doses	0	100	500		
	Presence of nipples in males *(PND 13)*					
	Litter incidence	2/7	2/7	4/4		
	Percent	29%	29%	100%		
Changes in penis length						
Drake et al. (2009) Rat (Wistar); 13-15 dams/group; 12-33 male offspring/group 0, 100, 500 mg/kg-day Gavage GDs 13-21	*response relative to control*					
	Doses	0	100	500		
	Penis length in adult offspring					
	>12 weeks of age[a]	0%	-3%	-15*%		
Macleod et al. (2010) Rat (Wistar); number of treated dams not reported; penis length assessed in 6-21 male offspring/group 0, 100, 500 mg/kg-day Gavage GDs 13-21	*response relative to control*					
	Doses	0	100	500		
	Penis length[a]					
	PND 25	0%	-3%	-9*%		
Changes in mean age at preputial separation (days)						
Mylchreest et al. (1999b) Rat (Sprague-Dawley); 10 dams/ group 0, 100, 250, 500 mg/kg-day Gavage GDs 12-21	*response relative to control*					
	Doses	0	0.5	5	50	100	500
	Day of preputial separation (litter means)						
		0%	-1%	-2%	-2%	0%	0%

Reference and study design	Results
Lee et al. (2004) Rat (Sprague-Dawley); 6-8 dams/group 0, 2-3, 14-29, 148-291, 712-1,372 mg/kg-day Diet GD 15-PND 21	*response relative to control* Doses: 0 / 2-3 / 14-29 / 148-291 / 712-1,372 **Day of preputial separation** 0% / -2% / -3*% / -1% / 1%
Salazar et al. (2004) Rat (Long-Evans); 15 dams/group; number of male offspring assessed was not reported 0, 610, 2,500 ppm in diet (0, 12, 50 mg/kg-day) Diet Dams: 2.5 months pre-mating-PND 22; Pups: PND 22-PNW 12	*response relative to control* Doses: 0 / 12 / 50 **Day of preputial separation[a]** 0% / 3% / 11*% Note: Details on dose estimation in mg/kg-day were not provided by the study authors. The unit of statistical comparison (e.g. litter or individual pup) was not reported.
Mylchreest et al. (1999a) Rat (Sprague-Dawley); 10 dams/group; PPS assessed in males from 9-10 litters/group 0, 100, 250, 500 mg/kg-day Gavage GDs 12-21	*response relative to control* Doses: 0 / 100 / 250 / 500 **Day of preputial separation (litter means)** 0% / 5*% / 4% / 9*% Note: The litter was the statistical unit of comparison.
Changes in Testis Descent	
Ahmad et al. (2014) Rat (Strain not specified); assessed in male offspring; sample size not reported 0, 2, 10, 50 mg/kg-day Gavage GD 14 to Parturition	*response relative to control* Doses: 0 / 2 / 10 / 50 **Day of testis descent** *PND 75*: 0% / -0% / 1% / 2%

[a]Values reported by the study authors were estimated from published graphs using "Grab It!", a Microsoft Excel based free software application used to digitize data from image files. Publisher: datatrendsoftware.com.
[b]Numbers of pregnant rats treated were not reported. In the absence of reporting of average daily intakes or body weights of the dams, respective average daily intakes were estimated using U.S. EPA RfVs for female Wistar rat body weight (0.156 kg) and food intake (0.016 kg/day) as 0, 2.1, 21, 205, and 1,025 mg/kg-day. Dose calculation for the 20 ppm group: (20 mg/kg × 0.016 kg/day)/0.156 kg = 2.1 mg/kg-day.
*Statistically different from controls ($p < 0.05$), as reported by study authors.

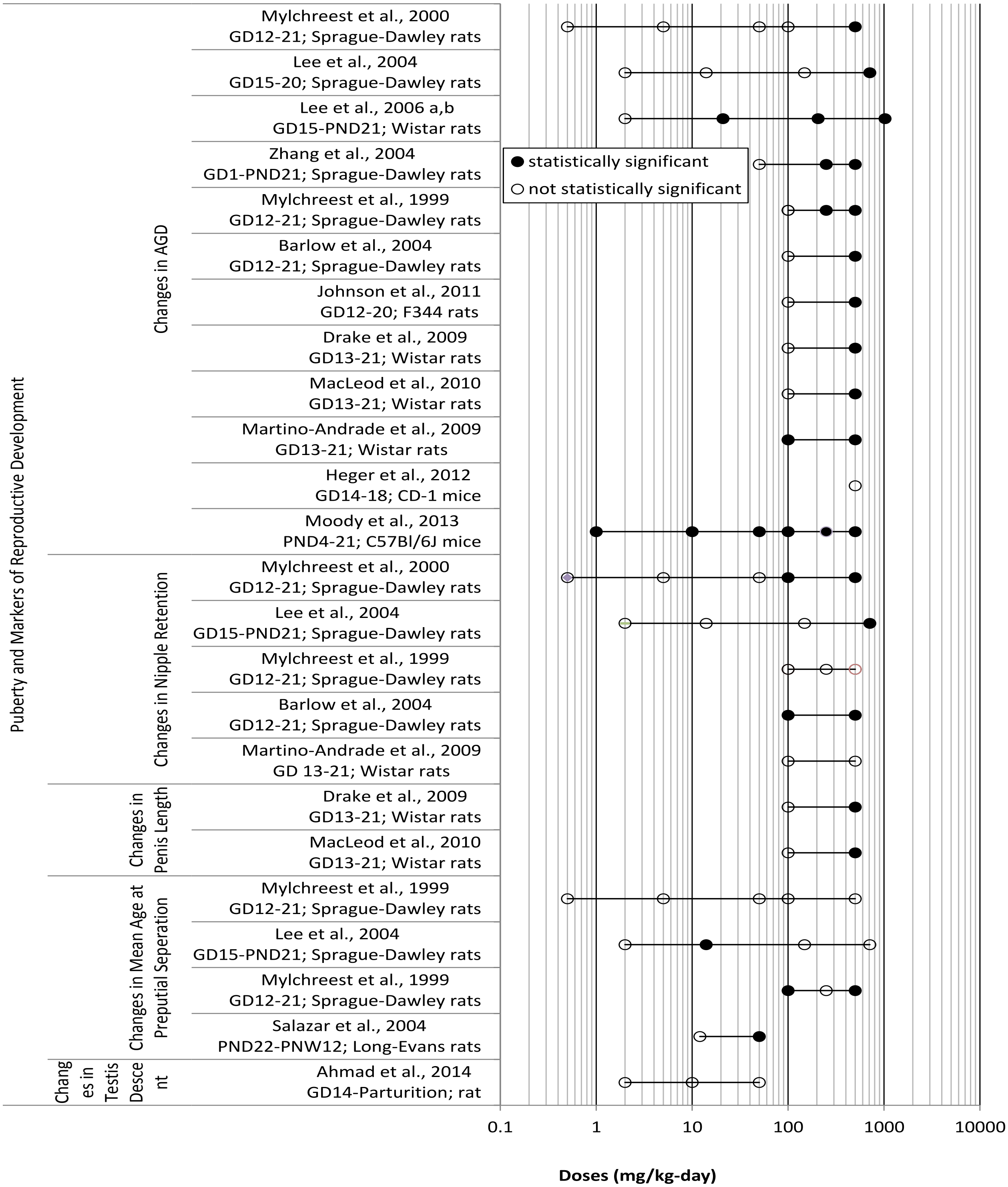


Figure 3-8. Exposure-response array of male reproductive toxicity following oral exposure to DBP: effects on puberty and markers of reproductive development.

Table 3-23. Evidence pertaining to male reproductive toxicity following oral exposure to DBP: alterations in testosterone concentration/ production in animals

Reference and study design	Results								
DBP-induced effects on testosterone levels or production after gestational exposure									
Lehmann et al. (2004) Rat (Sprague-Dawley); 5-7 dams/group; testosterone measured in 3-4 male fetuses from 1-4 litters/ group 0, 0.1, 1, 10, 30, 50, 100, 500 mg/kg-day Gavage GDs 12-19	*response relative to control*								
	Doses	0	0.1	1	10	30	50	100	500
	Testicular T concentration								
	GD 19	0%	10%	0%	-2%	-26%	-61*%	-69*%	-93*%
Johnson et al. (2007) Rat (Sprague-Dawley);3-5 dams/group; testosterone measured in 2 male fetuses/litter 0, 1, 10, 100, 500 mg/kg-day Gavage Single exposure on GD 19 (dams sacrificed 1, 3, or 6 hours post-exposure)	*response relative to control*								
	Doses	0	1	10	100	500			
	Testicular T concentration[a] *(GD 19)*								
	1 hour	0%	-13%	-33%	-13	-61*%			
	3 hour	0%	61%	67*%	9	-21%			
	6 hour	0%	11%	-29%	-14	-50%			
Lee et al. (2006b) Rat (Wistar); number of treated dams not reported; AGD assessed in 16-47 males/group 0, 20, 200, 2,000, 10,000 ppm Diet: (0, 2, 21, 205, 1,025 mg/kg-day)[b] Diet GD 15-PND 21	*response relative to control*								
	Doses	0	2	21	205	1,025			
	Serum T concentration in pups *(PND 7)*[a]								
	Males	0%	15%	59%	15%	-3%			
	Females	0%	-15%	-35%	-29%	-15%			
Mahood et al. (2007) Rat (Wistar); 4-6 dams/group; testosterone measured in 4-6 litters/ group 0, 4, 20, 100, 500 mg/kg-day Gavage GDs 13-20	*response relative to control*								
	Doses	0	4	20	100	500			
	Testicular T concentration[a]								
	GD 21	0%	3%	-2%	-14*	-31*%			
	Note: The litter was the unit of statistical comparison.								
Shirai et al. (2013) Rat (Sprague-Dawley); 4 males/group, 20 litters/ group 0, 10, 30, 50, 100 mg/kg-day	*response relative to control*								
	Doses	0	10	30	50	100			
	Serum testosterone[a]								
	PND 35	0%	-2%	-5%	-2%	-94*%			

Reference and study design	Results						
Gavage PNDs 12-21	*PND 49*	0%	1%	-7%	-2%	-92*%	
	PND 63	0%	1%	1%	3%	-84*%	
	PND 98	0%	2%	14%	7%	-72*%	
	PND 119	0%	-14%	1%	-3%	-64*%	
van Den Driesche et al. (2012) Rat (Wistar); 3 dams/group; testosterone measured in 4-21 male fetuses/group 0, 20, 100, 500 mg/kg-day Gavage GDs 13-21	*response relative to control*						
	Doses	0	20	100	500		
	Testicular T concentration[a]						
	GD 21	0%	-4%	-59*%	-86*%		
Howdeshell et al. (2008) Rat (Sprague-Dawley); 3-4 dams/group; testosterone measured in 3-4 litters/group (9-12 male fetuses/group) 0, 33, 50, 100, 300, 600 mg/kg-day Gavage GDs 8-18	*response relative to control*						
	Doses	0	33	50	100	300	600
	Testicular T production						
	GD 18	0%	-6%	-22%	-16%	-34*%	-67*%
	Note: The litter was the unit of statistical comparison.						
Clewell et al. (2009) Rat (Sprague-Dawley); 4 dams/group/ time-point; testosterone measured in 3-4 litters/group (fetal tissue pooled by litter) 0, 48, 89, 502 mg/kg-day Gavage GDs 12-19; for the testosterone measurements, dams were sacrificed at 0.5, 12, 24 and 48 hours after the final dose	*response relative to control*						
	Doses	0	48	89	502		
	Testicular T concentration at 0.5 hours post treatment[a]						
		0%	-17%	-41*%	-75*%		
	Testicular T concentration at 24 hours post treatment[a]						
		0%	-36%	-14%	-81*%		
	Testicular T concentration at 48 hours post treatment[a]						
		0%	NA	45*%	-45%		
	Note: The litter was the unit of statistical comparison.						
Martino-Andrade et al. (2009) Rat (Wistar); 7-8 dams/group; testosterone measured in 7-8 litters/ group (11-12 male fetuses/dose) 0, 100, 500 mg/kg-day Gavage GDs 13-21	*response relative to control*						
	Doses	0	100	500			
	Testicular T concentration						
	GD 21	0%	-30%	-63*%			
	Note: The litter was the unit of statistical comparison.						

Reference and study design	Results			
Johnson et al. (2011) Rat (F344); 5-6 dams/group; testosterone measured in 5-6 litters/ group (pooled samples from 2 male fetuses/litter) 0, 100, 500 mg/kg-day Gavage GDs 12-20	*response relative to control*			
	Doses	0	100	500
	Testicular T concentration[a]			
	GD 20	0%	-26%	-91*%
Kuhl et al. (2007b) Rat (Sprague-Dawley); 10 dams/group; testosterone measured in 8 male fetuses/group 0, 100, 500 mg/kg-day Gavage GD 18; dams were sacrificed 24 hours after the final dose	*response relative to control*			
	Doses	0	100	500
	Testicular T concentration[a]			
	GD 19	0%	-76*%	-86*%
Kuhl et al. (2007a) Rat (Sprague-Dawley); 10 dams/group; testosterone measured in 8 male fetuses/group 0, 100, 500 mg/kg-day Gavage GD 18; dams were sacrificed 24 hours after the final dose	*response relative to control*			
	Doses	0	100	500
	Testicular T concentration[a]			
		0%	-30%	-85*%
	Note: Study authors report that T was decreased by 85% in animals exposed to 500 mg/kg-day DBP. Percent change in the low dose group was estimated from digitized image[a]			
Drake et al. (2009) Rat (Wistar); 13-15 dams/group; testosterone measured in 32-45 male offspring/group 0, 100, 500 mg/kg-day Gavage GDs 13-21	*response relative to control*			
	Doses	0	100	500
	Serum T concentration in adults			
	>12 weeks[a]	0%	69*%	23%
Gaido et al. (2007) Mouse (C57Bl/6J); 5-6 litters/group 0, 1,500 mg/kg-day Gavage GDs 14-16	*response relative to control*			
	Doses	0		1,500
	Testicular T concentration			
	GD 17	0%		68%

Reference and study design	Results						
DBP-induced effects on testosterone levels or production after exposure in sexually immature animals							
Bao et al. (2011) Rat (Sprague-Dawley); 5-week old males, 20/group 0, 0.1, 1, 10, 100, 500 mg/kg-day Gavage 30 days	*response relative to control*						
	Doses	0	0.1	1	10	100	500
	Serum testosterone						
		0%	8%	31%	-10%	-19%	-49*%
Moody et al. (2013) Mouse (C57Bl/6J); 4-10 four day old males/group 0, 10, 100, 250, 500 mg/kg-day Gavage PNDs 4-14	*response relative to control*						
	Doses	0	10	100	250	500	
	Serum testosterone						
	PND 14	0%	36%	-6%	-37%	-52*%	
Zheng et al. (2010) Rat (Sprague-Dawley); 6 week-old males; 8/group/time-point 0, 50, 250 mg/kg-day Gavage 30 or 90 days	*response relative to control*						
	Doses	0	50	250			
	Decreased testicular testosterone concentration[a]						
	30 days	0%	-3%	-30*%			
	90 days	0%	-20*%	-51*%			

NA = Not available

[a]Values reported by the study authors were estimated from published graphs using “Grab It!”, a Microsoft Excel based free software application used to digitize data from image files. Publisher: datatrendsoftware.com.

[b]Numbers of pregnant rats treated were not reported. In the absence of reporting of average daily intakes or body weights of the dams, respective average daily intakes were estimated using U.S. EPA RfVs for female Wistar rat body weight (0.156 kg) and food intake (0.016 kg/day) as 0, 2.1, 21, 205, and 1,025 mg/kg-day. Dose calculation for the 20 ppm group: (20 mg/kg × 0.016 kg/day)/0.156 kg = 2.1 mg/kg-day.

*Statistically different from controls ($p < 0.05$), as reported by study authors.

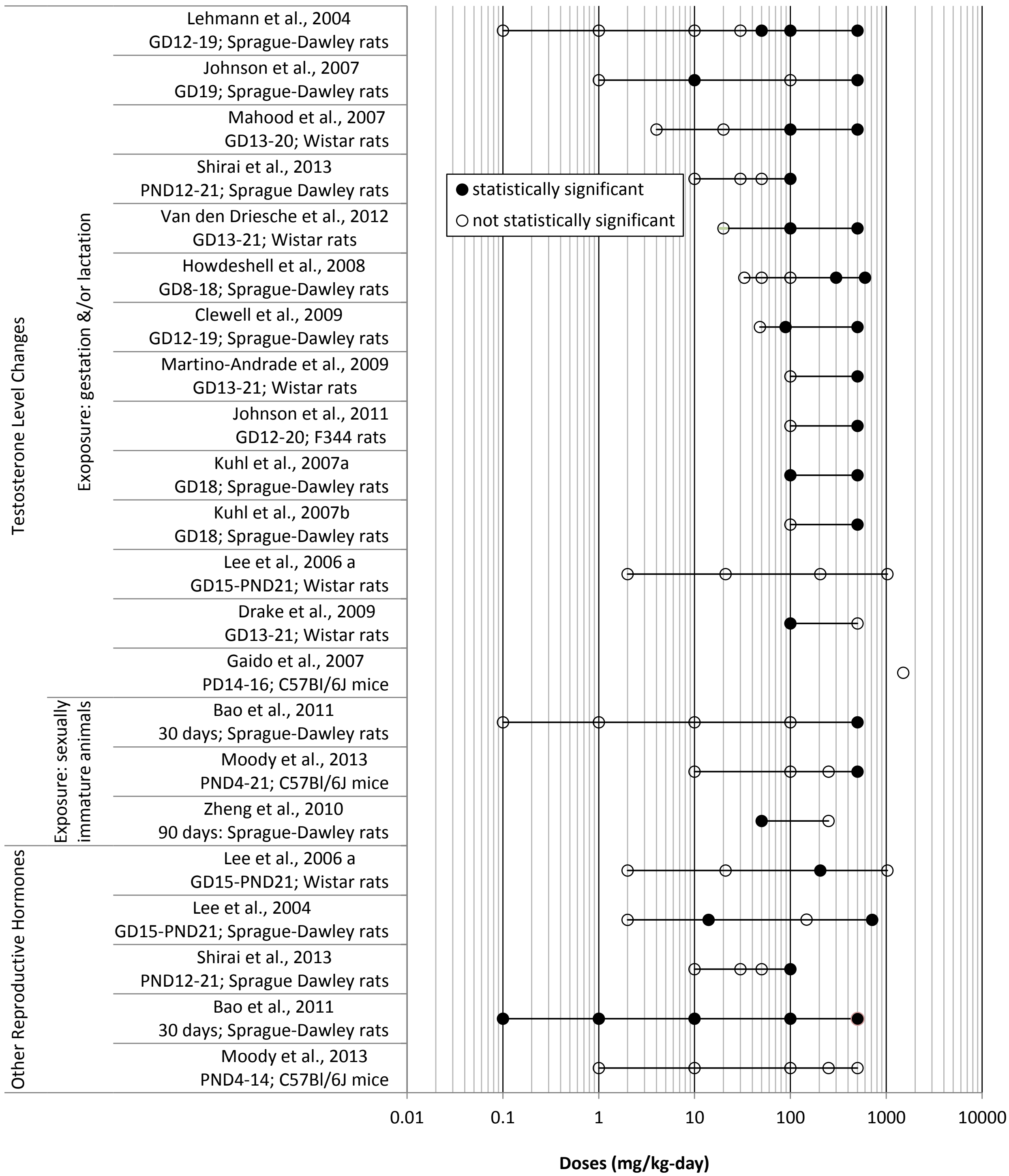


Figure 3-9. Exposure-response array of male reproductive toxicity following oral exposure to DBP: testicular or serum testosterone changes.

Table 3-24. Evidence pertaining to male reproductive toxicity following oral exposure to DBP: alterations in other reproductive hormones in animals

Reference and study design	Results					
Lee et al. (2006b) Rat (Wistar); number of treated dams not reported; AGD assessed in 16-47 males/group 0, 20, 200, 2,000, 10,000 ppm Diet (0, 2, 21, 205, 1,025 mg/kg-day)[b] Diet GD 15-PND 21	*response relative to control*					
	Doses	0	2	21	205	1,025
	Serum E_2 concentration in pups *(PND 7)*[a]					
	M	0%	7%	-1%	-28%	-52%
	F	0%	3%	-11%	-69*%	-44%
Lee et al. (2004) Rat (Sprague-Dawley); 6-8 dams/group; assessed in 8-10 male offspring/group (including ≥1 male/litter) 0, 20, 200, 2,000, 10,000 ppm Diet (0,2-3, 14-29,148-291, 712-1,372 mg/kg-day) Diet GD 15-PND 21	*response relative to control*					
	Doses	0	2-3	14-29	148-291	712-1,372
	Follicle stimulating hormone (FSH) positive cells in anterior pituitary of pups[a] *(PND 21)*					
	M	0%	-6%	-7%	-2%	-10*%
	F	0%	-6%	-17*%	-13*%	-7*%
	Follicle stimulating hormone (FSH) positive cells in anterior pituitary of pups[a] *(PND 77)*					
	M	0%	11%	-7%	9%	15*%
	F	0%	6%	3%	3%	58*%
	Luteinizing hormone (LH) positive cells in anterior pituitary of pups[a] *(PND 21)*					
	M	0%	-4%	1%	6%	23*%
	F	0%	6%	3%	24*%	31*%
	Luteinizing hormone (LH) positive cells in anterior pituitary of pups[a] *(PND 77)*					
	M	0%	-2%	6%	1%	1%
	F	0%	8%	17%	25%	8%
	Prolactin (PRL) positive cells in anterior pituitary of pups[a] *(PND 21)*					
	M	0%	-1%	-5%	-3%	-17*%
	F	0%	1%	-8%	-5%	-19*%
	Prolactin (PRL) positive cells in anterior pituitary of pups[a] *(PND 77)*					
	M	0%	-6%	-7%	-2%	5%
	F	0%	6%	-2%	-1%	4%
	Note: Doses represent a range estimated by the study authors for three different time periods (GDs 15-20, PNDs 2-10, and PNDs 10-21).					
	response relative to control					
	Doses	0	10	30	50	100

Reference and study design	Results					
Shirai et al. (2013) Rat (Sprague-Dawley); 4 males/group, 20 litters/ group 0, 10, 30, 50, 100 mg/kg-day Gavage PNDs 12-21	**Serum Luteinizing hormone[a]**					
	PND 35	0%	-7%	5%	0%	-42*%
	PND 49	0%	-3%	-3%	-6%	-40*%
	PND 63	0%	2%	-2%	-2%	41*%
	PND 98	0%	-5%	-2%	-3%	19*%
	PND 119	0%	0%	1%	3%	19*%
DBP-induced effects on the levels or production of other reproductive hormones in exposed sexually immature animals						
Bao et al. (2011) Rat (Sprague-Dawley); 5-week old males, 20/group 0, 0.1, 1, 10, 100, 500 mg/kg-day Gavage 30 days	*response relative to control*					
	Doses	0	0.1	1	10	100	500
	Serum E_2					
		0%	54*%	37%	10%	-26%	84*%
	Serum LH					
		0%	18*%	11%	30*%	-50*%	-60*%
	Serum FSH					
		0%	20%	59*%	55*%	35*%	61*%
Moody et al. (2013) Mouse (C57Bl/6J); 4-10 four day old males/group 0, 1, 10, 100, 500 mg/kg-day from PNDs 4-7; 0, 10, 100, 250, 500 mg/kg-day from PNDs 4-14; 0, 100, 250, 500 mg/kg-day from PNDs 4-14 Gavage PNDs 4-7, PNDs 4-14	*response relative to control*					
	Doses	0	1	10	100	250	500
	Serum FSH					
	PND 7	0%	7%	7%	19%	-	20%
	Serum FSH					
	PND 14	0%	-	-6%	9%	2%	26%
	Serum Inhibin-alpha					
	PND 14	0%	-	-	-2%	7%	221%
	Serum Inhibin-alpha/testis weight					
	PND 14	0%	-	-	28%	34%	137%

[a]Values reported by the study authors were estimated from published graphs using “Grab It!”, a Microsoft Excel based free software application used to digitize data from image files. Publisher: datatrendsoftware.com.

[b]Numbers of pregnant rats treated were not reported. In the absence of reporting of average daily intakes or body weights of the dams, respective average daily intakes were estimated using U.S. EPA RfVs for female Wistar rat body weight (0.156 kg) and food intake (0.016 kg/day) as 0, 2.1, 21, 205, and 1,025 mg/kg-day. Dose calculation for the 20 ppm group: (20 mg/kg × 0.016 kg/day)/0.156 kg = 2.1 mg/kg-day.

*Statistically different from controls ($p < 0.05$), as reported by study authors.

Table 3-25. Evidence pertaining to male reproductive toxicity following oral exposure to DBP: alterations in sperm and fertility measures in animals

Reference and study design	Results					
Sperm measures after gestational exposure						
Lee et al. (2004) Rat (Sprague-Dawley); 6-8 dams/ group; spermatocyte/germ cell development assessed in 8-10 male offspring/group/time-point 0, 20, 200, 2,000, 10,000 ppm Diet (0,2-3, 14-29,148-291, 712-1,372 mg/kg-day) Diet GD 15-PND 21	*response relative to control*					
	Doses	0	2-3	14-29	148-291	712-1,372
	Reduced spermatocyte development *(PND 21)*					
	Incidence	0/8	4/8*	4/8*	8/8*	8/8*
	Percent	0%	50*%	50*%	100*%	100*%
	Loss of germ cell development *(PND 77)*					
	Incidence	0/8	0/8	1/8	4/8*	9/10*
	Percent	0%	0%	13%	50*%	90*%
	Loss of germ cell development *(PND 140)*					
	Incidence	1/10	2/10	2/8	5/10	NA
	Percent	10%	20%	25%	50%	NA
	Note: Doses represent a range estimated by the study authors for three different time periods (GDs 15-20, PNDs 2-10, and PNDs 10-21).					
Zhang et al. (2004b) Rat (Sprague-Dawley); 14-16 dams/group; sperm parameters assessed in 20 male offspring/group 0, 50, 250, 500 mg/kg-day Gavage GD 1-PND 21	*response relative to control*					
	Doses	0	50	250	500	
	Epididymal sperm measures *(PND 70)*					
	sperm number	0%	-5%	-29%	-46*%	
	% Motile	0%	-6%	-29*%	-37*%	
	% Abnormal	0%	1%	4%	-1%	
	Testis sperm measures *(PND 70)*					
	Sperm Heads/Testis	0%	-7%	-41*%	-49*%	
	Sperm Heads/g Testis	0%	-7%	-37*%	-43*%	
Martino-Andrade et al. (2009) Rat (Wistar); 4-7 dams/group; sperm parameters assessed in 4-7 litters/ group (7-12 male offspring/group) 0, 100, 500 mg/kg-day Gavage GDs 13-21	*response relative to control*					
	Doses	0	100	500		
	Number of spermatids per testis					
	PND 90	0%	-3%	11%		
	Note: The litter was the statistical unit of comparison					
Sperm measures after postnatal exposure						
Bao et al. (2011)	*response relative to control*					
	Doses	0	0.1	1	10	100	500

Reference and study design	Results						
Rat (Sprague-Dawley); 5-week old males, 20/group 0, 0.1, 1, 10, 100, 500 mg/kg-day Gavage 30 days	**Number of Spermatogonia/seminiferous tubule**[a]						
		0%	-9%	-8%	-12%	-24*%	-56*%
	Number of Spermatocytes/seminiferous tubule[a]						
		0%	0%	0%	-4%	-22*%	-53*%
	Number of Spermatids/seminiferous tubule[a]						
		0%	-4%	-2%	-4%	-16*%	-61*%
Tsutsumi et al. (2004) Rat (F344); 11-week old males, 5/group 0, 61, 255, 1,536 mg/kg-day Diet 4 weeks	*response relative to control*						
	Doses	0	61	255	1,536		
	Epididymal sperm measures						
	Sperm Number	0%	3%	14%	-8%		
	Sperm Movement	0%	2%	-5%	-21*%		
	Abnormal Sperm	0%	-0.4%	-0.2%	0.8%		
Infertility							
Mahood et al. (2007) Rat (Wistar); 3-7 dams/group; infertility assessed in 8-20 male offspring/group 0, 4, 20, 100, 500 mg/kg-day Gavage GDs 13-21	*response relative to control*						
	Doses	0	4	20	100	500	
	Male infertility *(PND 90)*						
	Incidence	1/16	2/11	1/8	5/20	15/20*	
	Percent	6%	18%	13%	25%	75*%	
	Note: Study authors report that infertility was also significantly elevated in the 500 mg/kg-day group when the litter was used as the statistical unit of comparison (p = 0.03).						

NA = Not available

[a]Values reported by the study authors were estimated from published graphs using “Grab It!”, a Microsoft Excel based free software application used to digitize data from image files. Publisher: datatrendsoftware.com.

*Statistically different from controls as reported by study authors.

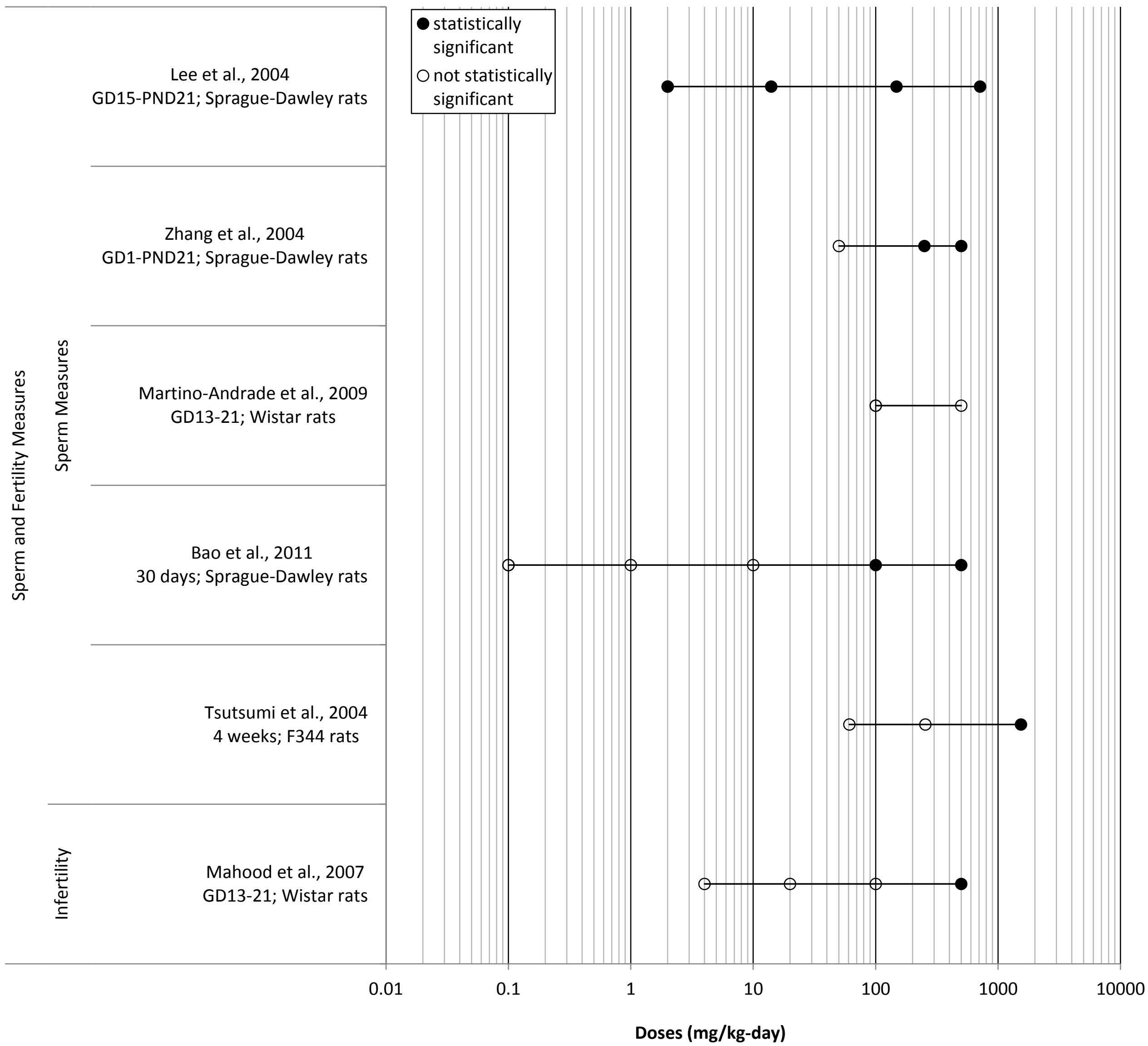


Figure 3-10. Exposure-response array of male reproductive toxicity following oral exposure to DBP: sperm changes and fertility measures.

3.3.2. Female Reproductive Effects

Table 3-26. Evidence pertaining to female reproductive toxicity following oral exposure to DBP: alterations in fertility, maternal body weight and food consumption, number of implantation sites and live pups per litter

Reference and study design	Results					
Fertility & Pregnancy Outcome						
Monsanto (1984) Rat (CD); 20 breeding pairs/group 18-20 animals evaluated [females exposed only] 0, 5, 50, 500 mg/kg-day Diet 14 days before mating and continued through weaning [PND 21]	*response relative to control* Doses	0	5	50	500	
	Percent pregnancy					
		65%	75%	72%	65%	
Salazar et al. (2004) Rat (Long Evans); 15 dams/group 0, 12, 50 mg/kg-day[a] Diet 2.5 months before mating-PND 14	*response relative to control* Doses	0	12	50		
	Percent pregnancy					
		82%	82%	58*%		
Lee et al. (2004) Rat (Sprague-Dawley); 6-8 dams/group 0, 20, 200, 2,000, 10,000 ppm Diet (0,2-3, 14-29,148-291, 712-1,372 mg/kg-day) Diet GD 15-PND 21	*response relative to control* Doses	0	2-3	14-29	148-291	712-1,372
	Gestation length					
		0%	1%	2%	0%	0%
	Notes: Doses represent a range estimated by the study authors for three different time periods (GDs 15-20, PNDs 2-10, and PNDs 10-21). Doses presented above correspond to exposure during GDs 15-20.					
Zhang et al. (2004b) Rat (Sprague-Dawley); 14-16 dams/group 0, 50, 250, 500 mg/kg-day Gavage GD 1-PND 21	*response relative to control* Doses	0	50	250	500	
	Gestation length					
		0%	1%	1%	2%	
NTP (1991) Rat (Sprague-Dawley); 10 dams/group/generation; 40 F0 control breeding pairs, 20 F1 control breeding pairs 0, 0.1, 0.5, 1% (0, 66, 320, or 651 mg/kg-day) Diet	Doses	0	66	320	651	
	Average litters per pair *Response relative to control*					
	F0	0%	4%	2%	2%	
	Mating index *Percent incidence*					
	F1	100%	95%	90%	30*%	

Reference and study design	Results
F0 exposure: 7-day pre-cohabitation; 112 day cohabitation; ~60 days post-cohabitation (continuous breeding) F1 exposure: gestation, lactation, and post-weaning through ~PND 142 Note: study authors did not specify date of necropsy for F1 animals.	**Pregnancy index** *Percent incidence* *F1* 95% 85% 85% 5*% **Fertility index** *Percent incidence* *F1* 95% 89% 94% 17*%
NTP (1995) Rat (F344/N); 24 females/dose, 48 control females 0, 1,250, 2,500, 5,000, 7,500, 10,000, 20,000 ppm (0, 138, 275, 550, 825, 1,100, 2,200 mg/kg-day)[b] Diet GD 1-PND 28	Doses 0 138 275 550 825 1,100 2,200 **Gestation index** *Percent incidence of females that delivered one live pup/sperm-positive females* 93% 79% 83% 68*% 78% 89% 21*% **Gestation length** *Response relative to controls* 0% -0.2% -1% -2*% -1% -1% 3*%
NTP (1984) Lamb et al. (1987) Lamb et al. (1997) Mouse (CD-1); 18-40 breeding pairs/group 0, 0.03, 0.3, 1% Diet (0, 170, 390, 1,400 mg/kg-day) Diet 18 weeks (1 week pre-mating, 14 weeks cohabitation, 3 weeks observation)	Doses 0 170 390 1,400 **Percent fertility** *(No. fertile/No. cohabited)×100* 100% 100% 100% 75*% **Litters per pair** *Response relative to control* 0% 3% -3% -63*%
NTP (1995) Mouse (B6C3F1); 20 females/group 0, 1,250, 2,500, 5,000, 7,500, 10,000 ppm or 20,000 (0, 244, 488, 975, 1,463, 1,950, 3,900 mg/kg-day)[c] Diet GD 1-PND 28	Doses 0 244 488 975 1,463 1,950 3,900 **Gestation index** *Percent incidence of females that delivered one live pup/sperm-positive females* 55% 53% 63% 47% 61% 25% 0*% **Gestation length** *Response relative to controls* 0% 1% 2*% 3*% 5*% 6*% 4% Note: Only one litter in the high-dose group.
Jiang et al. (2007) Rat (Wistar); 10 dams/group 0, 250, 500, 750, 1,000 mg/kg-day Gavage GDs 14-18	*response relative to control* Doses 0 250 500 750 1,000 **Gestation length** 0% 2% 1% 7% NA Note: No live pups per offspring reported in the 1,000 mg/kg-day treatment group.

Reference and study design	Results				
Gray et al. (2006) Rat (Long Evans); weanling females, 11-13/group 0, 250, 500, 750 mg/kg-day Gavage; 5 days/week: PNDs 24-~PND 110 7 days/week: ~PND 110 to GD 13 of F1b litter (F1a litter delivered ~PND 140)	*response relative to control*				
	Doses	0	250	500	750
	Percent pregnant F0 females delivering F1a litter				
		0%	-16	-85*%	-99*%
	Note: Treated females were mated to untreated males.				

Reference and study design	Results							
Ema et al. (2000) Rat (Wistar); 13 dams/group 0, 250, 500, 750, 1,000, 1,250, 1,500 mg/kg-day Gavage GDs 0-8; dams sacrificed at GD 20	Doses	0	250	500	750	1,000	1,250	1,500
	Non pregnant females *Percent incidence*							
		0%	0%	0%	0%	0%	38*%	54*%
	Number corpora lutea *Response relative to controls*							
		0%	0%	3%	3%	-1%	-1%	7%
	Number of completely resorbed litters *Percent incidence*							
		0%	0%	0%	8%	8%	0%	0%

Changes in maternal body weight gain and/or food consumption

Reference and study design	Results						
Mylchreest et al. (2000) Rat (Sprague-Dawley); 11-20 dams/group 0, 0.5, 5, 50, 100, 500 mg/kg-day Gavage GDs 12-21	*response relative to control*						
	Doses	0	0.5	5	50	100	500
	Maternal body weight gain						
	GDs 12-21	0%	-1%	1%	2%	-8%	-13%
	Maternal food consumption						
	GDs 8-19	0%	-2%	3%	3%	-4%	-1%
	Maternal food consumption						
	GD 20-PND 20	0%	3%	7%	8%	5%	-91%

Reference and study design	Results						
Lee et al. (2004) Rat (Sprague-Dawley); 6-8 dams/ group 0, 20, 200, 2,000, 10,000 ppm Diet (0,2-3, 14-29,148-291, 712-1,372 mg/kg-day) Diet GD 15-PND 21 Note: Doses represent a range estimated by the study authors for three different time periods (GDs 15-20, PNDs 2-10, and PNDs 10-21).	*response relative to control*						
	Doses	0	2-3	14-29	148-291	712-1,372	
	Maternal body weight gain						
	GDs 15-20	0%	-18*%	-2%	-7%	-21*%	
	Maternal food consumption						
	GDs 15-19	0%	-4%	-5%	-10%	7%	
	Maternal food consumption						
	PNDs 2-10	0%	5%	1%	-0.3%	-2%	
	Maternal food consumption						
	PNDs 10-21	0%	15%	9%	10%	4%	
Monsanto (1984) Rat (CD); 20 breeding pairs/group 13-17 animals evaluated [females exposed only] 0, 5, 50, 500 mg/kg-day Diet 14 days before mating and continued through weaning [PND 21]	*response relative to control*						
	Doses	0	5	50	500		
	Maternal body weight at weaning of F1 animals						
	GD 20	0%	-4%	-6*%	-7*%		
	LD 21	0%	-3%	-8%	-6%		
Salazar et al. (2004) Rat (Long Evans); 15 dams/group 0, 12, 50 mg/kg-day[a] Diet 2.5 months before mating to PND 14	*response relative to control*						
	Doses	0	12	50			
	Maternal body weight gain after 3 months of treatment						
		0%	-26%	-26%			
Howdeshell et al. (2008) Rat (Sprague-Dawley); 3-4 dams/group 0, 33, 50, 100, 300, 600 mg/kg-day Gavage GDs 8-18	*response relative to control*						
	Doses	0	33	50	100	300	600
	Maternal weight at end of experiment						
	GD 18	0%	1%	1%	6%	6%	5%
	Maternal body weight gain						
	GDs 8-18	0%	6%	-9%	6%	0.1%	-11%
Zhang et al. (2004b) Rat (Sprague-Dawley); 14-16 dams/group 0, 50, 250, 500 mg/kg-day Gavage GD 1-PND 21	*response relative to control*						
	Doses	0	50	250	500		
	Maternal body weight gain						
	GDs 1-21	0%	-6%	-6%	-12%		

<table>
<tr><th>Reference and study design</th><th colspan="8">Results</th></tr>
<tr><td rowspan="12">NTP (1991)
Rat (Sprague-Dawley); 20 breeding pairs/dose, 40 control breeding pairs
0, 0.1, 0.5, 1% (0, 66, 320, or 651 mg/kg-day)
Diet
Exposure: 7 days pre-cohabitation, 112-day cohabitation, ~60 days post-cohabitation (continuous breeding; five litters)
Note: study authors did not specify date of necropsy for F1 animals.</td><td colspan="8">response relative to control</td></tr>
<tr><td>Doses</td><td>0</td><td>66</td><td>320</td><td>651</td><td></td><td></td><td></td></tr>
<tr><td colspan="8">Maternal body weight</td></tr>
<tr><td>First litter</td><td>0%</td><td>-3%</td><td>-2%</td><td>-6*%</td><td></td><td></td><td></td></tr>
<tr><td>Second litter</td><td>0%</td><td>-4%</td><td>-3%</td><td>-8*%</td><td></td><td></td><td></td></tr>
<tr><td>Third litter</td><td>0%</td><td>-4%</td><td>-4%</td><td>-9*%</td><td></td><td></td><td></td></tr>
<tr><td>Fourth litter</td><td>0%</td><td>-4%</td><td>-5%</td><td>-12*%</td><td></td><td></td><td></td></tr>
<tr><td>Fifth litter</td><td>0%</td><td>-5%</td><td>-5%</td><td>-12*%</td><td></td><td></td><td></td></tr>
<tr><td colspan="8">Maternal food consumption</td></tr>
<tr><td>Week 17</td><td>0%</td><td>1%</td><td>-1%</td><td>-4%</td><td></td><td></td><td></td></tr>
<tr><td colspan="8">Note: Maternal food consumption was significantly decreased in high-dose females only during week 1 and week 6 of the treatment period.</td></tr>
<tr><td colspan="8"></td></tr>
<tr><td rowspan="6">Shiota et al. (1980)
Shiota and Nishimura (1982)
Mouse (ICR); 6-21 dams/group
0, 80, 180,370, 660, 2,100 mg/kg-day
Diet
GDs 0-18</td><td colspan="8">response relative to control</td></tr>
<tr><td>Doses</td><td>0</td><td>80</td><td>180</td><td>370</td><td>660</td><td>2,100</td><td></td></tr>
<tr><td colspan="8">Maternal weight</td></tr>
<tr><td>GD 18</td><td>0%</td><td>7%</td><td>-1%</td><td>0%</td><td>2%</td><td>-24*%</td><td></td></tr>
<tr><td colspan="8">Maternal food consumption</td></tr>
<tr><td>GDs 0-18</td><td>0%</td><td>11%</td><td>18%</td><td>15%</td><td>11%</td><td>15%</td><td></td></tr>
<tr><td rowspan="4">Mylchreest et al. (1999a)
Rat (Sprague-Dawley); 10 dams/group
0, 100, 250, 500 mg/kg-day
Gavage
GDs 12-21</td><td colspan="8">response relative to control</td></tr>
<tr><td>Doses</td><td>0</td><td>100</td><td>250</td><td>500</td><td></td><td></td><td></td></tr>
<tr><td colspan="8">Maternal body weight gain</td></tr>
<tr><td>GDs 0-21</td><td>0%</td><td>-8%</td><td>1%</td><td>-9%</td><td></td><td></td><td></td></tr>
<tr><td rowspan="5">Martino-Andrade et al. (2009)
Rat (Wistar); 4-8/group
0, 100, 500 mg/kg-day
Gavage
GDs 13-21
Note: One group of dams was sacrificed on GD 21, and a second group was allowed to deliver.</td><td colspan="8">response relative to control</td></tr>
<tr><td>Doses</td><td>0</td><td>100</td><td>250</td><td></td><td></td><td></td><td></td></tr>
<tr><td colspan="8">Maternal body weight gain GDs 13-21</td></tr>
<tr><td>At GD 21</td><td>0%</td><td>-15%</td><td>-32%</td><td></td><td></td><td></td><td></td></tr>
<tr><td>At delivery</td><td>0%</td><td>24%</td><td>35%</td><td></td><td></td><td></td><td></td></tr>
<tr><td rowspan="5">NTP (1995)
Mouse ($B6C3F_1$); 20 females/group
0, 1,250, 2,500, 5,000, 7,500, 10,000 ppm or 20,000 (0, 244, 488, 975, 1,463, 1,950, 3,900 mg/kg-day)
Diet</td><td colspan="8">response relative to control</td></tr>
<tr><td>Doses</td><td>0</td><td>138</td><td>275</td><td>550</td><td>825</td><td>1,100</td><td>2,200</td></tr>
<tr><td colspan="8">Maternal body weight gain</td></tr>
<tr><td>GDs 0-18</td><td>0%</td><td>-9%</td><td>3%</td><td>6%</td><td>6%</td><td>12%</td><td>-36*%</td></tr>
<tr><td>LDs 0-28</td><td>0%</td><td>-31%</td><td>0%</td><td>-63%</td><td>-38%</td><td>88%</td><td>NA</td></tr>
</table>

Reference and study design	Results							
GD 1-PND 28	Note: There were no high-dose dams or litters at PND 1.							
Mylchreest et al. (1998) Rat (Sprague-Dawley); 10 dams/group 0, 250, 500, 750 mg/kg-day Gavage GD 3-PND 20 (2-day interruption at parturition, PNDs 1-2)	*response relative to control*							
	Doses	0	250	500	750			
	Maternal body weight							
	GDs 0-6 (n = 7-10)	0%	-1%	-2%	-6%			
	GDs 7-13 (n = 6-10)	0%	-1%	-2%	-7%			
	GDs 14-20 (n = 4-10)	0%	-0.1%	-2%	-7%			
	PNDs 1-7 (n = 4-9)	0%	2%	-4%	-6%			
	PNDs 8-14 (n = 4-9)	0%	1%	-4%	-5%			
	PNDs 15-21 (n= 4-9)	0%	1%	-3%	-5%			
	Maternal food consumption							
	GDs 0-6 (n = 7-10)	0%	0%	-9%	-2%			
	GDs 7-13 (n = 6-10)	0%	3%	-2%	-1%			
	GDs 14-20 (n= 4-10)	0%	-0.4%	-4%	-6%			
	PNDs 1-7 (n = 4-9)	0%	8%	-8%	-21%			
	PNDs 15-21 (n =4-9)	0%	32%	37%	7%			
Jiang et al. (2007) Rat (Sprague-Dawley); 10 dams/group 0, 250, 500, 750, 1,000 mg/kg-day Gavage GDs 14-18	*response relative to control*							
	Doses	0	250	500	750	1,000		
	Maternal body weight gain							
	GDs 14-18	0%	-3%	-5%	-17*%	-73*%		
	GDs 18-20	0%	-3%	2%	-19*%	-88*%		
Ema et al. (2000) Rat (Wistar); 13 dams/group 0, 250, 500, 750, 1,000, 1,250, 1,500 mg/kg-day Gavage GDs 0-8; dams sacrificed at GD 20	*response relative to control*							
	Doses	0	250	500	750	1,000	1,250	1,500
	Maternal body weight gain							
	0-9	0%	27%	-120*%	-207*%	-253*%	-280*%	-187*%
	9-20	0%	9%	15%	11%	-5%	-22%	-40*%
		0%	21%	18%	11%	-7%	-39%	-21%
	Maternal food consumption							
	0-9	0%	3%	-41*%	-56*%	-56*%	-55*%	-44*%
	9-20	0%	2%	9%	9%	9%	-2%	6%
	Note: Adjusted for uterine weight in pregnant animals.							
Gray et al. (2006) (Study 2) Rat (Long Evans); weanling females, 11-13/group	*response relative to control*							
	Doses	0	250	500	750			
	Maternal body weight							

Reference and study design	Results
0, 250, 500, 750 mg/kg-day Gavage 5 days/week: PNDs 24-~PND 110 7 days/week: ~PND 110 to GD 13 of F1b litter (F1a litter delivered at PND 140; F1A delivered at 170 days of age) Note: treated females mated to untreated males	*At GD 13 of F1a litter* 0% 1% -1% 7% *At delivery of F1b litter* 0% 2% 5% -1% Note: Body weights were only measured in F0 females pregnant at necropsy (number not provided by study authors).
Changes in number of implantation sites	
[Mylchreest et al. (2000)](#) Rat (Sprague-Dawley); 11-20 dams/group 0, 0.5, 5, 50, 100, 500 mg/kg-day Gavage GDs 12-21	*response relative to control* Doses: 0 / 0.5 / 5 / 50 / 100 / 500 **Implantation sites per litter** 0% / -2% / -4% / 1% / -4% / -12%
[Monsanto (1984)](#) Rat (CD); 20 breeding pairs/group; 13-15 resulting litters [females exposed only] 0, 5, 50, 500 mg/kg-day Diet 14 days before mating and continued through weaning [PND 21]	*response relative to control* Doses: 0 / 5 / 50 / 500 **Number implantation sites** 0% / 25% / -5% / -2%
[Howdeshell et al. (2008)](#) Rat (Sprague-Dawley); 4 dams/group 0, 33, 50, 100, 300, 600 mg/kg-day Gavage GDs 8-18	*response relative to control* Doses: 0 / 33 / 50 / 100 / 300 / 600 **Number of implantations** 0% / -18% / -1% / -5% / -18% / 4%
[Shiota et al. (1980)](#) [Shiota and Nishimura (1982)](#) Mouse (ICR); 6-21 dams/group 0, 80, 180, 370, 660, 2,100 mg/kg-day Diet GDs 0-18	*response relative to control* Doses: 0 / 80 / 180 / 370 / 660 / 2,100 **Number of implants per litter** 0% / 18% / 11% / 15% / 11% / 12%
[Mylchreest et al. (1999a)](#) Rat (Sprague-Dawley); 10 dams/group	*response relative to control* Doses: 0 / 100 / 250 / 500 **Implantation sites per litter**

Reference and study design	Results							
0, 100, 250, 500 mg/kg-day Gavage GDs 12-21		0%	0%	1%	-8%			
Mylchreest et al. (1998) Rat (Sprague-Dawley); 10 dams/group 0, 250, 500, 750 mg/kg-day Gavage GD 3-PND 20 (2-day interruption at parturition, PNDs 1-2)	*response relative to control*							
	Doses	0	250	500	750			
	Implantation sites per litter							
		0%	-6%	10%	1%			
Ema et al. (2000) Rat (Wistar); 13 dams/group 0, 250, 500, 750, 1,000, 1,250, 1,500 mg/kg-day Gavage GDs 0-8; dams sacrificed at GD 20	*response relative to control*							
	Doses	0	250	500	750	1,000	1,250	1,500
	Implantation sites							
	Per female	0%	-1%	0%	-7%	-10%	-41*%	-57*%
	Per litter	0%	-1%	0%	-7%	-10%	-5%	-8%
Changes in number of live pups per litter								
Mylchreest et al. (2000) Rat (Sprague-Dawley); 11-20 dams/group 0, 0.5, 5, 50, 100, 500 mg/kg-day Gavage GDs 12-21	*response relative to control*							
	Doses	0	0.5	5	50	100	500	
	Live pups per litter							
		0%	-4%	-7%	-1%	-6%	-14%	
Lee et al. (2004) Rat (Sprague-Dawley); 6-8/group 0, 20, 200, 2,000, 10,000 ppm Diet (0,2-3, 14-29,148-291, 712-1,372 mg/kg-day) Diet GD 15-PND 21 Note: Doses represent a range estimated by the study authors for three different time periods (GDs 15-20, PNDs 2-10, and PNDs 10-21).	*response relative to control*							
	Doses	0	2	14	148	712		
	Live pups per litter							
		0%	-17%	3%	-7%	-4%		
	Note: Intake reported for GDs 15-20.							
	response relative to control							
	Doses	0	5	50	500			
	Number of pups delivered							
		0%	32%	-1%	0%			
	Live pups							
		0%	21%	22%	-2%			

Reference and study design	Results					
Monsanto (1984) Rat (CD); 20 breeding pairs/group 13-15 resulting litters [females exposed only] 0, 5, 50, 500 mg/kg-day Diet 14 days before mating and continued through weaning [PND 21]	**Dead pups**					
		0%	0%	100%	100%	
	Pup survival to PND 21					
		100%	100%	100%	100%	
Salazar et al. (2004) Rat (Long Evans); 15 dams/group 0, 12, 50 mg/kg-day[a] Diet Dams: 2.5 months before mating to PND 22; Pups: Pups: PND 22-PNW 12	Doses	0	12	50		
	Litter size (number of animals/litter) *Response relative to controls*					
		0%	3%	-7%		
	Pup survival *Percent incidence*					
		72%	60%	71%		
Howdeshell et al. (2008) Rat (Sprague-Dawley); 4 dams/group 0, 33, 50, 100, 300, 600 mg/kg-day Gavage GDs 8-18	Doses	0	33	50	100	300	600
	Percent Fetal mortality *Resorptions/implantations*					
		2%	3%	3%	4%	4%	10%
	Number of live fetuses per litter *Response relative to controls*					
		0%	-14%	-2%	-6%	-21%	-3%
Zhang et al. (2004b) Rat (Sprague-Dawley); 14-16 dams/group 0, 50, 250, 500 mg/kg-day Gavage GD 1-PND 21	*response relative to control*					
	Doses	0	50	250	500	
	Live pups per litter					
		0%	1%	0%	-14*%	
NTP (1991) Rat (Sprague-Dawley); 20 breeding pairs/dose/generation; 40 control F0 breeding pairs, 20 control F1 breeding pairs 0, 0.1, 0.5, 1% (0, 66, 320, or 651 mg/kg-day) Diet F0 exposure: 7-day pre-cohabitation, 112-day cohabitation, ~60 days post-cohabitation (continuous breeding) F1 exposure: gestation, lactation, and post-weaning through ~PND 142	*response relative to control*					
	Doses	0	66	320	651	
	Live F1 pups per litter					
	M	0%	-8%	-11*%	-25*%	
	F	0%	-8%	-17*%	-9*%	
	Combined	0%	-8*%	-15*%	-17*%	
	Live F2 pups per litter					
	M	0%	6%	-17%	-15%	
	F	0%	-12%	-1%	1%	
	Combined	0%	11%	-9%	-7%	

<table>
<tr><th>Reference and study design</th><th>Results</th></tr>
<tr><td>Note: study authors did not specify date of necropsy for F1 animals.</td><td>Note: Only one F2 litter was produced in the high-dose group.</td></tr>
<tr><td>Shiota et al. (1980)
Shiota and Nishimura (1982)
Mouse (ICR); 6-21 dams/group
0, 80, 180, 350, 660, 2,100 mg/kg-day
Diet
GDs 0-18</td><td><table>
<tr><td colspan="7">response relative to control</td></tr>
<tr><td>Doses</td><td>0</td><td>80</td><td>180</td><td>30</td><td>660</td><td>2,100</td></tr>
<tr><td colspan="7">Resorptions and dead fetuses</td></tr>
<tr><td></td><td>5%</td><td>4%</td><td>11%</td><td>22%</td><td>11%</td><td>98*%</td></tr>
</table></td></tr>
<tr><td>Mylchreest et al. (1999a)
Rat (Sprague-Dawley); 10 dams/group
0, 100, 250, 500 mg/kg-day
Gavage
GDs 12-21</td><td><table>
<tr><td colspan="5">response relative to control</td></tr>
<tr><td>Doses</td><td>0</td><td>100</td><td>250</td><td>500</td></tr>
<tr><td colspan="5">Live pups per litter</td></tr>
<tr><td></td><td>0%</td><td>3%</td><td>3%</td><td>-2%</td></tr>
</table></td></tr>
<tr><td>Nikonorow et al. (1973)
Rat (Wistar); 20 dams/group
0, 120, 600 mg/kg-day
Gavage
3 months before mating; animals sampled at GD 21</td><td><table>
<tr><td colspan="4">response relative to control</td></tr>
<tr><td>Doses</td><td>0</td><td>120</td><td>600</td></tr>
<tr><td colspan="4">Dead fetuses (GD 21)</td></tr>
<tr><td>Incidence</td><td>0/9</td><td>0/106</td><td>0/81</td></tr>
<tr><td>Percent</td><td>0%</td><td>0%</td><td>0%</td></tr>
</table></td></tr>
<tr><td>NTP (1995)
Rat (F344/N); 24 females/dose, 48 control females
0, 1,250, 2,500, 5,000, 7,500, 10,000, 20,000 ppm (0, 138, 275, 550, 825, 1,100, 2,200 mg/kg-day)[b]
Diet
GD 1-PND 28</td><td><table>
<tr><td colspan="8">response relative to control</td></tr>
<tr><td>Doses</td><td>0</td><td>138</td><td>275</td><td>550</td><td>825</td><td>1,100</td><td>2,200</td></tr>
<tr><td colspan="8">Live pups per litter</td></tr>
<tr><td></td><td>0%</td><td>-10%</td><td>7%</td><td>13%</td><td>15%</td><td>10%</td><td>-93*%</td></tr>
</table></td></tr>
<tr><td>NTP (1984)
Lamb et al. (1987)
Lamb et al. (1997)
Mouse (CD-1); 18-40 breeding pairs/group
0, 0.03, 0.3, 1% Diet
(0, 170, 390, 1,400 mg/kg-day)
Diet
18 weeks (1 week pre-mating, 14 weeks cohabitation, 3 weeks observation)</td><td><table>
<tr><td colspan="5">response relative to control</td></tr>
<tr><td>Doses</td><td>0</td><td>170</td><td>390</td><td>1,400</td></tr>
<tr><td colspan="5">Live pups per litter</td></tr>
<tr><td></td><td>0%</td><td>3%</td><td>-3%</td><td>-63*%</td></tr>
<tr><td colspan="5">Proportion of pups born alive</td></tr>
<tr><td></td><td>0%</td><td>0%</td><td>-1%</td><td>-50*%</td></tr>
</table></td></tr>
</table>

Reference and study design	Results
NTP (1995) Mouse (B6C3F$_1$); 20 females/group 0, 1,250, 2,500, 5,000, 7,500, 10,000 ppm or 20,000 (0, 244, 488, 975, 1,463, 1,950, 3,900 mg/kg-day)[c] Diet GD 1-PND 28	*response relative to control* Doses: 0, 244, 488, 975, 1,463, 1,950, 3,900 **Live pups per litter** 0%, 5%, -1%, 7%, -58*%, -94*%, -100%
Mylchreest et al. (1998) Rat (Sprague-Dawley); 10 dams/group; 4-9 litters/group 0, 250, 500, 750 mg/kg-day Gavage GD 3-PND 20 (2-day interruption at parturition, PNDs 1-2)	*response relative to control* Doses: 0, 250, 500, 750 **Live pups per litter** 0%, 0%, 9%, -27*% **Percent pups surviving to weaning** 0%, 4%, -6%, -11*%
Ema et al. (2000) Rat (Wistar); 13 dams/group 0, 250, 500, 750, 1,000, 1,250, 1,500 mg/kg-day Gavage GDs 0-8	*response relative to control* Doses: 0, 250, 500, 750, 1,000, 1,250, 1,500 **Live fetuses per litter** 0%, 5%, -15%, -28*%, -60*%, -59*%, -62*% **Resorbed and dead fetuses/litter** 0%, -64%, 143%, 200%, 464*%, 514*%, 521*%
Jiang et al. (2007) Rat (Sprague-Dawley); 10 dams/group 0, 250, 500, 750, 1,000 mg/kg-day Gavage GDs 14-18	*response relative to control* Doses: 0, 250, 500, 750, 1,000 **Live pups per litter** 0%, -1%, -2%, -27*%, -100%
Gray et al. (2006) Rat (Long Evans); weanling females, 11-13/group 0, 250, 500, 750 mg/kg-day Gavage 5 days/week: PNDs 24-~PND 110 7 days/week: ~PND 110 to GD 13 of F1b litter (F1a litter delivered ~PND 140) Note: treated females were mated to untreated males	*response relative to control* Doses: 0, 250, 500, 750 **Total number of fetuses per F1b litter** *GD 13*: 0%, -5%, -45*%, -32*% **Live fetuses per F1b litter** *GD 13*: 0%, -4%, -60*%, -85*% **Live pups per F1a litter** *PND 1*: 0%, -5%, -77*%, -92*% *PND 15*: 0%, -10%, -84*, -100*% Note: For F1a litter only one pup was born in the single high-dose litter, and it died before PND 5. The number F0 females pregnant with an F1b litter were not provided by study authors.

Reference and study design	Results

[a]DBP concentrations in the diet were 0, 610, 2,500 ppm in diet; details on dose estimation in mg/kg-day were not provided by the study authors.
[b]Doses calculated using U.S. EPA (1988) reference subchronic values for food intake (0.014 kg/day) and body weight (0.124 kg) in female F344 rats.
[c]Doses calculated using U.S. EPA (1988) reference subchronic values for food intake (0.0048 kg/day) and body weight (0.0065 kg) in female B6C3F1 mice.
*Statistically different from controls ($p < 0.05$), as reported by study authors.

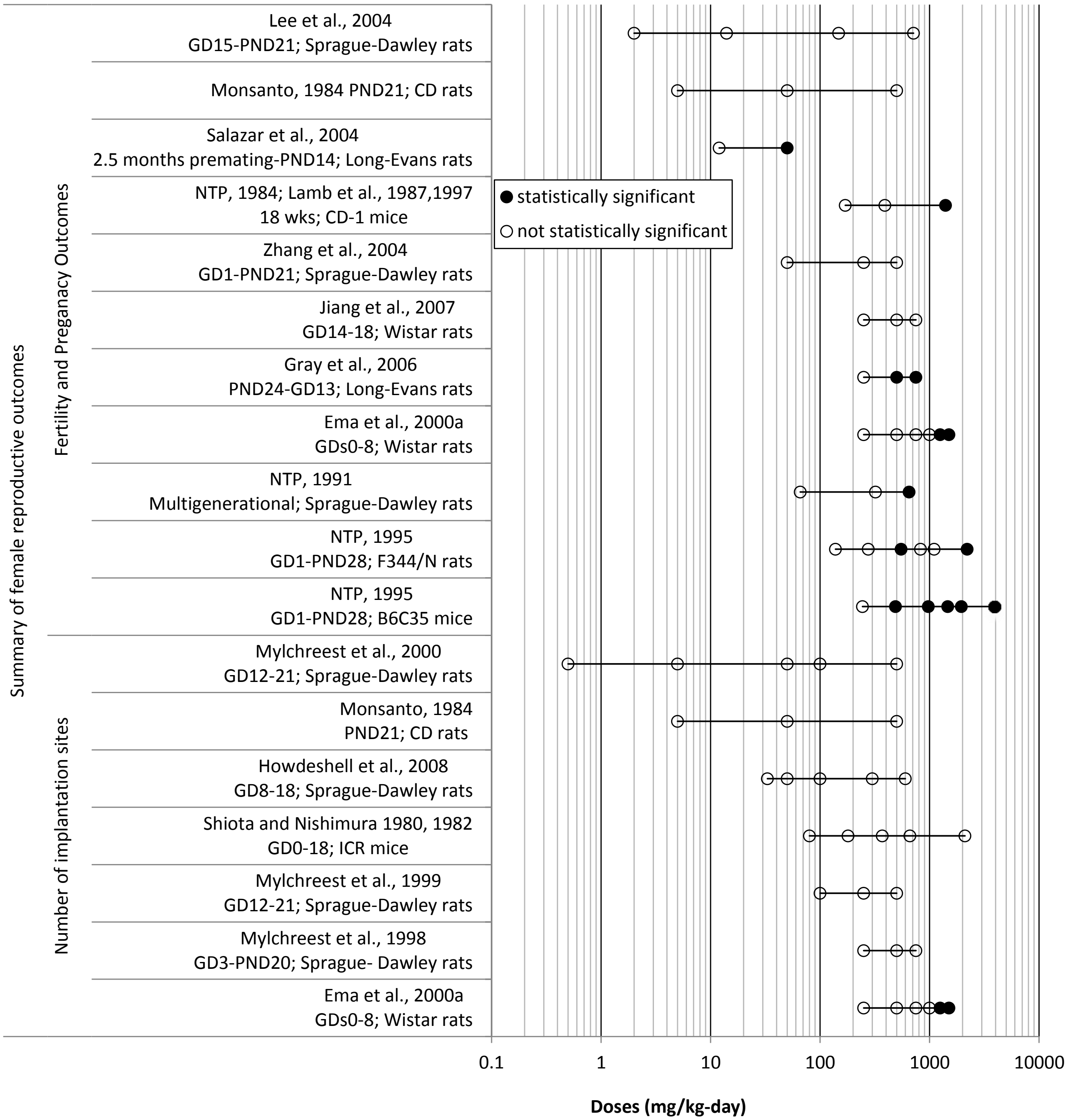
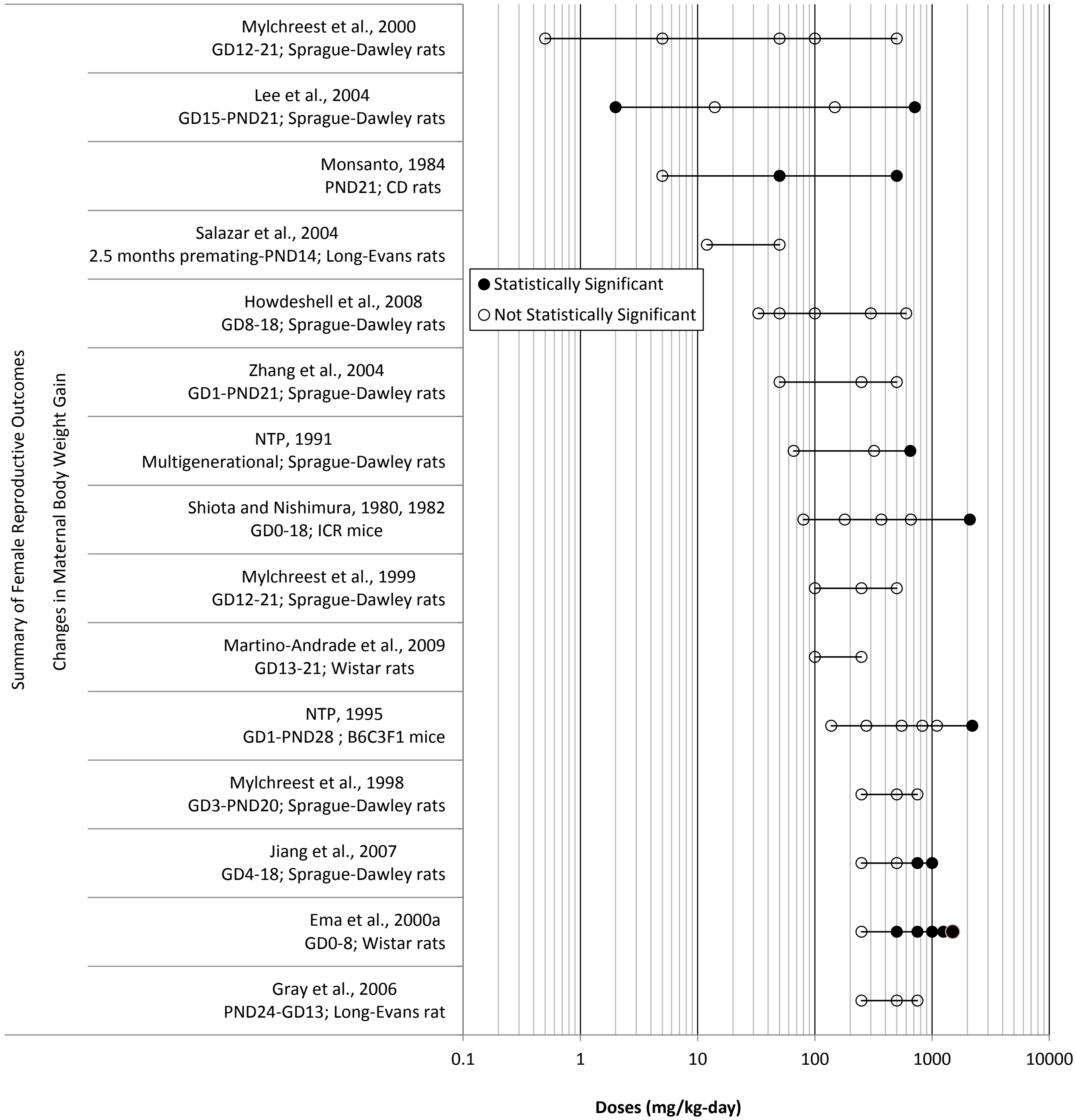


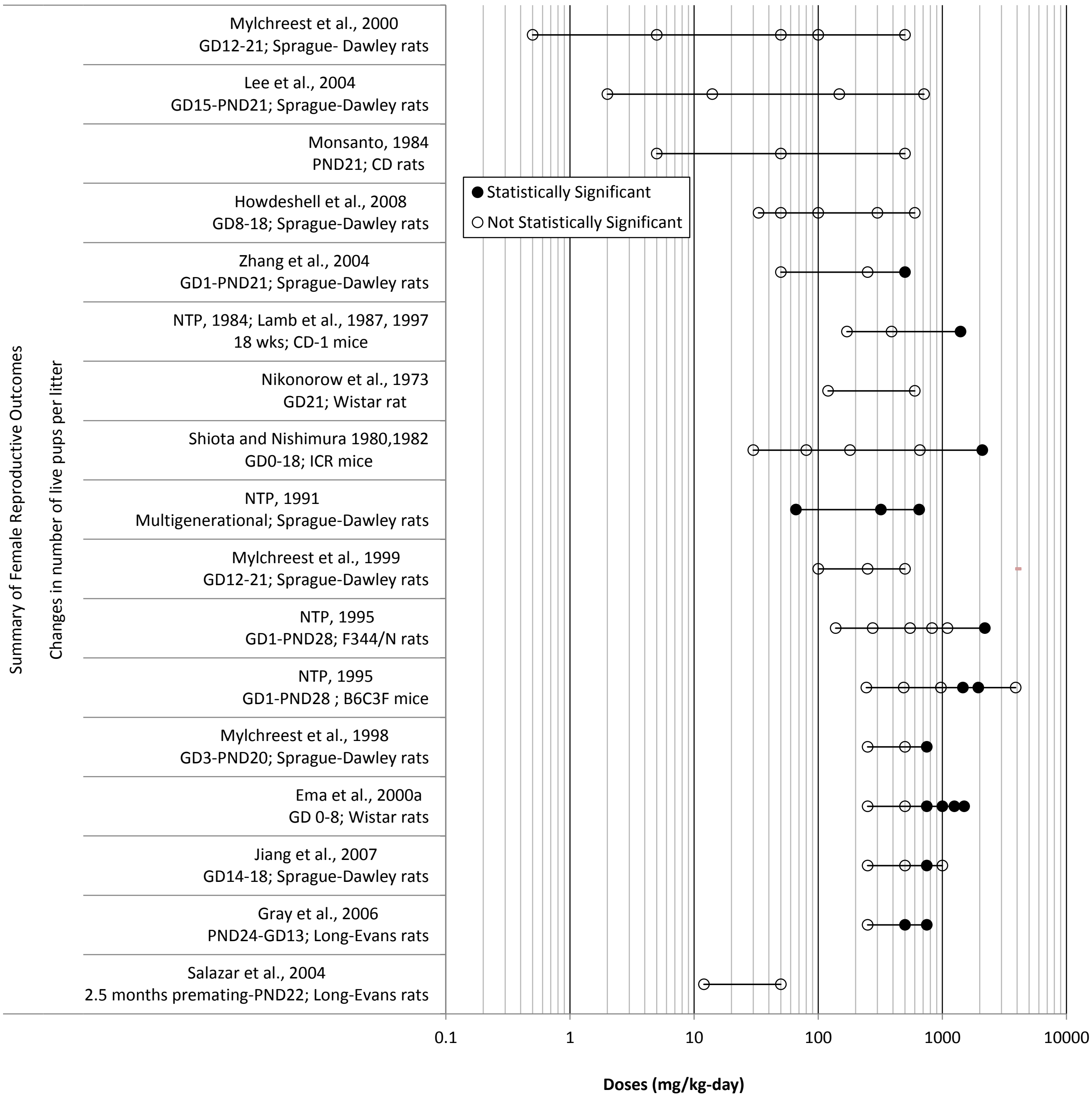
Figure 3-11. Exposure-response array of female reproductive toxicity following oral exposure to DBP: fertility and pregnancy outcome, and number of implantations.



1

2 **Figure 3-12. Exposure-response array of female reproductive toxicity**
3 **following oral exposure to DBP: alterations in maternal body weight.**

4



1

2 **Figure 3-13. Exposure-response array of female reproductive toxicity**
3 **following oral exposure to DBP: alterations in the number of live pups per**
4 **litter.**

5

Table 3-27. Evidence pertaining to female reproductive toxicity following oral exposure to DBP: alterations in reproductive organ weights, biomarkers of sexual development, reproductive hormone levels, and reproductive behavior

Reference and study design	Results				
Reproductive organ weights					
Ahmad et al. (2013) Rat (Strain not specified); 6 females/group 0, 10, 100 mg/kg-day Oral exposure - method not specified PNDs 20-23, or PNDs 20-40	*response relative to control*				
	Doses	0	10	100	
	Uterus weight[b]				
	PNDs 20-23	0%	-13%	-32*%	
	PNDs 20-40	0%	-63*%	-65*%	
	Ovary weight[b]				
	PNDs 20-23	0%	0%	-16%	
	PNDs 20-40	0%	-24*%	-32*%	
	Vagina weight[b]				
	PNDs 20-40	0%	-6%	-14%	
NTP (1991) Rat (Sprague-Dawley); 10 dams/group/generation; 40 F0 control breeding pairs, 20 F1 control breeding pairs 0, 0.1, 0.5, 1% (0, 66, 320, or 651 mg/kg-day) Diet F0: 7-day pre-cohabitation; 112 day cohabitation; ~60 days post-cohabitation (continuous breeding) F1: gestation, lactation, and post-weaning through ~PND 142 Note: study authors did not specify date of necropsy for F1 animals.	*response relative to control*				
	Doses	0	66	320	651
	Maternal right ovary weight in F1 animals				
		0%	10%	7%	-22*%
Nikonorow et al. (1973) Rat (Wistar); 20 dams/group 0, 120, 600 mg/kg-day Gavage 3 months before mating; animals sampled at GD 21	*response relative to control*				
	Doses	0	120	600	
	Placenta weight				
	GD 21	0%	-15*%	-9*%	
Mylchreest et al. (1998) Rat (Sprague-Dawley); 10 dams/group; organ weight evaluated in 4-9 dams/group	*response relative to control*				
	Doses	0	250	500	750
	Maternal uterus weight				
	PND 21	0%	-3%	-20*%	-22%

Reference and study design	Results
0, 250, 500, 750 mg/kg-day Gavage GD 3-PND 20 (2-day interruption at parturition, PNDs 1-2)	**Maternal ovaries weight** *PND 21* 0% -11% 1% 7%
[Ema et al. (2000)](#) Rat (Wistar); 10-13 pseudopregnant females/group 0, 250, 500, 750, 1,000, 1,250, 1,500 mg/kg-day Gavage GDs 0-8	*response relative to control* Doses 0 250 500 750 1,000 1,250 1,500 **Uterine weight on day 9 pseudopregnancy[a]** 0% -4% -4% -22*% -19*% -47*% -52*% **Ovarian weight on day 9 pseudopregnancy[a]** 0% -5% -3% -0.4% -5% -10*% -10*%
[Gray et al. (2006)](#) Rat (Long Evans); weanling females, 11-13/group 0, 250, 500, 750 mg/kg-day Gavage 5 days/week: PNDs 24-~PND 110 7 days/week: ~PND 110 to GD 13 of F1b litter (F1a litter delivered ~PND 140) Note: treated females were mated to untreated males	*response relative to control* Doses 0 250 500 750 **Maternal gravid uterine weight** *GD 13 of F1b litter* 0% 1% -32*% -32*% **Maternal ovaries weight** *GD 13 of F1b litter* 0% -3% -6% -10% Note: Organ weights were only measured in F0 females pregnant with F1b litter (number not provided by study authors).
Biomarkers of sexual development and function	
[Lee et al. (2004)](#) Rat (Sprague-Dawley); 6-8 dams/ group 0, 20, 200, 2,000, 10,000 ppm Diet (0,2-3, 14-29,148-291, 712-1,372 mg/kg-day) Diet GD 15-PND 21 Note: Doses represent a range estimated by the study authors for three different time periods (GDs 15-20, PNDs 2-10, and PNDs 10-21).	*response relative to control* Doses 0 2-3 14-29 148-291 712-1,372 **Female AGD** *PND 2* 0% 0% 0% 0% 0% Note: Intake reported for GDs 15-20.
[Lee et al. (2006b)](#) Rat (Wistar); number of treated dams not reported, AGD assessed in 16-47 female offspring/group 0, 2, 21, 205, 1,025 mg/kg-day[b] Diet GD 15-PND 21	*response relative to control* Doses 0 2 21 205 1,025 **Female AGD** *PND 1[a]* 0% -2% 1% 2% 7% **Female AGD/body weight** *PND 1[a]* 0% -1% 1% 4% 11%

Reference and study design	Results
Salazar et al. (2004) Rat (Long Evans); 15 dams/group 0, 12, 50 mg/kg-day[c] Diet 2.5 months before mating to PND 14	*response relative to control* Doses: 0 / 12 / 50 **Age of vaginal opening[a]**: 0% / 4*% / 5*% **Age at first estrous[a]**: 0% / 4% / 5*%
Mylchreest et al. (1998) Rat (Sprague-Dawley); 10 dams/group; female offspring from 4-9 litters/group were evaluated for sexual maturity starting at PND 29 0, 250, 500, 750 mg/kg-day Gavage GD 3-PND 20 (2-day interruption at parturition, PNDs 1-2)	*response relative to control* Doses: 0 / 250 / 500 / 750 **Age of vaginal opening**: 0% / -0.3% / -2% / 0% **Age at first estrous**: 0% / 2% / -4% / -1% **Length of estrus cycle**: 0% / 10% / -8% / -10% **AGD at PND 1[a]** (F): 0% / 7% / 7% / 0.1% **Percent cornified smears**: 26% / 25% / 31% / 25% Note: The litter was the unit of statistical comparison.
Ema et al. (2000) Rat (Wistar); 10-13 pseudopregnant females/group 0, 250, 500, 750, 1,000, 1,250, 1,500 mg/kg-day Gavage GDs 0-8	*response relative to control* Doses: 0 / 250 / 500 / 750 / 1,000 / 1,250 / 1,500 **Number of corpora lutea on day 9 pseudopregnancy**: 0% / 0% / 3% / 3% / -1% / -1% / 7%
Changes in reproductive hormone levels	
Lee et al. (2006b) Lee et al. (2006a) Rat (Wistar); number of treated dams not reported, hormones assessed in 5-12 female offspring/group 0, 2, 21, 205, 1,025 mg/kg-day[b] Diet GD 15-PND 21	*response relative to control* Doses: 0 / 2 / 21 / 205 / 1,025 **Serum estradiol** *PND 7[a]*: 0% / 3% / -11% / -69*% / -44% **Serum estradiol at proestrus** *1,100h[a]*: 0% / -14% / -18% / -5% / 69% **Serum estradiol at proestrus** *1,600h[a]*: 0% / 12% / -31% / -8% / 169% **Serum FSH at proestrus**

Reference and study design	Results							
	1,100h[a]	0%	0%	-24%	0%	-16%		
	Serum FSH at proestrus							
	1,600h[a]	0%	79%	-5%	67%	42%		
	Serum LH at proestrus							
	1,100h[a]	0%	20%	-20%	-8%	-12%		
	Serum LH at proestrus							
	1,600h[a]	0%	88%	-16%	23%	40%		
Gray et al. (2006) (Study 2) Rat (Long Evans); weanling females, 11-13/group 0, 250, 500, 750 mg/kg-day Gavage 5 days/week: PNDs 24-~PND 110 7 days/week: ~PND 110 to GD 13 of F1b litter (F1a litter delivered ~PND 140) Note: treated females were mated to untreated males	*response relative to control*							
	Doses	0	250	500	750			
	Ex vivo ovarian progesterone production[a]							
		0%	-7%	-30*%	-58*%			
	Serum progesterone[a]							
		0%	-6%	-21%	-50*%			
	Ex vivo ovarian estradiol production[a]							
		0%	0%	388%	329%			
	Ex vivo ovarian testosterone production[a]							
		0%	10%	15%	68%			
	Note: Reproductive hormones were only measured in F0 females pregnant with F1b litter (number not provided by study authors). Statistics were not reported by study authors for estradiol production.							
Ema et al. (2000) Rat (Wistar); 10-13 pseudopregnant dams/group 0, 250, 500, 750, 1,000, 1,250, 1,500 mg/kg-day Gavage GDs 0-8	*response relative to control*							
	Doses	0	250	500	750	1,000	1,250	1,500
	Serum progesterone on day 9 of psuedopregnancy[a]							
		0%	14%	13%	10%	17%	-10%	-61*%
	Serum estradiol on day 9 of psuedopregnancy[a]							
		0%	29%	-8%	5%	-24%	-18%	-2%
Changes in reproductive behavior								
Lee et al. (2006b) Lee et al. (2006a) Rat (Wistar); number of treated dams not reported; reproductive behavior evaluated in 6-12 female offspring/group 0, 2, 21, 205, 1,025 mg/kg-day[b] Diet GD 15-PND 21	Doses	0	2	21	205	1,025		
	Lordosis quotient *Percent*							
	PNW 20[a]	75%	48*%	30*%	30*%	15*%		

Reference and study design	Results				
Histopathological effects					
Monsanto (1984) Rat (CD); 20 breeding pairs/group 17-20 animals examined [females exposed only] 0, 5, 50, 500 mg/kg-day Diet 14 days before mating and continued through weaning [PND 21]	Doses	0	5	50	500
	Incidence uterus atrophy				
	Incidence	7/20	4/20	7/18	7/19
	Percent	35%	20%	39%	37%
	Incidence ovary cyst				
	Incidence	0/20	0/20	0/17	1/19
	Percent	0%	0%	0%	5%
	Incidence cervicitis				
	Incidence	0/19	1/19	1/17	1/18
	Percent	0%	5%	6%	6%
	Incidence cervical squamous moderate metaplasia				
	Incidence	0/19	0/19	1/17	0/18
	Percent	0%	0%	6%	0%

[a]Values reported by the study authors were estimated from published graphs using "Grab It!", a Microsoft Excel based free software application used to digitize data from image files. Publisher: datatrendsoftware.com.

[b]In the absence of reporting of average daily intakes or body weights of the dams, respective average daily intakes were estimated using U.S. EPA RfVs for female Wistar rat body weight (0.156 kg) and food intake (0.016 kg/day) as 0, 2.1, 21, 205, and 1,025 mg/kg-day.

[c]Doses were 0, 610, 2,500 ppm in diet; details on dose estimation in mg/kg-day were not provided by the study authors.

*Statistically different from controls ($p < 0.05$), as reported by study authors.

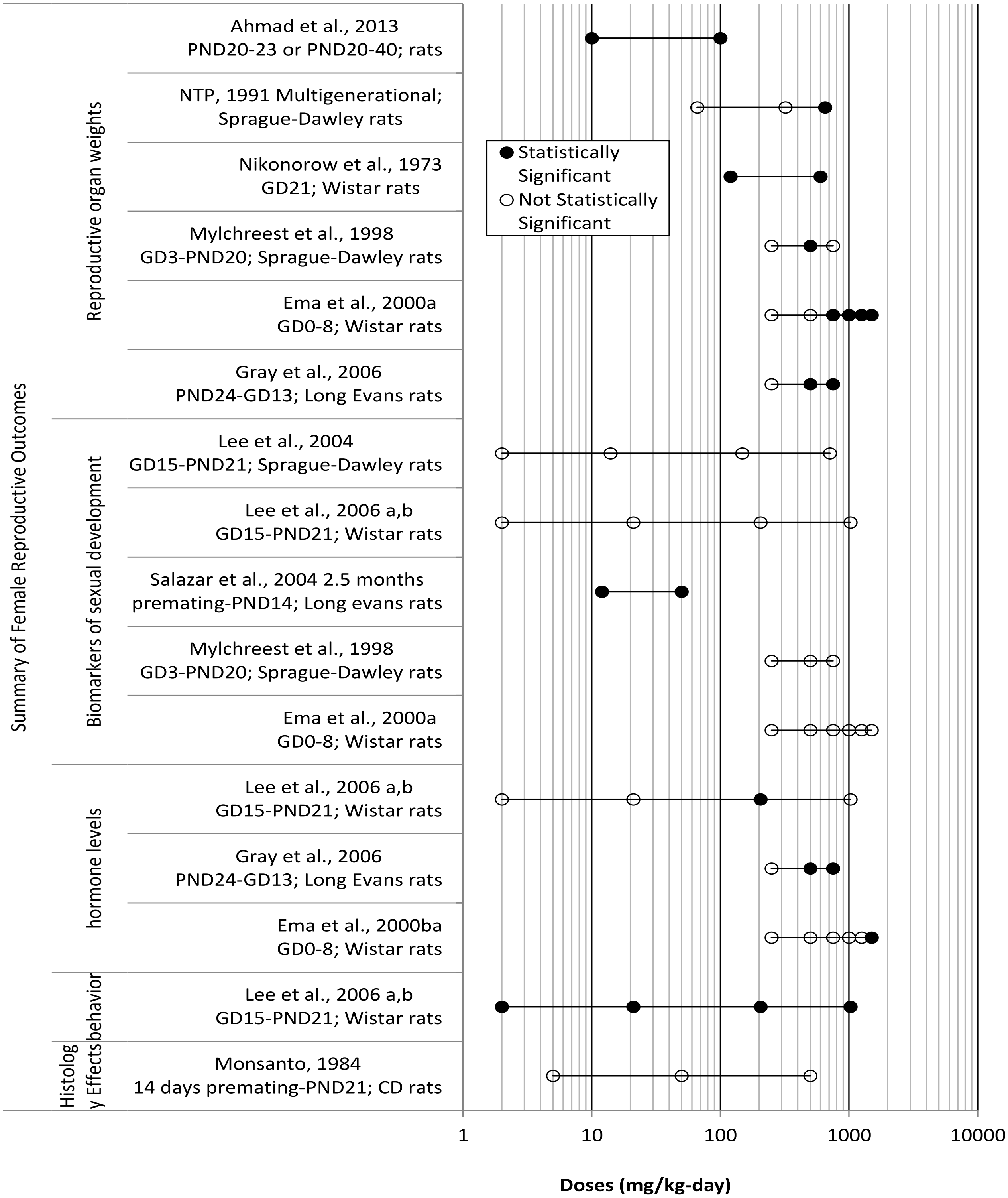


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Figure 3-14. Exposure-response array of female reproductive toxicity following oral exposure to DBP: alterations in female sexual development, reproductive hormone levels in animals, organ weight and reproductive behavior.

3.3.3. Developmental Effects

Table 3-28. Evidence pertaining to developmental effects following oral exposure to DBP: alterations in body weight, skeletal development and external malformations

Reference and study design	Results						
Changes in offspring body weight							
Mylchreest et al. (2000) Rat (Sprague-Dawley); 11-20 dams/group 0, 0.5, 5, 50, 100, 500 mg/kg-day Gavage GDs 12-21	*response relative to control*						
	Doses	0	0.5	5	50	100	500
	Pup Weight (M)						
	Birth	0%	0%	6%	2%	2%	-2%
	Weaning	0%	5%	12*%	8%	9%	10%
	PND 110	0%	2%	3%	3%	1%	-2%
	Pup Weight (F)						
	Birth	0%	-2%	3%	-2%	2%	-3%
	Weaning	0%	9%	18*%	12*%	13*%	17*%
	Note: Litter is the statistical unit of comparison.						
Lee et al. (2004) Rat (Sprague-Dawley); 6-8/group 0, 20, 200, 2,000, 10,000 ppm Diet: 0, 2-3, 14-29, 148-291, 712-1,372 mg/kg-day Diet GD 15-PND 21	*response relative to control*						
	Doses	0	2-3	14-29	148-291	712-1,374	
	Pup Weight (M)						
	PND 2	0%	13*%	6%	4%	-3%	
	PND 77	0%	0%	8%	3%	7%	
	PND 140	0%	8%	13%	5%	NA	
	Pup Weight (F)						
	PND 2	0%	14*%	6%	2%	-6%	
	PND 77	0%	-0.4%	7%	1%	1%	
	PND 140	0%	2%	13%	12%	-0.3%	
	Note: Litter is the statistical unit of comparison. The study authors indicated that a sufficient number of male animals could not be obtained in the highest dose group at PND 140. Doses represent a range estimated by the study authors for three different time periods (GDs 15-20, PNDs 2-10, and PNDs 10-21).						
Lee et al. (2006b) Rat (Wistar); number of treated dams not reported; bodyweight measured in 16-47 pups/sex/group 0, 20, 200, 2,000, 10,000 ppm Diet 0, 2, 21, 205, 1,025 mg/kg-day[a]	*response relative to control*						
	Doses	0	2	21	205	1,025	
	Pup Weight (M)[b]						
	PND 1	0%	-4%	-4*%	-7*%	-16*%	
	Pup Weight (F)[b]						

Reference and study design	Results					
Diet GD 15-PND 21	*PND 1*	0%	-0.3%	-3%	-7*%	-14*%
Monsanto (1984) Rat (CD); 20 breeding pairs/group 13-15 animals evaluated [females exposed only] 0, 5, 50, 500 mg/kg-day Diet 14 days before mating and continued through weaning [PND 21]	*response relative to control*					
	Doses	0	5	50	500	
	F1 male weight					
	PND 21	0%	-1%	-1%	-5%	
	F1 female weight					
	PND 21	0%	-4%	2%	-6%	
	F1 male weight					
	PND 70	0%	-3%	-8*%	-4%	
	F1 female weight					
	PND 70	0%	-4%	-4%	-5%	
Salazar et al. (2004) Rat (Long Evans); 15 dams/group 0, 610, 2,500 ppm (0, 12, 50 mg/kg-day) Diet Dams: 2.5 months before mating to PND 22; Pups: PNDs 22-84	*response relative to control*					
	Doses	0	12	50		
	Pup Weight (M+F)					
	PND 2	0%	-10*%	-23*%		
	PND 6	0%	-12*%	-1%		
	Pup Weight (M)					
	PND 14	0%	-5%	2%		
	Note: Doses were 0, 610, 2,500 ppm in diet; details on dose estimation in mg/kg-day were not provided by the study authors. The unit of statistical comparison (e.g. litter or individual pup) was not reported.					
Zhang et al. (2004b) Rat (Sprague-Dawley); 14-16 dams/group 0, 50, 250, 500 mg/kg-day Gavage GD 1-PND 21	*response relative to control*					
	Doses	0	50	250	500	
	Pup Weight (M)					
	Birth	0%	-4%	-12*%	-13*%	
	Pup Weight (F)					
	Birth	0%	-4%	-10*%	-18*%	
	Note: Litter is the statistical unit of comparison.					
Johnson et al. (2008) Rat (Long Evans); 3-7 dams/group 0, 50, 100, 200 mg/kg-day Gavage GDs 12-21	*response relative to control*					
	Doses	0	50	100	200	
	Pup Weight (M)					
	PND 21	0%	-15%	-4%	-19%	
	Note: Litter is the statistical unit of comparison.					

<table>
<tr><th>Reference and study design</th><th colspan="7">Results</th></tr>
<tr><td rowspan="15"><u>NTP (1991)</u>
Rat (Sprague-Dawley); 20 breeding pairs/dose/generation; 40 F0 control breeding pairs, 20 F1 control breeding pairs
0, 0.1, 0.5, 1% Diet (0, 66, 320, or 651 mg/kg-day)
Multigenerational study
Note: study authors did not specify date of necropsy for F1 animals.</td><td colspan="7">response relative to control</td></tr>
<tr><td>Doses</td><td colspan="2">0</td><td colspan="2">66</td><td>320</td><td>651</td></tr>
<tr><td colspan="7">Live F1 pup weights at birth (litter means, first F1 litter)</td></tr>
<tr><td>M</td><td colspan="2">0%</td><td colspan="2">1%</td><td>-5*%</td><td>-10*%</td></tr>
<tr><td>F</td><td colspan="2">0%</td><td colspan="2">0.2%</td><td>-3%</td><td>-9*%</td></tr>
<tr><td>Combined</td><td colspan="2">0%</td><td colspan="2">1%</td><td>-4*%</td><td>-10*%</td></tr>
<tr><td colspan="7">Adult F1 weights at ~PND 119 (individual means, fifth F1 litter)</td></tr>
<tr><td>M</td><td colspan="2">0%</td><td colspan="2">1%</td><td>-0.4%</td><td>-8*%</td></tr>
<tr><td>F</td><td colspan="2">0%</td><td colspan="2">-4%</td><td>-4%</td><td>-20*%</td></tr>
<tr><td>Combined</td><td colspan="2">0%</td><td colspan="2">-1%</td><td>-2%</td><td>-13*%</td></tr>
<tr><td colspan="7">Live F2 pup weights at birth (litter means)</td></tr>
<tr><td>M</td><td colspan="2">0%</td><td colspan="2">-5*%</td><td>-5*%</td><td>-17%</td></tr>
<tr><td>F</td><td colspan="2">0%</td><td colspan="2">-7*%</td><td>-7*%</td><td>-15%</td></tr>
<tr><td>Combined</td><td colspan="2">0%</td><td colspan="2">-6*%</td><td>-6*%</td><td>-16%</td></tr>
<tr><td colspan="7">Note: Only one F2 litter was produced in the high-dose group.</td></tr>
<tr><td rowspan="7"><u>Shiota et al. (1980)</u>
<u>Shiota and Nishimura (1982)</u>
Mouse (ICR); 6-21 dams/group
0, 80, 180, 370, 660, 2,100 mg/kg-day
Diet
GDs 0-18</td><td colspan="7">response relative to control</td></tr>
<tr><td>Doses</td><td>0</td><td>80</td><td>180</td><td>370</td><td>660</td><td>2,100</td></tr>
<tr><td colspan="7">Fetal Weight (M)</td></tr>
<tr><td>GD 18</td><td>0%</td><td>-7%</td><td>-9%</td><td>-7%</td><td>-22*%</td><td>-20%</td></tr>
<tr><td colspan="7">Fetal Weight (F)</td></tr>
<tr><td>GD 18</td><td>0%</td><td>-4%</td><td>-10%</td><td>-8%</td><td>-21%</td><td>-41%</td></tr>
<tr><td colspan="7">Note: Litter is the statistical unit of comparison. Only 3 pups (two males, one female) from 2 dams survived to term at the high-dose.</td></tr>
<tr><td rowspan="9"><u>Mylchreest et al. (1999a)</u>
Rat (Sprague-Dawley); 10 dams/group; offspring weight assessed in 9-10 litters/group
0, 100, 250, 500 mg/kg-day
Gavage
GDs 12-21</td><td colspan="7">response relative to control</td></tr>
<tr><td>Doses</td><td colspan="2">0</td><td colspan="2">100</td><td>250</td><td>500</td></tr>
<tr><td colspan="7">Pup Weight (M)</td></tr>
<tr><td>PND 1</td><td colspan="2">0%</td><td colspan="2">0%</td><td>-11%</td><td>-6%</td></tr>
<tr><td colspan="7">Pup Weight (F)</td></tr>
<tr><td>PND 1</td><td colspan="2">0%</td><td colspan="2">-5%</td><td>-13%</td><td>-8%</td></tr>
<tr><td colspan="7">Adult Weight (M)</td></tr>
<tr><td>PNDs 105-110</td><td colspan="2">0%</td><td colspan="2">-3%</td><td>-3%</td><td>-4%</td></tr>
<tr><td colspan="7">Note: Litter is the statistical unit of comparison.</td></tr>
<tr><td rowspan="3"></td><td colspan="7">response relative to control</td></tr>
<tr><td>Doses</td><td colspan="2">0</td><td colspan="2">100</td><td colspan="2">500</td></tr>
<tr><td colspan="7">Adult Weight (M)</td></tr>
</table>

<table>
<tr><th>Reference and study design</th><th>Results</th></tr>
<tr><td>Martino-Andrade et al. (2009)
Rat (Wistar); 4-7 dams/group; offspring body weight was assessed in 4-7 litters/group (8-17 males/group)
0, 100, 500 mg/kg-day
Gavage
GDs 13-21</td>
<td><table>
<tr><td>PND 90</td><td>0%</td><td>-2%</td><td>4%</td></tr>
</table>
Note: Litter is the statistical unit of comparison</td></tr>
<tr><td>Nikonorow et al. (1973)
Rat (Wistar); 20 dams/group
0, 120, 600 mg/kg-day
Gavage
3 months before mating; animals sampled at GD 21</td>
<td>response relative to control
<table>
<tr><td>Doses</td><td>0</td><td>120</td><td>600</td></tr>
<tr><td colspan="4">Fetal weight</td></tr>
<tr><td>GD 21</td><td>0%</td><td>-5%</td><td>-22*%</td></tr>
</table></td></tr>
<tr><td>NTP (1995)
Rat (F344/N); 24 females/dose, 48 control females; 10 offspring/sex/group
0, 1,250, 2,500, 5,000, 7,500, 10,000, or 20,000 ppm (dams [gestation/lactation]: 0, 138, 275, 550, 825, 1,100, 2,200 mg/kg-day[c]; pups [post-weaning]: 0, 143, 284, 579, 879, 1,165 mg/kg-day in males; 0, 133, 275, 500, 836, 1,104 mg/kg-day in females
Diet
Dams: GD 1-PND 28; Pups: PNDs 29-56</td>
<td>response relative to control
<table>
<tr><td>Doses</td><td>0</td><td>138</td><td>275</td><td>550</td><td>825</td><td>1,100</td></tr>
<tr><td colspan="7">F1 pup weight (litter means)</td></tr>
<tr><td>Birth</td><td>0%</td><td>-3%</td><td>-5%</td><td>-7*%</td><td>-9%</td><td>-9%</td></tr>
<tr><td>PND 28</td><td>0%</td><td>-2%</td><td>-4%</td><td>-8*%</td><td>-10%</td><td>-10%</td></tr>
<tr><td>Doses (M)</td><td>0</td><td>143</td><td>284</td><td>579</td><td>879</td><td>1,165</td></tr>
<tr><td colspan="7">F1 weight (individual means)</td></tr>
<tr><td>PND 56</td><td>0%</td><td>-1%</td><td>-3%</td><td>-7%*</td><td>-13%*</td><td>-8%*</td></tr>
<tr><td>Doses (F)</td><td>0</td><td>133</td><td>275</td><td>500</td><td>836</td><td>1,104</td></tr>
<tr><td colspan="7">F1 weight (individual means)</td></tr>
<tr><td>PND 56</td><td>0%</td><td>0%</td><td>-2%</td><td>1%</td><td>-4%</td><td>-5%</td></tr>
</table>
Note: There were no surviving high-dose offspring.</td></tr>
<tr><td>NTP (1984)
Lamb et al. (1987)
Lamb et al. (1997)
Mouse (CD-1); 18-40 breeding pairs/group
0, 0.03, 0.3, 1% Diet
(0, 170, 390, 1,400 mg/kg-day)
Diet
18 weeks (1 week pre-mating, 14 weeks cohabitation, 3 weeks observation)</td>
<td>response relative to control
<table>
<tr><td>Doses</td><td>0</td><td>170</td><td>390</td><td>1,400</td></tr>
<tr><td colspan="5">Live pup weight</td></tr>
<tr><td></td><td>0%</td><td>-1%</td><td>-1%</td><td>4%</td></tr>
</table></td></tr>
<tr><td></td><td>response relative to control</td></tr>
</table>

Reference and study design	Results						
NTP (1995) Mouse (B6C3F$_1$); 20 females/group; 10 offspring/sex/group 0, 1,250, 2,500, 5,000, 7,500, 10,000 ppm or 20,000 (dams [gestation/lactation]:0, 244, 488, 975, 1,463, 1,950, 3,900 mg/kg-day[d]; pups [post-weaning]: 0, 199, 437, 750, 1,286, 3,804 mg/kg-day in males; 0, 170, 399, 714, 1,060 mg/kg-day in females) Diet Dams: GD 1-PND 28; Pups: PNDs 29-56	Doses	0	244	488	975	1,463	1,950
	F1 pup weight *(litter means)*						
	Birth	0%	1%	-4%	-7*%	-4%	-14*%
	PND 28	0%	7%	1%	-6*%	-3%	0%
	Doses (M)	0	199	437	750	1,286	3,804
	F1 weight *(individual means)*						
	PND 56	0%	-2%	-6*%	-10*%	-12*%	-26%
	Doses (F)	0	170	399	714	1,060	
	F1 weight *(individual means)*						
	PND 56	0%	5%	-1%	-2%	-11*%	
	Note: There were no surviving high-dose offspring (20,000 ppm maternal dose group). Only 1 male offspring in the 10,000 ppm group survived until necropsy; no female offspring survived at this exposure.						
Gray et al. (2006) Rat (Long Evans); weanling females, 11-13/group 0, 250, 500, 750 mg/kg-day Gavage 5 days/week: PNDs 24-~PND 110 7 days/week: ~PND 110 to GD 13 of F1b litter (F1a litter delivered ~PND 140) Note: treated females were mated to untreated males	*response relative to control*						
	Doses	0	250	500	750		
	F1a pup weight						
	PND 1	0%	-3%	0%	-8%		
	PND 21	0%	0%	6%	NA		
	Note: Numbers of live F1a litters for the 0, 250, 500, and 750 mg/kg-day groups were 12, 9, 5, and 1, respectively. Only one pup was born in the single high-dose litter, and it died before PND 5. The body weight data for the F1b litter were not provided by study authors.						
Mylchreest et al. (1998) Rat (Sprague-Dawley); 10 dams/group; 4-9 litters/group 0, 250, 500, 750 mg/kg-day Gavage GD 3-PND 20	*response relative to control*						
	Doses	0	250	500	750		
	Pup Weight (M) *(litter means)*						
	PND 1	0%	3%	2%	-5%		
	PND 21	0%	6%	-4%	-13%		
	PND 100	0%	-3%	-4%	-10%		
	Pup Weight (F) *(litter means)*						
	PND 1	0%	2%	-2%	-7%		
	PND 21	0%	7%	-3%	-8%		
	PND 100	0%	3%	-1%	0%		
	Note: Litter was the statistical unit of comparison.						

<table>
<tr><th>Reference and study design</th><th colspan="8">Results</th></tr>
<tr><td rowspan="6">Jiang et al. (2007)
Rat (Sprague-Dawley); 10 dams/group
0, 250, 500, 750, 1,000 mg/kg-day
Gavage
GDs 14-18</td><td colspan="8">response relative to control</td></tr>
<tr><td>Doses</td><td>0</td><td>250</td><td>500</td><td>750</td><td colspan="3">1,000</td></tr>
<tr><td colspan="8">Live pup weight (M) (litter means)</td></tr>
<tr><td>PND 1</td><td>0%</td><td>-4%</td><td>-16*%</td><td>-26*%</td><td colspan="3">NA</td></tr>
<tr><td colspan="8">Pup Weight (M) (n = 21-57)</td></tr>
<tr><td>PND 70</td><td>0%</td><td>-1%</td><td>-8*%</td><td>-22*%</td><td colspan="3">NA</td></tr>
<tr><td></td><td colspan="8">Note: No live pups were delivered in the high-dose group. Litter was the statistical unit of comparison for PND 1 pup weights.</td></tr>
<tr><td rowspan="4">Kim et al. (2010)
Rat (Sprague-Dawley) 4-9 dams/group; body weight was assessed in 8 male offspring/group
0, 250, 500, 700 mg/kg-day
Gavage
GDs 10-19</td><td colspan="8">response relative to control</td></tr>
<tr><td>Doses</td><td>0</td><td>250</td><td>500</td><td colspan="4">700</td></tr>
<tr><td colspan="8">Pup Weight (M)</td></tr>
<tr><td>PND 31</td><td>0%</td><td>-5%</td><td>-1</td><td colspan="4">-10*%</td></tr>
<tr><td rowspan="6">Ema et al. (2000)
Rat (Wistar); 13 dams/group
0, 250, 500, 750, 1,000, 1,250, or 1,500 mg/kg-day
Gavage
GDs 0-8</td><td colspan="8">response relative to control</td></tr>
<tr><td>Doses</td><td>0</td><td>250</td><td>500</td><td>750</td><td>1,000</td><td>1,250</td><td>1,500</td></tr>
<tr><td colspan="8">Live fetus weight (M)</td></tr>
<tr><td>GD 20</td><td>0%</td><td>4*%</td><td>-12*%</td><td>-22*%</td><td>-32*%</td><td>-36*%</td><td>-32*%</td></tr>
<tr><td colspan="8">Live fetus weight (F)</td></tr>
<tr><td>GD 20</td><td>0%</td><td>2*%</td><td>-14*%</td><td>-26*%</td><td>-34*%</td><td>-37*%</td><td>-37*%</td></tr>
<tr><td colspan="9">External Malformations</td></tr>
<tr><td rowspan="7">Ema et al. (1994)
Rat (Wistar); 9-11 litters/group
0, 750, 1,000, 1,500 mg/kg-day
Gavage
GDs 7-9 or 10-12 or 13-15</td><td colspan="8">response relative to control</td></tr>
<tr><td>Doses</td><td>0</td><td>750</td><td>1,000</td><td colspan="4">1,500</td></tr>
<tr><td colspan="8">Litter incidence of cleft palate</td></tr>
<tr><td>GDs 7-9</td><td>-</td><td>10%</td><td>0%</td><td colspan="4">-</td></tr>
<tr><td>GDs 10-12</td><td>-</td><td>0%</td><td>0%</td><td colspan="4">-</td></tr>
<tr><td>GDs 13-15</td><td>-</td><td>44*%</td><td>88*%</td><td colspan="4">-</td></tr>
<tr><td colspan="8">Note: Incidence not reported for controls and high dose group.</td></tr>
<tr><td rowspan="5">Ema et al. (1997)
Rat (Wistar); 10-12 litters/group
0, 1,500 mg/kg-day
Gavage
GDs 7, 8, 9, 10, 11, 12, 13, 14, 15, 16
Controls received vehicle on GDs 6-16</td><td colspan="8">percent incidence</td></tr>
<tr><td>Doses</td><td colspan="3">0</td><td colspan="4">1,500</td></tr>
<tr><td colspan="8">Litter incidence of cleft palate</td></tr>
<tr><td>GD 12</td><td colspan="3">0%</td><td colspan="4">10%</td></tr>
<tr><td>GD 15</td><td colspan="3">0%</td><td colspan="4">42*%</td></tr>
<tr><td colspan="9">Skeletal Development Effects</td></tr>
</table>

Reference and study design	Results						
Shiota et al. (1980) Shiota and Nishimura (1982) Mouse (ICR); 6-21 dams/group 0, 80, 180, 370, 660, 2,100 mg/kg-day Diet GDs 0-18	Doses	0	80	180	370	660	2,100
	Ossified coccygia *Response relative to control*						
		0%	-46*%	-52*%	-36*%	-72*%	NA
	Lumbar rib variations *Percent incidence*						
		13%	24%	17%	26%	37%	NA
	Deficient sternebrae ossification *Percent incidence*						
		0%	6%	0%	0%	0%	NA
	Note: Litter is the statistical unit of comparison. Only 3 pups (two males, one female) from 2 dams survived to term at the high-dose.						
Changes in body weight after pre-pubertal or pubertal exposure							
Ahmad et al. (2013) Rat (Strain not specified); 6 females/group 0, 10, 100 mg/kg-day Oral exposure - method not specified PNDs 20-40	*response relative to control*						
	Doses	0	10	100			
	Final body weight[b]						
		0%	-11%	-14*%			
Srivastava et al. (1990a) Rat (Wistar); 6/group 0, 250, 500, 1,000 mg/kg-day Gavage 15 days	*response relative to control*						
	Doses	0	250	500	1,000		
	Final body weight						
		0%	-5%	-1	-10*%		

[a]Rats were exposed to DBP (>98% purity) in the diet at concentrations of 0, 20, 200, 2,000, or 10,000 ppm. Doses calculated using U.S. EPA (1988) reference subchronic values for food intake (0.016 kg/day) and body weight (0.156 kg) in female Wistar rats.

[b]Values reported by the study authors were estimated from published graphs using “Grab It!”, a Microsoft Excel based free software application used to digitize data from image files. Publisher: datatrendsoftware.com.

[c]Doses calculated using U.S. EPA (1988) reference subchronic values for food intake (0.014 kg/day) and body weight (0.124 kg) in female F344 rats

[d]Doses calculated using U.S. EPA (1988) reference subchronic values for food intake (0.0048 kg/day) and body weight (0.0065 kg) in female B6C3F1 mice

*Statistically different from controls ($p < 0.05$), as reported by study authors.

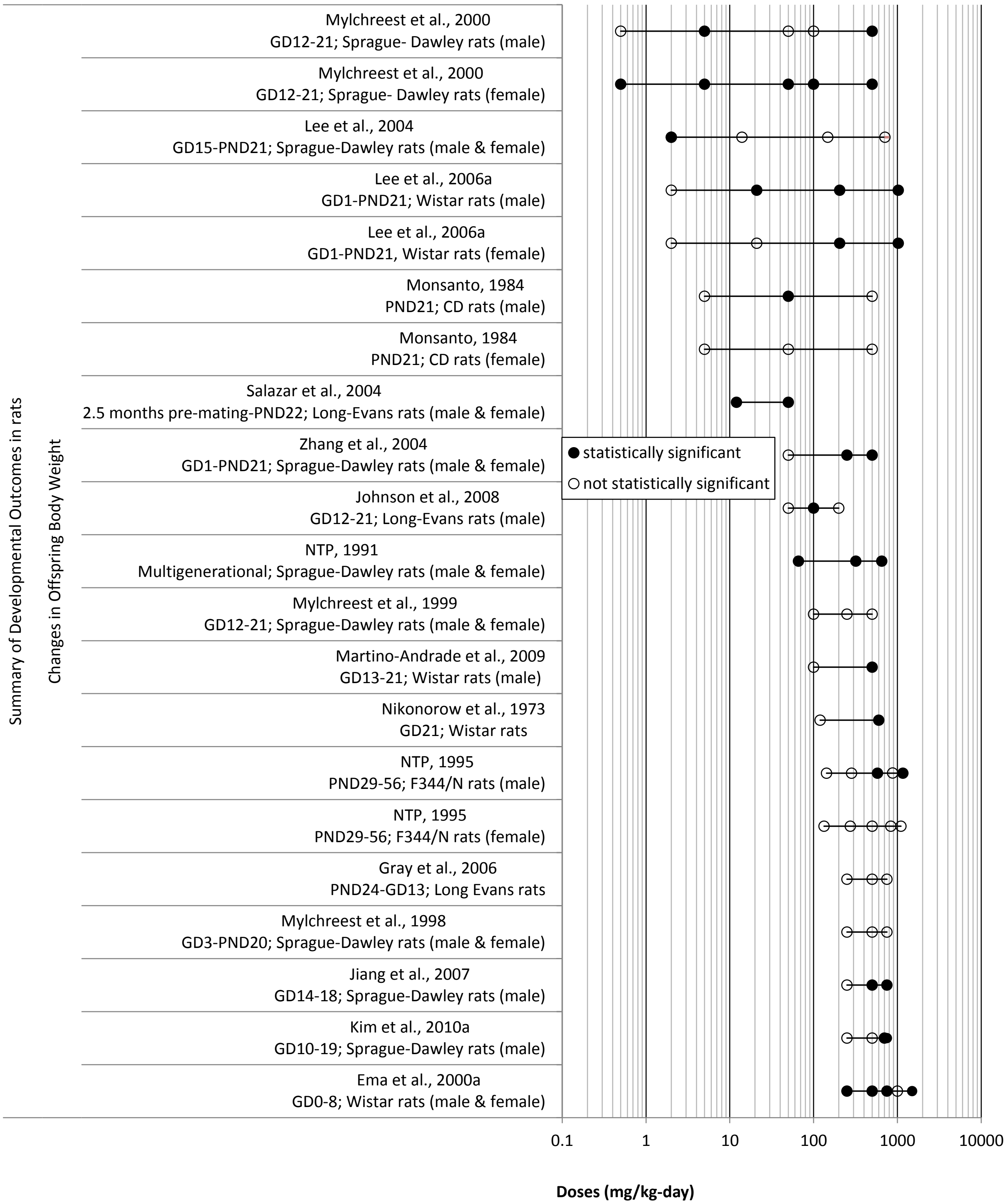

Figure 3-15. Exposure-response array of developmental effects following oral exposure to DBP: alterations in offspring body weight in rats.

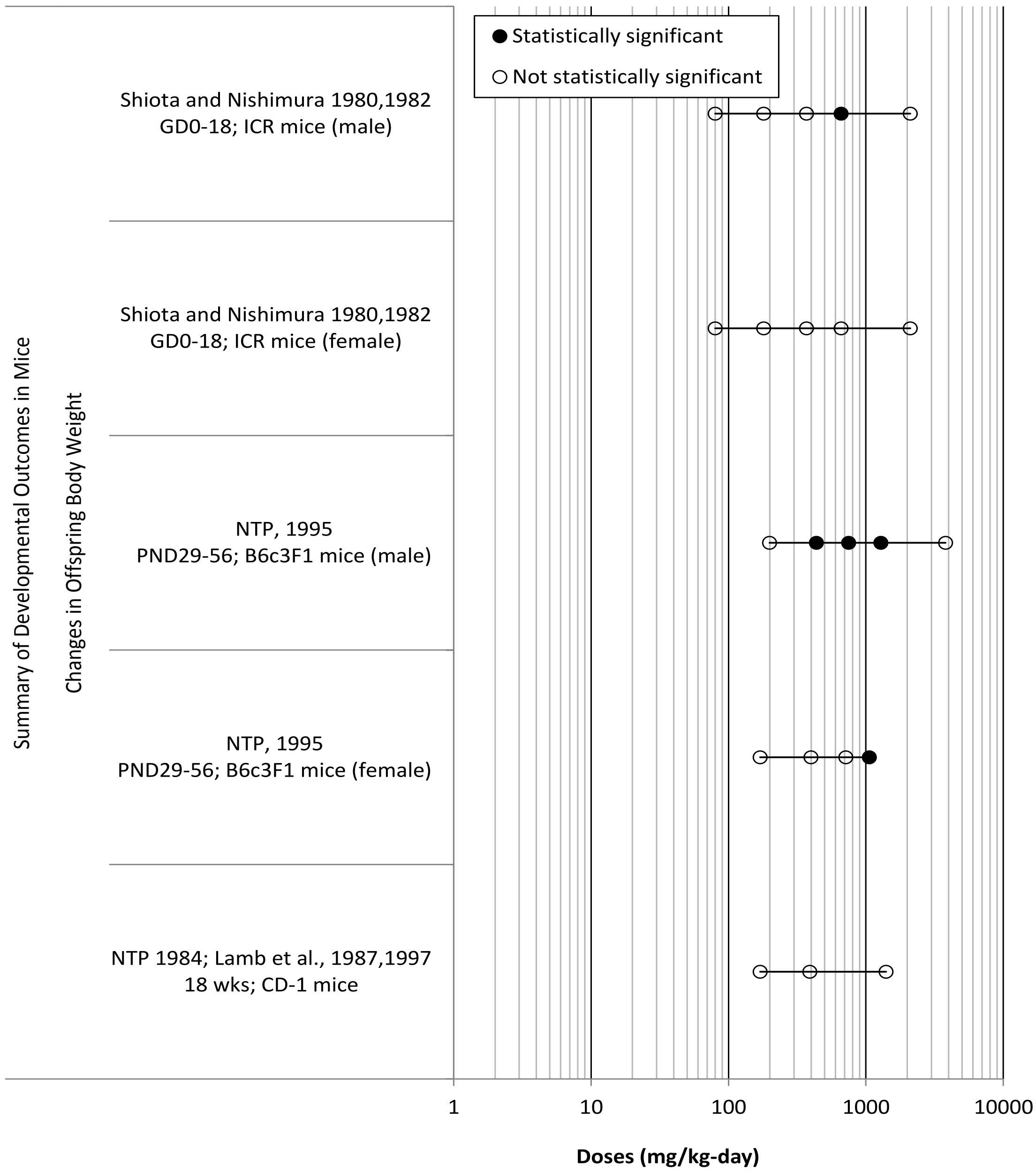

Figure 3-16. Exposure-response array of developmental effects following oral exposure to DBP: alterations in offspring body weight in mice.

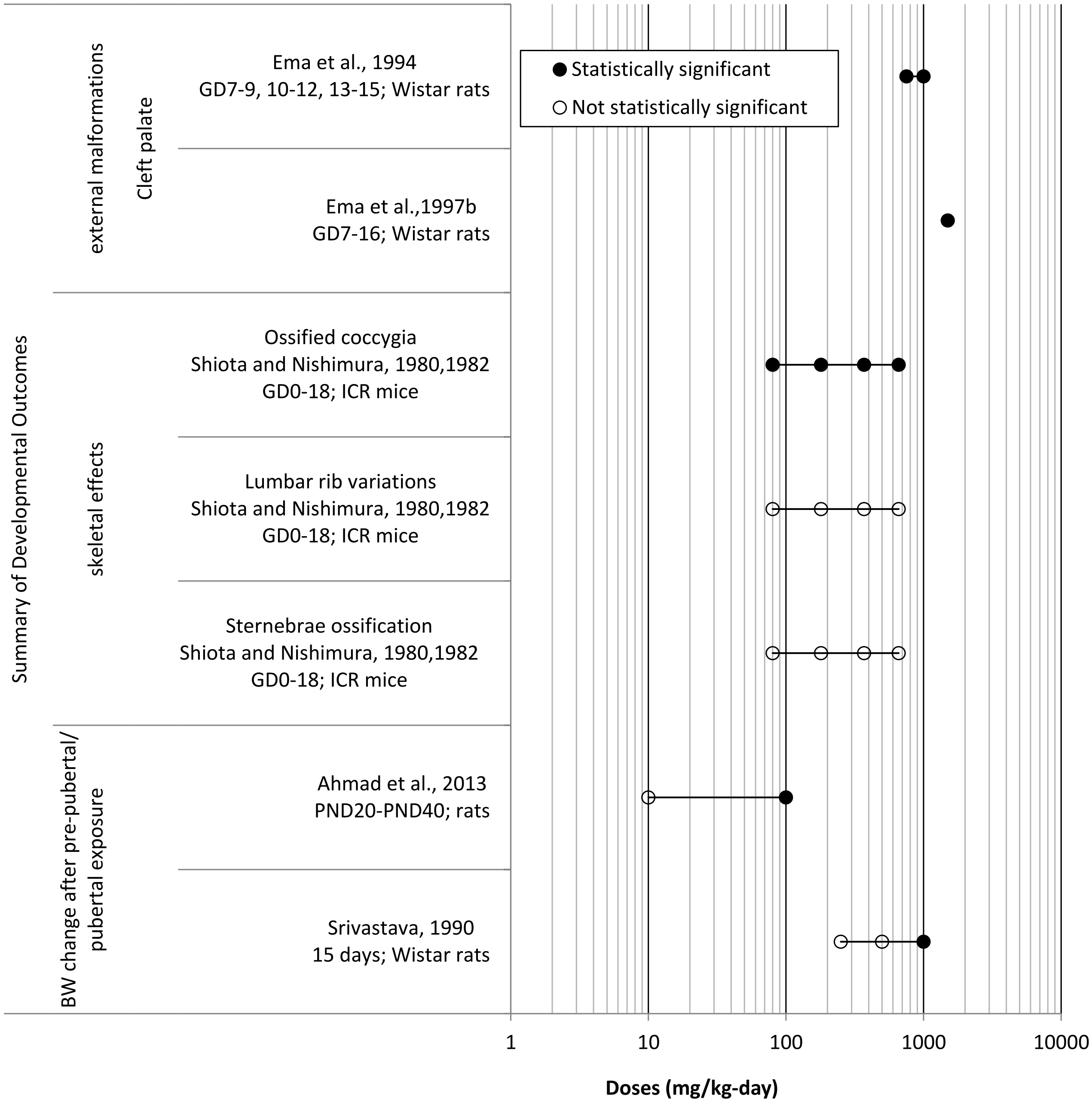

Figure 3-17. Exposure-response array of developmental effects following oral exposure to DBP: external malformations, skeletal effects and body changes after pre-pubertal and pubertal exposure.

Table 3-29. Evidence pertaining to developmental effects following oral exposure to DBP: alterations in offspring sex ratio in animals

Reference and study design	Results						
Sex ratio							
Mylchreest et al. (2000) Rat (Sprague-Dawley); 11-20 dams/group 0, 0.5, 5, 50, 100, 500 mg/kg-day Gavage GDs 12-21	Doses	0	0.5	5	50	100	500
	Sex ratio						
	Live M/total	51	50	47	49	59	47
Lee et al. (2004) Rat (Sprague-Dawley); 6-8/group 0, 2, 14, 148, 712 mg/kg-day Diet GDs 15-20	Doses	0	2	14	148	712	
	Sex ratio						
	Percent M	66%	51%	47%	44*%	25*%	
Zhang et al. (2004b) Rat (Sprague-Dawley); 14-16 dams/group 0, 50, 250, 500 mg/kg-day Gavage GD 1-PND 21	Doses	0	50	250	500		
	Total numbers of live F1 pups						
	M/F	77/68	74/73	68/81	63/79		
	Sex ratio						
	Percent M	53%	50%	46%	44%		
NTP (1991) Rat (Sprague-Dawley); 20 breeding pairs/dose; 40 F0 control breeding pairs 0, 0.1, 0.5, 1% Diet (0, 66, 320, or 651 mg/kg-day) Diet 7-day pre-cohabitation, 112-day cohabitation, ~60 days post-cohabitation (continuous breeding)	Doses	0	80	385	794		
	Sex ratio F1 litter						
	Percent M	50%	50%	51%	45%		

Reference and study design	Results							
Salazar et al. (2004) Rat (Long Evans); 15 dams/group 0, 12, 50 mg/kg-day Diet Dams: 2.5 months before mating to PND 22; Pups: PND 22-PNW 12	Doses	0	12	50				
	Sex prevalence							
	F:M	1.1	0.9	1.1				
Mylchreest et al. (1999a) Rat (Sprague-Dawley); 10 dams/group; offspring weight assessed in 9-10 litters/group 0, 100, 250, 500 mg/kg-day Gavage GDs 12-21	Doses	0	100	250	500			
	Sex ratio							
	M/total	0.5	0.6	0.5	0.5			
Mylchreest et al. (1998) Rat (Sprague-Dawley); 10 dams/group; 4-7 litters/group 0, 250, 500, 750 mg/kg-day Gavage GD 3–PND 20 (2-day interruption at parturition, PNDs 1-2)	Doses	0	250	500	750			
	Sex ratio							
	M/total	0.5	0.5	0.5	0.5			
Ema et al. (2000) Rat (Wistar); 13 dams/group 0, 250, 500, 750, 1,000, 1,250, or 1,500 mg/kg-day Gavage GDs 0-8	Doses	0	250	500	750	1,000	1,250	1,500
	Total numbers of live F1 pups							
	M/F	91/86	99/87	77/74	60/67	39/33	26/19	20/11
	Sex ratio							
	Percent M	51%	53%	51%	47%	54%	58%	65%

*Statistically different from controls ($p < 0.05$), as reported by study authors.

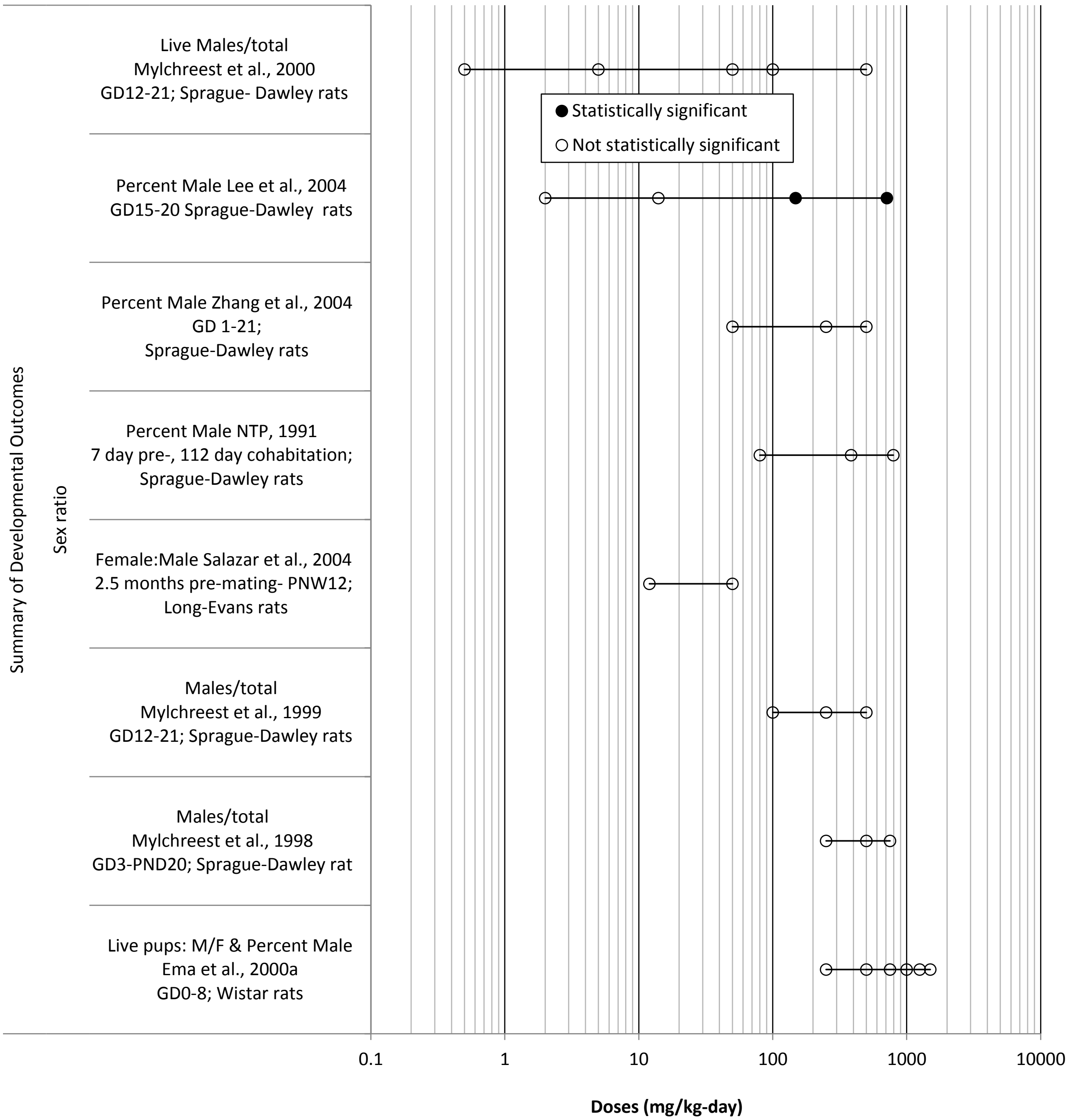

Figure 3-18. Exposure-response array of developmental effects following oral exposure to DBP: alterations on sex ratio changes after gestational exposure.

3.3.4. Liver Effects

Table 3-30. Evidence pertaining to liver effects in animals following oral exposure to DBP

Reference and study design	Results					
Liver weight change						
Mylchreest et al. (2000) Rat (Sprague-Dawley); 11-20 litters/group; assessed in 2 males/litter 0, 0.5, 5, 50, 100, 500 mg/kg-day Gavage GDs 12-21	*response relative to control*					
	Doses	0	0.5	5	50	100	500
	Absolute liver weight					
	PND 110±10	0%	-1%	3%	-2 %	-3%	-3%
Lee et al. (2004) Rat (Sprague-Dawley); 6-8 dams/group; assessed in 8-10 offspring/sex/group 0, 2-3, 14-29, 148-291, 712-1,372 mg/kg-day Diet GDs 15-PND 21 Note: Doses represent a range estimated by the study authors for three different time periods (GDs 15-20, PNDs 2-10, and PNDs 10-21).	*response relative to control*					
	Doses	0	2-3	14-29	148-291	712-1,372
	Relative liver weight *(PND 21)*					
	M	0%	-5%	0%	4%	29*%
	F	0%	-7%	1%	-2%	27*%
	Relative liver weight *(PND 77)*					
	M	0%	-1%	-1%	0%	-1%
	F	0%	-1%	9%	3%	-4%
	Relative liver weight *(PND 140)*					
	M	0%	4%	11%	4%	NA
	F	0%	4%	0%	1%	1%
Monsanto (1984) Rat (CD); 20 breeding pairs/group; 13-15 animals evaluated [females exposed only] 0, 5, 50, 500 mg/kg-day Diet 14 days before mating and continued through weaning [PND 21]	*response relative to control*					
	Doses	0	5	50	500	
	Absolute liver weight					
		0%	-2%	-14%	5%	
	Relative liver weight					
		0%	2%	-8%	13%	
Monsanto (1984) Rat (CD); 20 breeding pairs/group; 19-20 animals evaluated [males exposed only] 0, 5, 50, 500 mg/kg-day Diet 105 days	*response relative to control*					
	Doses	0	5	50	500	
	Absolute liver weight					
		0%	-2%	0.2%	15*%	
	Relative liver weight					
		0%	1%	3%	18*%	

<table>
<tr><th>Reference and study design</th><th colspan="5">Results</th></tr>
<tr><td rowspan="9">BASF (1992)
Rat (Wistar); 10 rats/sex/group
0, 30, 152, 752 mg/kg-day
Diet
3 months (PNDs 42-135)</td><td colspan="5">response relative to control</td></tr>
<tr><td>Doses</td><td>0</td><td>30</td><td>152</td><td>752</td></tr>
<tr><td colspan="5">Absolute liver weight</td></tr>
<tr><td>M</td><td>0%</td><td>1%</td><td>0%</td><td>14%</td></tr>
<tr><td>F</td><td>0%</td><td>2%</td><td>6%</td><td>16*%</td></tr>
<tr><td colspan="5">Relative liver weight</td></tr>
<tr><td>M</td><td>0%</td><td>0%</td><td>3%,</td><td>12*%</td></tr>
<tr><td>F</td><td>0%</td><td>4%</td><td>6%</td><td>19*%</td></tr>
<tr><td colspan="5"></td></tr>
<tr><td rowspan="6">Zhang et al. (2004b)
Rat (Sprague-Dawley); 14-16 dams/group; assessed in 20 male offspring/group
0, 50, 250, 500 mg/kg-day
Gavage
GD 1-PND 21</td><td colspan="5">response relative to control</td></tr>
<tr><td>Doses</td><td>0</td><td>50</td><td>250</td><td>500</td></tr>
<tr><td colspan="5">Absolute liver weight in adults</td></tr>
<tr><td>PND 70</td><td>0%</td><td>-10%</td><td>5%</td><td>-9*%</td></tr>
<tr><td colspan="5">Relative liver weight in adults</td></tr>
<tr><td>PND 70</td><td>0%</td><td>-8%</td><td>9*%,</td><td>-7*%</td></tr>
<tr><td rowspan="4">Mylchreest et al. (1999a)
Rat (Sprague-Dawley); 9-10 litters/group (52-62 male offspring/group)
0, 100, 250, 500 mg/kg-day
Gavage
GDs 12-21</td><td colspan="5">response relative to control</td></tr>
<tr><td>Doses</td><td>0</td><td>50</td><td>250</td><td>500</td></tr>
<tr><td colspan="5">Absolute liver weight in adult offspring</td></tr>
<tr><td>PNDs 100-105</td><td>0%</td><td>-6%</td><td>-6%</td><td>-8%</td></tr>
<tr><td rowspan="8">NTP (1991)
Rat (Sprague-Dawley); 20 sex/group/generation; 40 F0 control breeding pairs, 20 F1 control breeding pairs
0, 0.1, 0.5, 1% (0, 66, 320, or 651 mg/kg-day)
Diet
F0 exposure: 7-day pre-cohabitation; 112 day cohabitation; ~60 days post-cohabitation (continuous breeding)
F1 exposure: gestation, lactation, and post-weaning
Note: study authors did not specify date of necropsy for F1 animals.</td><td colspan="5">response relative to control</td></tr>
<tr><td>Doses</td><td>0</td><td>66</td><td>320</td><td>651</td></tr>
<tr><td colspan="5">Absolute liver weight in adult F1 rats</td></tr>
<tr><td>M</td><td>0%</td><td>-4%</td><td>-2%</td><td>7%</td></tr>
<tr><td>F</td><td>0%</td><td>-5*%</td><td>1%</td><td>-11*%</td></tr>
<tr><td colspan="5">Relative liver weight in adult F1 rats</td></tr>
<tr><td>M</td><td>0%</td><td>-4%</td><td>-1%</td><td>16*%</td></tr>
<tr><td>F</td><td>0%</td><td>-2%</td><td>1%</td><td>2%</td></tr>
<tr><td rowspan="3"></td><td colspan="5">response relative to control</td></tr>
<tr><td>Doses</td><td>0</td><td>100</td><td colspan="2">500</td></tr>
<tr><td colspan="5">Absolute liver weight in pre-pubertal rats</td></tr>
</table>

Reference and study design	Results						
Lee et al. (2008) Rat (Sprague-Dawley); 6 males/group 0, 100, 500 mg/kg-day Gavage 30 days in pre-pubertal male rats		0%	7%	45*%			
	Relative liver weight in pre-pubertal rats						
		0%	6%	44*%			
NTP (1995) Rat (F344); up to 24 dams/treatment group and 48 control dams; assessed in 10 offspring/sex/group 0, 1,250, 2,500, 5,000, 7,500, 10,000, 20,000 ppm (Gestation-lactation doses[a]: 0, 138, 275, 550, 825, 1,100, 2,200 mg/kg-day; Postweaning doses: 0, 143, 284, 579, 879, 1,165 mg/kg-day in males; 0, 133, 275, 500, 836, 1,104 mg/kg-day in females) Diet GD 1-PND 56	*response relative to control*						
	Doses (M)	0	143	284	579	879	1,165
	Liver weight F1 rats (*PND 56*)						
	Absolute	0%	8%	8%	23*%	30*%	41*%
	Relative	0%	8*%	10*%	29*%	44*%	49*%
	Doses (F)	0	133	275	500	836	1,104
	Liver weight F1 rats (*PND 56*)						
	Absolute	0%	3%	6*%	15*%	12*%	21*%
	Relative	0%	4%	6*%	14*%	16*%	27*%
	Note: no pups survived postpartum in 20,000 ppm treatment group						
NTP (1995) Mouse (B6C3F_1); 10 sex/group Males: 0, 163, 353, 812, 1,601, 3,689 mg/kg-day; Females: 0, 238, 486, 971, 2,137, 4,278 mg/kg-day Diet 91 days	*response relative to control*						
	Doses (M)	0	163	353	812	1,601	3,689
	Liver weight						
	Absolute	0%	-3%	4%	-2%	7%	19*%
	Relative	0%	-3%	6%	7*%	16*%	38*%
	Doses (F)	0	238	486	971	2,137	4,278
	Liver weight						
	Absolute	0%	8%	7%	0%	13*%	34*%
	Relative	0%	3%	2%	8*%	19*%	52*%
NTP (1995) Rat (F344); 10 sex/group Males: 0, 176, 359, 720, 1,540, 2,964 mg/kg-day; Females: 0, 177, 356, 712, 1,413, 2,943 mg/kg-day Diet 91 days	*response relative to control*						
	Doses (M)	0	176	359	720	1,540	2,964
	Liver weight						
	Absolute	0%	3%	17*%	22*%	28*%	-26*%
	Relative	0%	6%	18*%	32*%	54*%	70*%
	Doses (F)	0	177	356	712	1,413	2,943
	Liver weight						
	Absolute	0%	-2%	6%	9*%	15*%	30*%
	Relative	0%	0%	4%	11*%	25*%	78*%
NTP (1995)	*response relative to control*						
	Doses (M)	0	199	437	750	1,286	3,804

Reference and study design	Results					
Mouse ($B6C3F_1$); up to 20 dams/group; assessed in 10 offspring/sex/group 0, 1,250, 2,500, 5,000, 7,500, 10,000, 20,000 ppm (Gestation-lactation doses[b]: 0, 244, 488, 975, 1,463, 1,950, 3,900 mg/kg-day; Postweaning doses: 0, 199, 437, 750, 1,286, 3,804 mg/kg-day in males; 0, 170, 399, 714, 1,060, NA mg/kg-day in females)[5] Diet GD 1-PND 56	**Liver weight F1 rats** (*PND 56)*					
	Absolute	0%	3%	0%	5%	8*%	-6%
	Relative	0%	6*%	8*%	17*%	23*%	31%
	Doses (F)	0	170	399	714	1,060	NA
	Liver weight F1 rats (*PND 56)*					
	Absolute	0%	15%	11%	15%	-5%	-
	Relative	0%	9%	12%	17%	5%	-
	Note: no pups survived postpartum in 20,000 ppm treatment group. One male and no female pups survived postpartum in 10,000 ppm group					
Mylchreest et al. (1998) Rat (Sprague-Dawley); 10 dams/group; assessed in 4-9 dams/group at study termination 0, 250, 500, 750 mg/kg-day Gavage GD 3-PND 20	*response relative to control*					
	Doses	0	250	500	750		
	Absolute liver weight in dams						
	PND 21	0%	2%	3%	4%		
Jiang et al. (2007) Rat (Sprague-Dawley); 10 dams/group; assessed in 21-57 male offspring/group 0, 250, 500, 750, 1,000 mg/kg-day Gavage GDs 14-18 Note: no offspring survived in the high dose group (1,000 mg/kg-day)	*response relative to control*					
	Doses	0	250	500	750		
	Relative liver weight in adult male offspring						
	PND 70	0%	-2%	-13*%	-28*%		
	Relative liver weight in adult male offspring with hypospadias						
	PND 70	0%		-22*%	-37*%		
Murakami et al. (1986) Rat (Wistar); 5 males/group 0, 461, 4,610 mg/kg-day[c] Diet 34 or 36 days for low and high dose groups respectively	*response relative to control*					
	Doses	0	461	4,610			
	Liver weight						
	Absolute	0%	-12%	2%			
	Relative	0%	8%	70*%			
Histopathological effects							
	Doses	0	2-3	14-29	148-291	712-1,372	
	Cell hypertrophy (M) *(PND 21)*						
	Incidence	0/8	0/8	0/8	0/8	8/8*	
	Percent	0%	0%	0%	0%	100*%	
	Cell hypertrophy (F) *(PND 21)*						
	Incidence	0/8	0/8	0/8	0/8	8/8*	

Reference and study design	Results					
Lee et al. (2004) Rat (Sprague-Dawley); 6-8 dams/group; assessed in 8-10 offspring/sex/group 0, 2-3, 14-29, 148-291, 712-1,372 mg/kg-day Diet GD 15-PND 21 Note: Doses represent a range estimated by the study authors for three different time periods (GDs 15-20, PNDs 2-10, and PNDs 10-21).	*Percent*	0%	0%	0%	0%	100*%
Monsanto (1984) Rat (CD); 20 breeding pairs/group; 19-20 animals evaluated [males exposed only] 0, 5, 50, 500 mg/kg-day Diet 105 days	Doses	0	5	50	500	
	Moderate liver congestion					
	Incidence	0/19	0/20	0/19	0/19	
	Percent	0%	0%	0%	0%	
	Moderate liver hemorrhage					
	Incidence	0/19	0/20	0/19	0/19	
	Percent	0%	0%	0%	0%	
	Mononuclear cell infiltration					
	Incidence	0/19	0/20	1/19	0/19	
	Percent	0%	0%	5%	0%	
Monsanto (1984) Rat (CD); 20 breeding pairs/group; 18-20 animals evaluated [females exposed only] 0, 5, 50, 500 mg/kg-day Diet 14 days before mating and continued through weaning PND 21	Doses	0	5	50	500	
	Liver necrosis					
	Incidence	2/20	1/20	0/18	0/20	
	Percent	10%	5%	0%	0%	
	Mild lymphocytic infiltration					
	Incidence	0/20	0/20	1/18	0/20	
	Percent	0%	0%	6%	0%	
BASF (1992) Rat (Wistar); 10 rats/sex/group 0, 30, 152, 752 mg/kg-day Diet 3 months (PNDs 42-135)	Doses	0	30	152	752	
	Lipid vacuoles (M)					
	Incidence	10/10	10/10	10/10	4/10	
	Percent	100	100	100	40	
	Granulomas (M)					
	Incidence	10/10	9/10	10/10	10/10	
	Percent	100	90	100	100	
	Lipid vacuoles (F)					

Reference and study design	Results						
	Incidence	10/10	10/10	10/10	5/10		
	Percent	100	100	100	50		
	Granulomas (F)						
	Incidence	10/10	10/10	10/10	9/10		
	Percent	100	100	100	90		
NTP (1995) Mouse ($B6C3F_1$); 10 sex/group Males: 0, 163, 353, 812, 1,601, 3,689 mg/kg-day; Females: 0, 238, 486, 971, 2,137, 4,278 mg/kg-day Diet 13 weeks	Doses (M)	0	163	353	812	1,601	3,689
	Hepatocyte cytoplasmic alterations						
	Incidence	0/10	0/10	0/10	0/10	6/10*	10/10*
	Percent	-	0%	0%	0%	60*%	100*%
	Doses (F)	0	238	486	971	2,137	4,278
	Hepatocyte cytoplasmic alterations						
	Incidence	0/10	0/10	0/10	0/10	0/10	10/10*
	Percent	-	0%	0%	0%	0%	100*%
NTP (1995) Rat (F344/N); 10 sex/group Males: 0, 176, 359, 720, 1,540, 2,964 mg/kg-day; Females: 0, 177, 356, 712, 1,413, 2,943 mg/kg-day Diet 13 weeks	Doses (M)	0	176	359	720	1,540	2,964
	Hepatocyte cytoplasmic alterations						
	Incidence	0/10	0/10	0/10	10/10*	10/10*	10/10*
	Percent	0%	0%	0%	100*%	100*%	100*%
	Doses (F)	0	177	356	712	1,413	2,943
	Hepatocyte cytoplasmic alterations						
	Incidence	0/10	0/10	0/10	10/10*	10/10*	10/10*
	Percent	0%	0%	0%	100*%	100*%	100*%
NTP (1991) Rat (Sprague-Dawley); 20 sex/group/generation; 40 F0 control breeding pairs, 20 F1 control breeding pairs 0, 0.1, 0.5, 1% (0, 66, 320, or 651 mg/kg-day) Diet F0 exposure: 7-day pre-cohabitation; 112 day cohabitation; ~60 days post-cohabitation (continuous breeding) F1 exposure: gestation, lactation, and post-weaning Note: study authors did not specify date of necropsy for F1 animals.	Doses	0	320	651			
	Hepatocellular degeneration in adult F1 (M)						
	Incidence	7/10	1/10	3/10			
	Percent control	70%	10%	30%			

Reference and study design	Results						
Liver Enzymes and serum clinical chemistry							
BASF (1992) Rat (Wistar); 10 rats/sex/group 0, 30, 152, 752 mg/kg-day Diet 3 months (PNDs 42-135)	*response relative to control*						
	Doses (M)	0	30	152	752		
	Hepatic Palmitoyl CoA activity	0%	-5%	21%	166*%		
	Triglycerides	0%	36%	13%	-11%		
	Doses (F)	0	30	152	752		
	Hepatic Palmitoyl CoA activity	0%	21%	13%	121*%		
	Triglycerides	0%	20%	-8%	-45*%		
NTP (1995) Rat (F344); 5 dams/group; 15 control dams 0, 1,250, 2,500, 5,000, 7,500, 10,000, 20,000 ppm (0, 138, 275, 550, 825, 1,100, 2,258 mg/kg-day) during gestation[a] Diet Up to 20 days during gestation	*response relative to control*						
	Doses	0	138	275	550	825	1,100
	Hepatic Palmitoyl CoA activity						
	Dams	0%	220*%	240*%	160*%	40%	60%
	Fetuses	0%	33%	67%	33%	33%	33%
NTP (1995) Rat (F344); 10 sex/group; (palmitoyl CoA activity assessed in 5 rats/sex/group) Males: 0, 176, 359, 720, 1,540, 2,964 mg/kg-day Females: 0, 177, 356, 712, 1,413, 2,943 mg/kg-day Diet 13 weeks	*response relative to control*						
	Doses (M)	0	176	359	720	1,540	2,964
	Hepatic Palmitoyl CoA activity	0%	6%	94*%	471*%	868*%	1,210*%
	Serum ALP	0%	-2%	-5%	3%	54*%	75*%
	Serum bile acids	0%	-16%	13%	33%	141*%	291*%
	Alanine aminotransferase	0%	0%	-12%	-6%	-20%	20%
	Sorbitol dehydrogenase	0%	0%	-8%	-16%	-32*%	-24*%
	Cholesterol	0%	4%	5%	-5%	-34*%	-53*%
	Triglycerides	0%	-27*%	-28*%	-49*%	-79*%	-86*%
	Doses (F)	0	177	356	712	1,413	2,943
	Hepatic Palmitoyl CoA activity	0%	31%	69*%	156*%	1,000*%	3,144*%
	Serum ALP	0%	-1%	7%	28*%	31*%	92*%
	Serum bile acids	0%	39%	62*%	59*%	80*%	205*%
	Alanine aminotransferase	0%	-11%	-4%	-2%	2%	13*%

Reference and study design	Results						
	Sorbitol dehydrogenase	0%	-7%	-4%	4%	4%	0%
	Cholesterol	0%	-1%	-2%	-8%	-25*%	-49*%
	Triglycerides	0%	6%	-1%	-35*%	-48*%	-65*%

PND = Postnatal day; NA = Not available; a sufficient number of male animals could not be obtained.
[a]Doses calculated using U.S. EPA (1988) reference subchronic values for food intake (0.014 kg/day) and body weight (0.124 kg) in female F344 rats.
[b]Doses calculated using U.S. EPA (1988) reference subchronic values for food intake (0.0048 kg/day) and body weight (0.0065 kg) in female B6C3F1 mice.
[c]Murakami et al. (1986) provided information on dietary levels of DBP. Based on U.S. EPA (1988) default values for body weight (0.217 kg) and food consumption (0.020 kg/day).
*Statistically increased over control as reported by study authors.

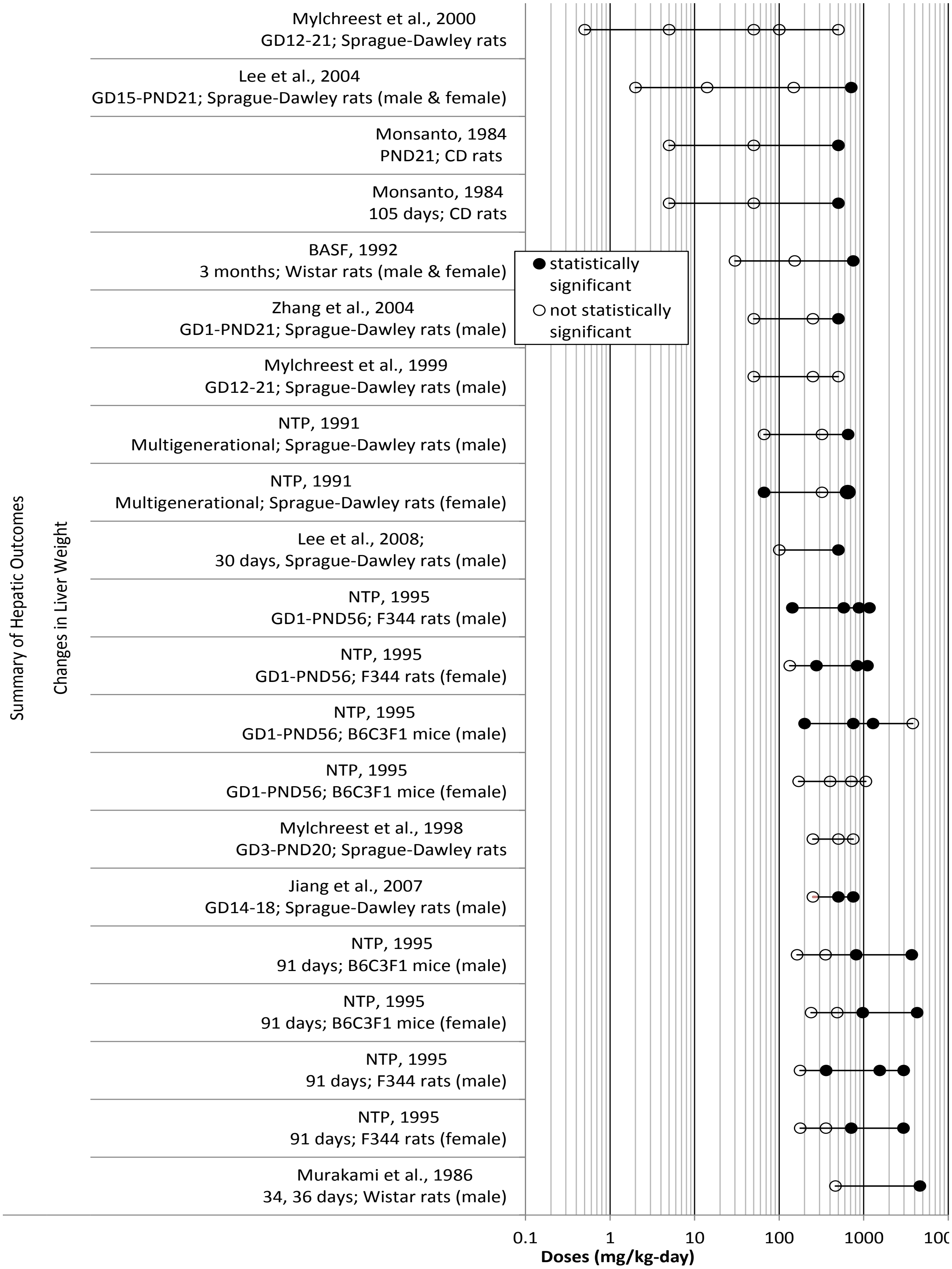

Figure 3-19. Exposure-response arrays of alterations in liver weight following oral exposure to DBP.

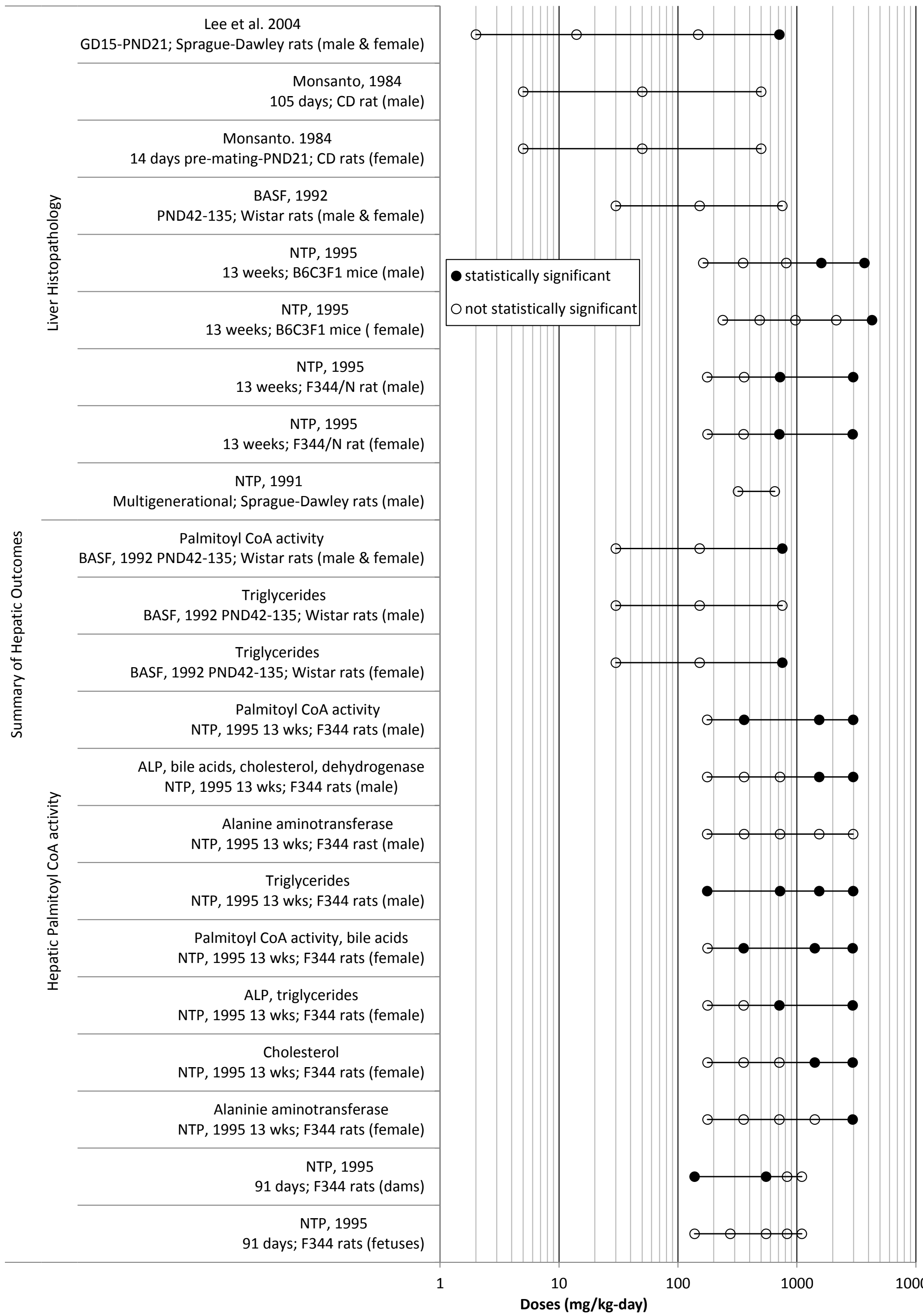

Figure 3-20. Exposure-response arrays of alterations in liver histopathology and serum markers following oral exposure to DBP.

3.3.5. Kidney Effects

Table 3-31. Evidence pertaining to kidney effects in animals following oral exposure to DBP

Reference and study design	Results						
Kidney weight change							
Mylchreest et al. (2000) Rat (Sprague-Dawley); 11-20 litters/group; assessed in 2 males/litter 0, 0.5, 5, 50, 100, 500 mg/kg-day Gavage GDs 12-21	*response relative to control*						
	Doses	0	0.5	5	50	100	500
	Absolute kidney weight						
	PND 110±10	0%	1%	1%	2%	-2%	-4%
Lee et al. (2004) Rat (Sprague-Dawley); 6-8 dams/group; assessed in 8-10 offspring/sex/group 0, 1.5-3.0, 14.4-28.5, 148.2-290.9, 712.3-1,371.8 mg/kg-day Diet GD 15-PND 21 Note: Doses represent a range estimated by the study authors for three different time periods (GDs 15-20, PNDs 2-10, and PNDs 10-21).	*response relative to control*						
	Doses	0	2-3	14-29	148-291	712-1,372	
	Relative kidney weight *(PND 21)*						
	M	0%	-3%	2%	4%	3%	
	F	0%	-3%	5%	11%	2%	
	Relative kidney weight *(PND 77)*						
	M	0%	-4%	-1%	-3%	-12*%	
	F	0%	5%	3%	5%	-3%	
	Relative kidney weight *(PND 140)*						
	M	0%	0%	2%	-3%	NA[a]	
	F	0%	8%	4%	0%	-2%	
Monsanto (1984) Rat (CD); 20 breeding pairs/group; 19-20 animals evaluated [males exposed only] 0, 5, 50, 500 mg/kg-day Diet 105 days	*response relative to control*						
	Doses	0	5	50	500		
	Absolute kidney weight						
		0%	5%	5%	10*%		
	Relative kidney weight						
		0%	8*%	8*%	13*%		
Monsanto (1984) Rat (CD); 20 breeding pairs/group; 13-15 animals evaluated [females exposed only] 0, 5, 50, 500 mg/kg-day Diet 14 days before mating and continued through weaning [PND 21]	*response relative to control*						
	Doses	0	5	50	500		
	Absolute kidney weight						
		0%	5%	-5%	7%		
	Relative kidney weight						
		0.5%	95%	2%	15*%		

Reference and study design	Results					
BASF (1992) Rat, Wistar; 6-week-old rats; assessed in 10 rats/sex/group 0, 30, 152, 752 mg/kg-day Diet 3 months PNDs 42-135	*response relative to control*					
	Doses	0	30	152	752	
	Absolute kidney weight					
	M	0%	-8*%	-2%	7%	
	F	0%	1%	6%	9*%	
	Relative kidney weight					
	M	0%	-8*%	1%	5%	
	F	0%	3%	6%	13*%	
Zhang et al. (2004b) Rat (Sprague-Dawley); 14-16 dams/group; assessed in 20 male offspring/group 0, 50, 250, 500 mg/kg-day Gavage GD 1-PND 21	*response relative to control*					
	Doses	0	50	250	500	
	Kidney weight in adult offspring *(PND 70)*					
	Absolute	0%	0%	-4%	-9*%	
	Relative	0%	1%	-1%	-7*%	
NTP (1991) Rat (Sprague-Dawley); 20 sex/group/generation; 40 F0 control breeding pairs, 20 F1 control breeding pairs 0, 0.1, 0.5, 1% (0, 66, 320, or 651 mg/kg-day) Diet F0 exposure: 7-day pre-cohabitation; 112 day cohabitation; ~60 days post-cohabitation (continuous breeding) F1 exposure: gestation, lactation, and post-weaning Note: study authors did not specify date of necropsy for F1 animals.	*response relative to control*					
	Doses	0	66	320	651	
	Absolute kidney weight in adult F1 rats					
	M	0%	3%	3%	-2%	
	F	0%	0%	3%	-9*%	
	Relative kidney weight in adult F1 rats					
	M	0%	3%	6*%	6*%	
	F	0%	4%	5%	5%	
Mylchreest et al. (1999a) Rat (Sprague-Dawley); 9-10 litters/group (52-62 male offspring/group) 0, 100, 250, 500 mg/kg-day Gavage GDs 12-21	*response relative to control*					
	Doses	0	100	250	500	
	Absolute kidney weight in adult offspring					
	3 months old	0%	-3%	-3%	-9*%	
	response relative to control					
	Doses (F1 M)	0	143	284	579	879	1,165
	Right kidney weight *(PND 56)*					
	Absolute	0%	6%	3%	5%	0%	5%

Reference and study design	Results						
NTP (1995) Rat (F344); up to 24 dams/treatment group and 48 control dams; assessed in 10 offspring/sex/group 0, 1,250, 2,500, 5,000, 7,500, 10,000, 20,000 ppm (Gestation-lactation doses[b]: 0, 138, 275, 550, 825, 1,100, 2,200 mg/kg-day; Postweaning doses: 0, 143, 284, 579, 879, 1,165 mg/kg-day in males; 0, 133, 275, 500, 836, 1,104 mg/kg-day in females) Diet GD 1-PND 56	*Relative*	0%	6*%	5*%	10*%	10*%	11*%
	Doses (F1 F)	0	133	275	500	836	1,104
	Right kidney weight *(PND 56)*						
	Absolute	0%	2%	3%	10*%	1%	1%
	Relative	0%	3%	3%	8*%	4*%	6*%
	Note: no pups survived postpartum in 20,000 ppm treatment group						
NTP (1995) Mouse ($B6C3F_1$); 10 sex/group Males: 0, 163, 353, 812, 1,601, 3,689 mg/kg-day; Females: 0, 238, 486, 971, 2,137, 4,278 mg/kg-day Diet 91 days	*response relative to control*						
	Doses (M)	0	163	353	812	1,601	3,689
	Right kidney weight						
	Absolute	0%	2%	-1%	-3%	-5%	-15*%
	Relative	0%	1%	1%	6%	2%	-2%
	Doses (F)	0	238	486	971	2,137	4,278
	Right kidney weight						
	Absolute	0%	16*%	13*%	16*%	15*%	9%
	Relative	0%	11*%	8*%	26*%	22*%	24*%
NTP (1995) Rat (F344); 10 sex/group Males: 0, 176, 359, 720, 1,540, 2,964 mg/kg-day; Females: 0, 177, 356, 712, 1,413, 2,943 mg/kg-day Diet 91 days	*response relative to control*						
	Doses (M)	0	176	359	720	1,540	2,964
	Right kidney weight						
	Absolute	0%	1%	7%	4%	-2%	-41*%
	Relative	0%	4%	8*%	12*%	18*%	36*%
	Doses (F)	0	177	356	712	1,413	2,943
	Right kidney weight						
	Absolute	0%	-2%	6%	6%	0%	-9*%
	Relative	0%	1%	3%	9*%	10*%	24*%
NTP (1995) Mouse ($B6C3F_1$); up to 20 dams/group; assessed in 10 offspring/sex/group 0, 1,250, 2,500, 5,000, 7,500, 10,000, 20,000 ppm (Gestation-lactation doses[c]: 0, 244, 488, 975, 1,463, 1,950,	*response relative to control*						
	Doses (F1 M)	0	199	437	750	1,286	3,804
	Right kidney weight *(PND 56)*						
	Absolute	0%	0%	-5%	-12*%	-12*%	-26%
	Relative	0%	2%	3%	-2%	0%	4%

<table>
<tr><th>Reference and study design</th><th colspan="7">Results</th></tr>
<tr><td rowspan="5">3,900 mg/kg-day; Postweaning doses: 0, 199, 437, 750, 1,286, 3,804 mg/kg-day in males; 0, 170, 399, 714, 1,060, NA mg/kg-day in females)
Diet
GD 1-PND 56</td><td>Doses (F1 F)</td><td>0</td><td>170</td><td>399</td><td>714</td><td>1,060</td><td>NA</td></tr>
<tr><td colspan="7">Right kidney weight (PND 56)</td></tr>
<tr><td>Absolute</td><td>0%</td><td>17*%</td><td>15*%</td><td>13*%</td><td>7*%</td><td>-</td></tr>
<tr><td>Relative</td><td>0%</td><td>12*%</td><td>16*%</td><td>17*%</td><td>21*%</td><td>-</td></tr>
<tr><td colspan="7">Note: no pups survived postpartum in 20,000 ppm treatment group. One male and no female pups survived postpartum in 10,000 ppm group</td></tr>
<tr><td rowspan="6">Jiang et al. (2007)
Rat (Sprague-Dawley); 10 dams/group; assessed in 21-57 male offspring/group
0, 250, 500, 750 mg/kg-day
Gavage
GDs 14-18</td><td colspan="7">response relative to control</td></tr>
<tr><td>Doses</td><td>0</td><td>250</td><td>500</td><td colspan="3">750</td></tr>
<tr><td colspan="7">Relative right kidney weight in adult offspring (M)</td></tr>
<tr><td>PND 70</td><td>0%</td><td>1%</td><td>-13*%</td><td colspan="3">-28*%</td></tr>
<tr><td colspan="7">Relative left kidney weight in adult offspring (M)</td></tr>
<tr><td>PND 70</td><td>0%</td><td>-5%</td><td>-18*%</td><td colspan="3">-33*%</td></tr>
<tr><td rowspan="4">Mylchreest et al. (1998)
Rat (Sprague-Dawley); 10 dams/group; assessed in 4-9 dams/group at study termination
0, 250, 500, 750 mg/kg-day
Gavage
GD 3-PND 20</td><td colspan="7">response relative to control</td></tr>
<tr><td>Doses</td><td>0</td><td>250</td><td>500</td><td colspan="3">750</td></tr>
<tr><td colspan="7">Absolute kidney weight in dams</td></tr>
<tr><td>PND 21</td><td>0%</td><td>8%</td><td>10%</td><td colspan="3">-19%</td></tr>
<tr><td rowspan="5">Murakami et al. (1986)
Rat (Wistar); 5 males/group
0, 461, 4,610 mg/kg-day[d]
Diet
34 or 36 days for low and high dose groups, respectively</td><td colspan="7">response relative to control</td></tr>
<tr><td>Doses</td><td>0</td><td colspan="2">461</td><td colspan="3">4,610</td></tr>
<tr><td colspan="7">Kidney weight</td></tr>
<tr><td>Absolute</td><td>0%</td><td colspan="2">-7%</td><td colspan="3">-21%</td></tr>
<tr><td>Relative</td><td>0%</td><td colspan="2">14%</td><td colspan="3">36*%</td></tr>
<tr><td colspan="8">Kidney histopathology</td></tr>
<tr><td rowspan="10">Monsanto (1984)
Rat (CD); 20 breeding pairs/group;
19-20 animals evaluated [males exposed only]
0, 5, 50, 500 mg/kg-day
Diet
105 days</td><td colspan="7">response relative to control</td></tr>
<tr><td>Doses</td><td>0</td><td>5</td><td>50</td><td colspan="3">500</td></tr>
<tr><td colspan="7">Mild kidney hydronephrosis</td></tr>
<tr><td>Incidence</td><td>0/19</td><td>0/20</td><td>1/19</td><td colspan="3">0/19</td></tr>
<tr><td>Percent</td><td>0%</td><td>0%</td><td>5%</td><td colspan="3">0%</td></tr>
<tr><td colspan="7">Mild kidney mineralization</td></tr>
<tr><td>Incidence</td><td>0/19</td><td>0/20</td><td>1/19</td><td colspan="3">0/19</td></tr>
<tr><td>Percent</td><td>0%</td><td>0%</td><td>5%</td><td colspan="3">0%</td></tr>
<tr><td colspan="7">Chronic nephropathy</td></tr>
<tr><td>Incidence</td><td>1/19</td><td>2/20</td><td>2/19</td><td colspan="3">0/19</td></tr>
</table>

Reference and study design	Results				
	Percent	5%	10%	11%	0%
Monsanto (1984) Rat (CD); 20 breeding pairs/group; 18-20 animals evaluated [females exposed only] 0, 5, 50, 500 mg/kg-day Diet 14 days before mating and continued through weaning [PND 21]	*response relative to control*				
	Doses	0	5	50	500
	Kidney microconcentration				
	Incidence	0/20	3/20	0/18	1/20
	Percent	0%	15%	0%	5%
	Mild kidney mineralization				
	Incidence	1/20	0/20	0/18	0/20
	Percent	5%	0%	0%	0%
	Chronic nephropathy				
	Incidence	0/20	1/20	0/18	1/20
	Percent	0%	5%	0%	5%
BASF (1992) Rat (Wistar); 6-week-old rats; assessed in 10 rats/sex/group 0, 30, 152, 752 mg/kg-day Diet 3 months PNDs 42-135	*response relative to control*				
	Doses	0	30	152	752
	Round cells (M)				
	Incidence	1/10	2/10	1/10	1/10
	Percent	10%	20%	10%	10%
	Urothelial proliferation (M)				
	Incidence	0/10	0/10	1/10	0/10
	Percent	0%	0%	10%	0%
	Intratubular lithiasis (M)				
	Incidence	0/10	0/10	0/10	0/10
	Percent	0%	0%	0%	0%
	Round cells (F)				
	Incidence	0/10	0/10	0/10	0/10
	Percent	0%	0%	0%	0%
	Urothelial proliferation (F)				
	Incidence	0/10	1/10	0/10	0/10
	Percent	0%	10%	0%	0%
	Intratubular lithiasis (F)				
	Incidence	10/10	10/10	10/10	10/10
	Percent	100%	100%	100%	100%

Reference and study design	Results						
Serum markers of renal toxicity							
BASF (1992) Rat (Wistar); 6-week-old rats; assessed in 10 rats/sex/group 0, 30, 152, 752 mg/kg-day Diet 3 months PNDs 42-135	*response relative to control*						
	Doses	0	30	152	752		
	Serum urea						
	M	0%	5%	0.2%	-4%		
	F	0%	-1%	7%	9%		
	Serum creatinine						
	M	0%	6%	1%	5%		
	F	0%	3%	7%	8*%		
NTP (1995) Rat (F344); 10 sex/group Males: 0, 176, 359, 720, 1,540, 2,964 mg/kg-day; Females: 0, 177, 356, 712, 1,413, 2,943 mg/kg-day Diet 13 weeks	*response relative to control*						
	Doses (M)	0	176	359	720	1,540	2,964
	Serum urea nitrogen	0%	1%	-1%	-2%	4%	9%
	Serum creatinine	0%	4%	3%	7%	4%	-6%
	Serum protein	0%	1%	3%	3%	-1%	-13*%
	Serum albumin	0%	5*%	9*%	14*%	19*%	5*%
	Doses (F)	0	177	356	712	1,413	2,943
	Serum urea nitrogen	0%	10%	14%	10%	10%	15%
	Serum creatinine	0%	0%	6%	7%	7%	3%
	Serum protein	0%	-3%	-3%	-1%	-7*%	-15*%
	Serum albumin	0%	-2%	0%	0%	0%	-4%

PND = Postnatal day

[a]NA = Not available; a sufficient number of male animals could not be obtained.

[b]Doses calculated using U.S. EPA (1988) reference subchronic values for food intake (0.014 kg/day) and body weight (0.124 kg) in female F344 rats.

[c]Doses calculated using U.S. EPA (1988) reference subchronic values for food intake (0.0048 kg/day) and body weight (0.0065 kg) in female B6C3F1 mice.

[d]Murakami et al. (1986) provided information on dietary levels of DBP. Based on U.S. EPA (1988) default values for body weight (0.217 kg) and food consumption (0.020 kg/day).

*Statistically increased over control as reported by study authors.

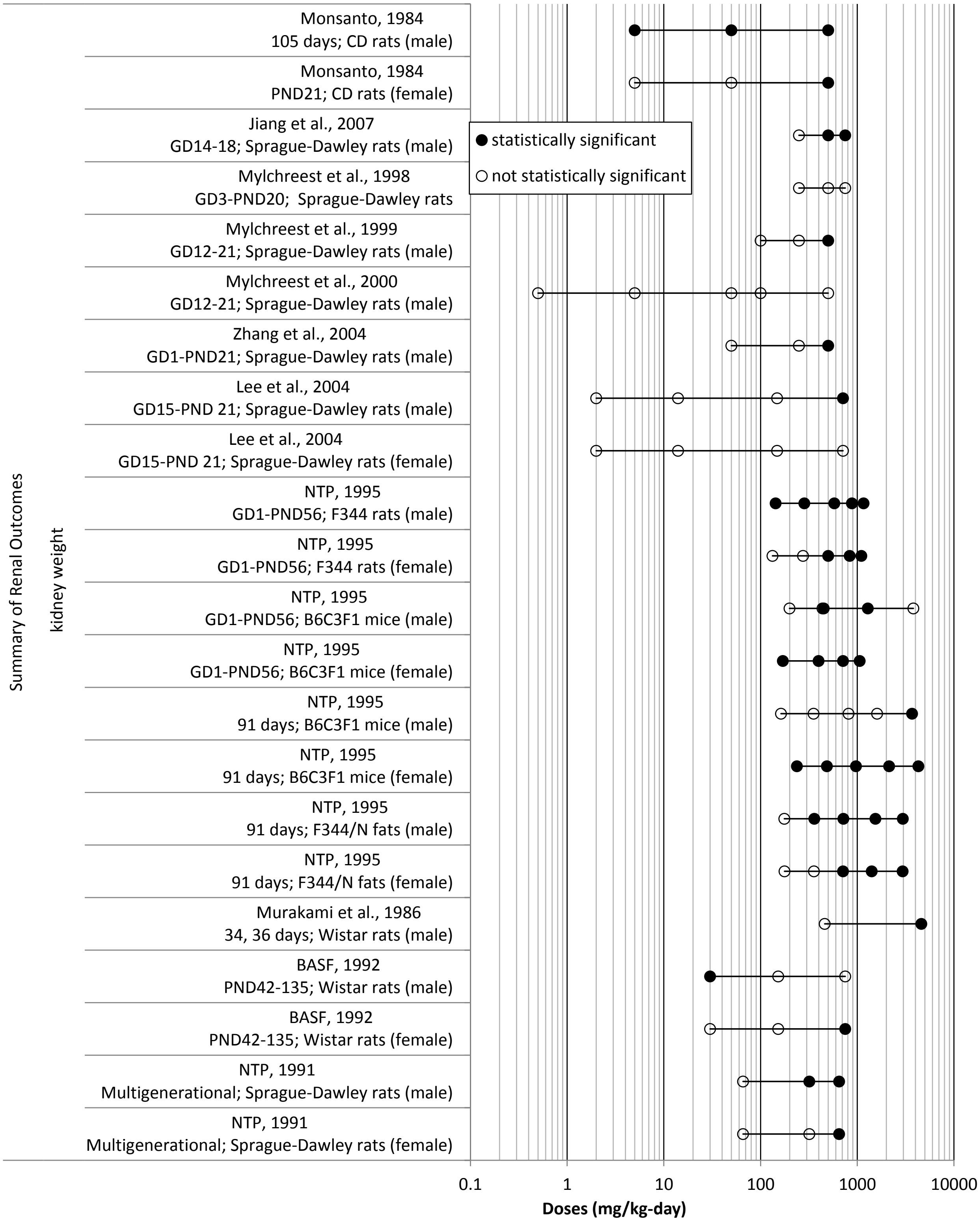

Figure 3-21. Exposure-response array of kidney weight following oral exposure to DBP.

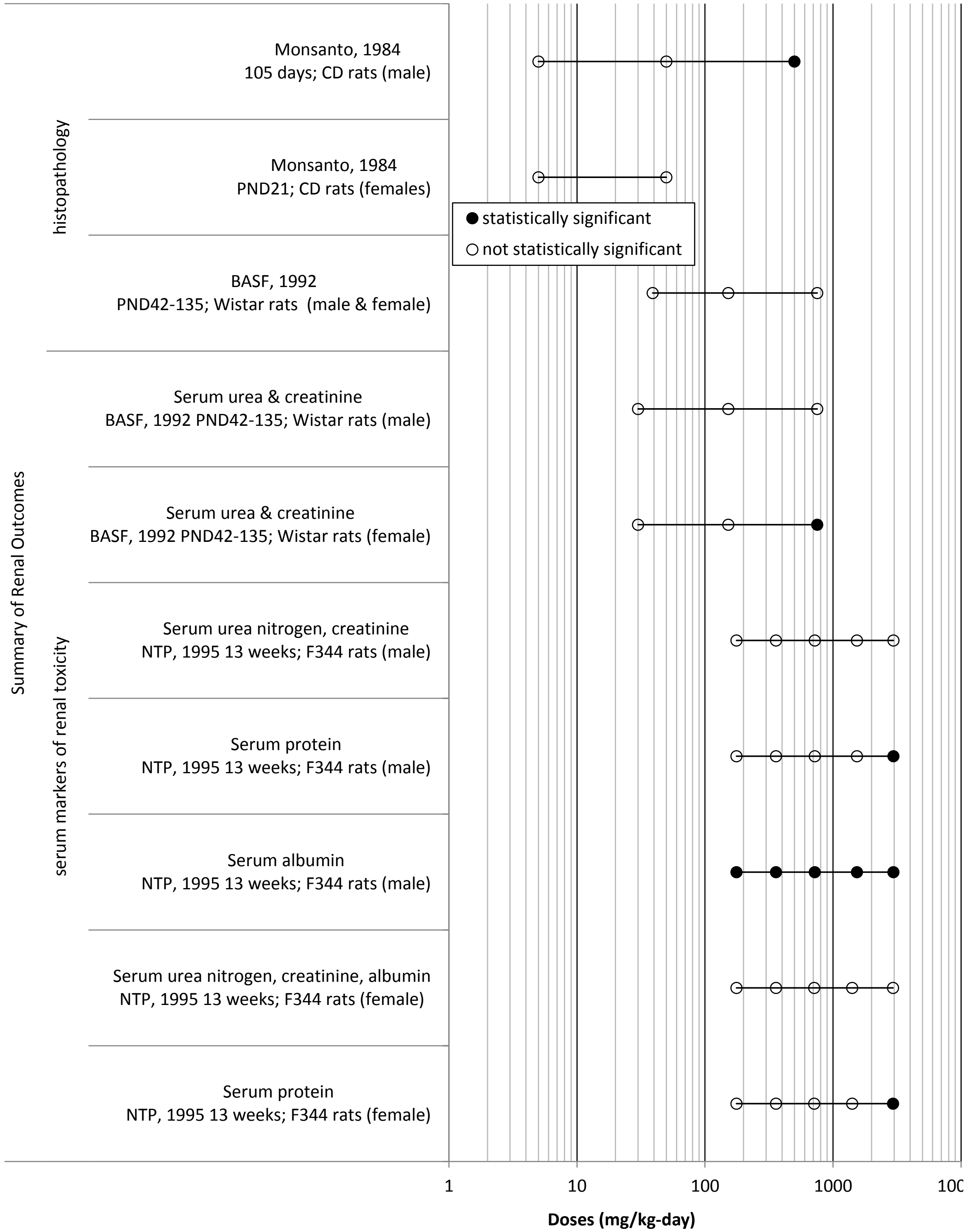

Figure 3-22. Exposure-response array of kidney histopathology and serum markers of renal toxicity following oral exposure to DBP.

3.3.6. Hematopoietic Effects

Table 3-32. Evidence pertaining to hematological effects in animals following oral exposure to DBP

Reference and study design	Results				
Changes in hematological parameters					
Monsanto (1984) Rat (CD); 20 breeding pairs/group; 13 to 20 animals evaluated; 0, 5, 50, 500 mg/kg-day Diet Males exposed for 105 days Females exposed 14 days before mating and continued through weaning [PND 21]	*response relative to control*				
	Doses	0	5	50	500
	Leukocytes				
	M	0%	-7%	-2%	-19*%
	F	0%	-4%	0%	1%
	Erythrocytes				
	M	0%	1%	1%	1%
	F	0%	3%	-1%	3%
	Hemoglobin				
	M	0%	-1%	0%	-1%
	F	0%	3%	-1%	2%
	Hematocrit				
	M	0%	0%	0.2%	0%
	F	0%	6%	1%	3%
	Mean corpuscular volume (MCV)				
	M	0%	-2%	-2%	-2%
	F	0%	2%	2%	0%
	Mean corpuscular hemoglobin (MCH)				
	M	0%	-1%	-1%	-2%
	F	0%	0.4%	0.4%	-1%
	Mean corpuscular hemoglobin concentration (MCH)				
	M	0%	-0.3%	0%	-1%
	F	0%	-2%	-1%	-1%
	Platelets				
	M	0%	3%	5%	9*%
	F	0%	6%	6%	11%
	Reticulocytes				
	M	0%	-24%	-17%	7%
	F	0%	-26*%	43%	35%
	Neutrophils				

Reference and study design	Results				
	M	0%	0%	0%	24%
	F	0%	-14%	-18%	0%
	Lymphocytes				
	M	0%	-9%	-2%	17%
	F	0%	3%	9%	5%
BASF (1992) Rat (Wistar); 10/sex/group 0, 30, 152, 752 mg/kg-day Diet 3 months (PNDs 42-135)	*response relative to control*				
	Doses	0	30	152	752
	Erythrocyte count (RBC) *(PND 86)*				
	M	0%	1%	0%	-3%
	F	0%	2%	-1%	-1%
	Hemoglobin *(PND 86)*				
	M	0%	2%	0%	-2%
	F	0%	1%	-1%	-1%
	Hematocrit *(PND 86)*				
	M	0%	1%	-1%	-4%
	F	0%	1%	-1%	-1%
	Leukocyte count (WBC) *(PND 86)*				
	M	0%	5%	-7%	11%
	F	0%	20%	12%	14%
	Mean corpuscular volume (MCV) *(PND 86)*				
	M	0%	0%	-1%	-1%
	F	0%	-1%	0%	-1%
	Mean corpuscular hemoglobin (MCH) *(PND 86)*				
	M	0%	2%	0%	2%
	F	0%	-1%	-1%	-1%
	Mean corpuscular hemoglobin concentration (MCHC) *(PND 86)*				
	M	0%	1%	1%	2%
	F	0%	0%	0%	0%
	Platelets *(PND 86)*				
	M	0%	4%	-4%	-3%
	F	0%	6%	-1%	-5%

Reference and study design	Results					
NTP (1995) Mouse (B6C3F$_1$); 10/sex/group Males: 0, 163, 353, 812, 1,601, 3,689 mg/kg-day; Females: 0, 238, 486, 971, 2,137, 4,278 mg/kg-day Diet 91 days	*At study termination*					
	Doses (M)	0	163	353	812	1,601	3,689
	Hemoglobin	0%	-2%	-1%	1%	-1%	-2%
	Hematocrit	0%	-2%	-1%	0.4%	-2%	-4%
	Erythrocytes	0%	-3%	-0%	1%	-1%	-2%
	Leukocytes	0%	-23%	10%	27%	-11%	-36%
	Nucleated erythrocytes	0%	0%	0%	0%	0%	0%
	Reticulocytes	0%	6%	0%	0%	24%	-6%
	Mean cell volume	0%	0 %	-1%	-1%	0%	-1*%
	Platelets	0%	2%	-1%	-8%	-4%	-4%
	Doses (F)	0	238	486	971	2,137	4,278
	Hemoglobin	0%	0%	-1%	-1%	-1%	-4%
	Hematocrit	0%	-1%	-1%	-3%	-2%	-6*%
	Erythrocytes	0%	-1%	-1%	-2%	-2%	-5%
	Leukocytes	0%	-8%	-19%	7%	-1%	-6%
	Nucleated erythrocytes	0%	0%	0%	0%	0%	0%
	Reticulocytes	0%	36%	18%	27%	27%	0%
	Mean cell volume	0%	1%	1%	-1%	0%	0%
	Platelets	0%	-8%	-8%	-10%	-2%	-9%
NTP (1995) Rat (F344); 10/sex/group Males: 0, 176, 359, 720, 1,540, 2,964 mg/kg-day; Females: 0, 177, 356, 712, 1,413, 2,943 mg/kg-day Diet 91 days	*At study termination*					
	Doses (M)	0	176	359	720	1,540	2,964
	Hemoglobin	0%	-1%	-3*%	-3*%	-5*%	-5*%
	Hematocrit	0%	-1%	-3%	-3%	-7*%	-6*%
	Erythrocytes	0%	-1%	-3*%	-4*%	-10*%	-9*%
	Leukocytes	0%	21%	40%	36%	-3%	-9%
	Nucleated erythrocytes	0%	-33%	-67%	0%	33%	333*%
	Reticulocytes	0%	-5%	5%	-5%	5%	26%
	Mean cell volume	0%	-0.2%	-0.2%	1*%	3*%	2*%
	Platelets	0%	0%	11*%	14*%	14*%	12*%
	Doses (F)	0	177	356	712	1,413	2,943
	Hemoglobin	0%	0%	-1%	1%	0%	-3%

Reference and study design	Results						
	Hematocrit	0%	1%	-1%	2%	1%	-4%
	Erythrocytes	0%	0%	-1%	2%	1%	-3%
	Leukocytes	0%	5%	-4%	16%	16%	42*%
	Nucleated erythrocytes	0%	200%	0%	0%	100%	450*%
	Reticulocytes	0%	0%	7%	14%	0%	21%
	Mean cell volume	0%	1%	1%	1%	0%	-1%
	Platelets	0%	11%	0%	2%	0%	-1%

*Statistically different from ($p < 0.05$) control as reported by study authors.

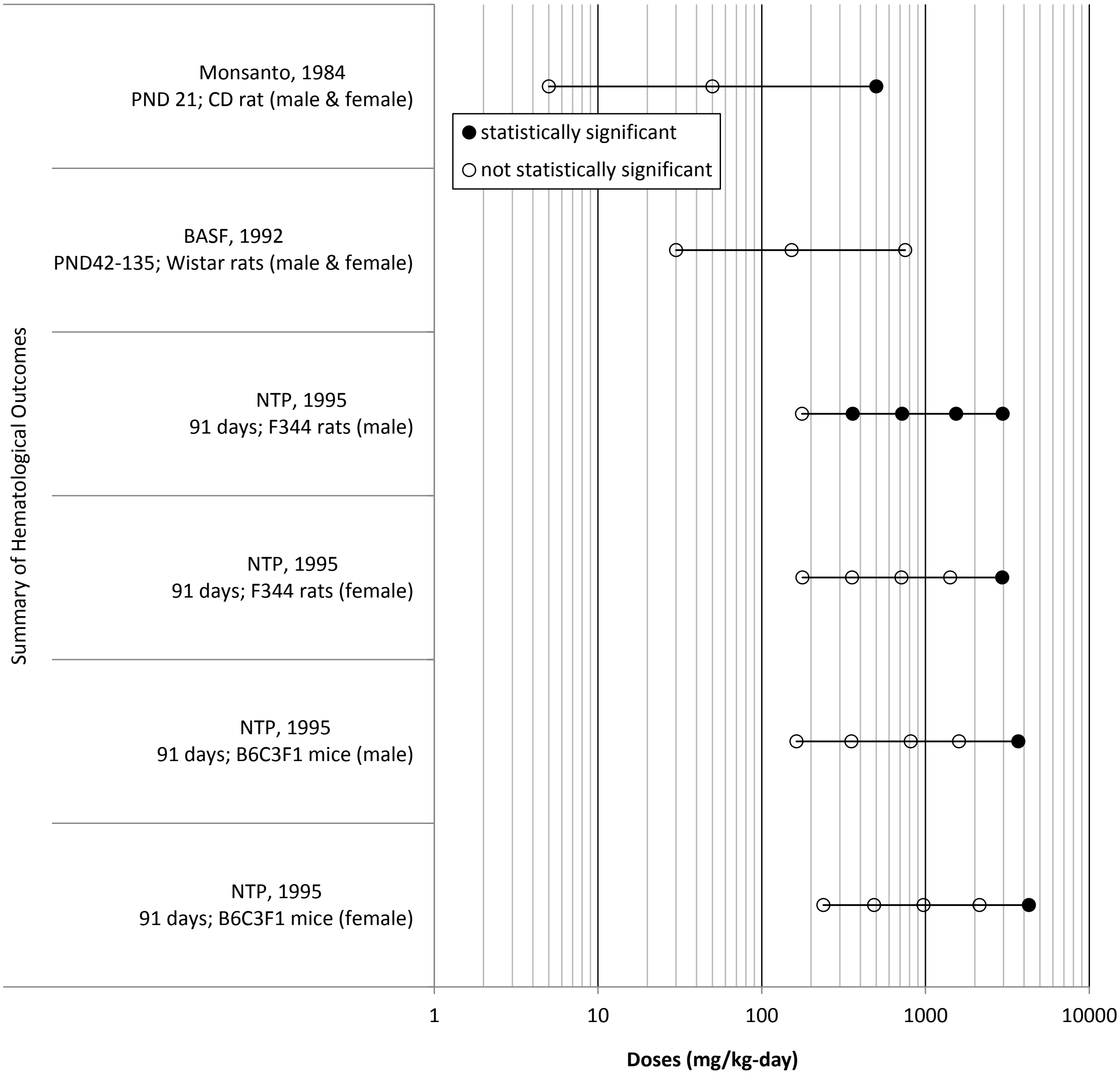

Figure 3-23. Exposure-response array of hematological outcomes following oral exposure to DBP.

3.3.7. Thyroid Effects

Table 3-33. Evidence pertaining to thyroid effects in animals following oral exposure to DBP

Reference and study design	Results				
Changes in thyroid weight					
Lee et al. (2008) Rat (Sprague-Dawley); 6 males/group 0, 100, 500 mg/kg-day Gavage 30 days (PNDs 28-58)	*response relative to control*				
	Doses	0	100	500	
	Absolute thyroid weight				
		0%	24%	16%	
	Relative thyroid weight				
		0%	23%	15%	
Levels of thyroid hormones					
BASF (1992) Rat (Wistar); 10/sex/group 0, 30, 152, 752 mg/kg-day Diet 3 months (PNDs 42-135)	*response relative to control*				
	Doses	0	30	152	752
	Serum T3 levels				
	M	0%	-7%	5%	-15*%
	F	0%	-3%	-2%	-17*%
	Serum T4 levels				
	M	0%	2%	3%	-3%
	F	0%	1%	14*%	13%
Lee et al. (2008) Rat (Sprague-Dawley); 6 males/group 0, 100, 500 mg/kg-day Gavage 30 days (PNDs 28-58)	*response relative to control*				
	Doses	0	100	500	
	Serum T3 levels[a]				
		0%	-7%	-8%	
	Serum T4 levels[a]				
		0%	-13%	-3%	
	Serum TSH levels[a]				
		0%	-6%	0%	

[a]Values reported by the study authors were estimated from published graphs using "Grab It!", a Microsoft Excel based free software application used to digitize data from image files. Publisher: datatrendsoftware.com.
*Statistically different from control (p < 0.05), as reported by study authors.

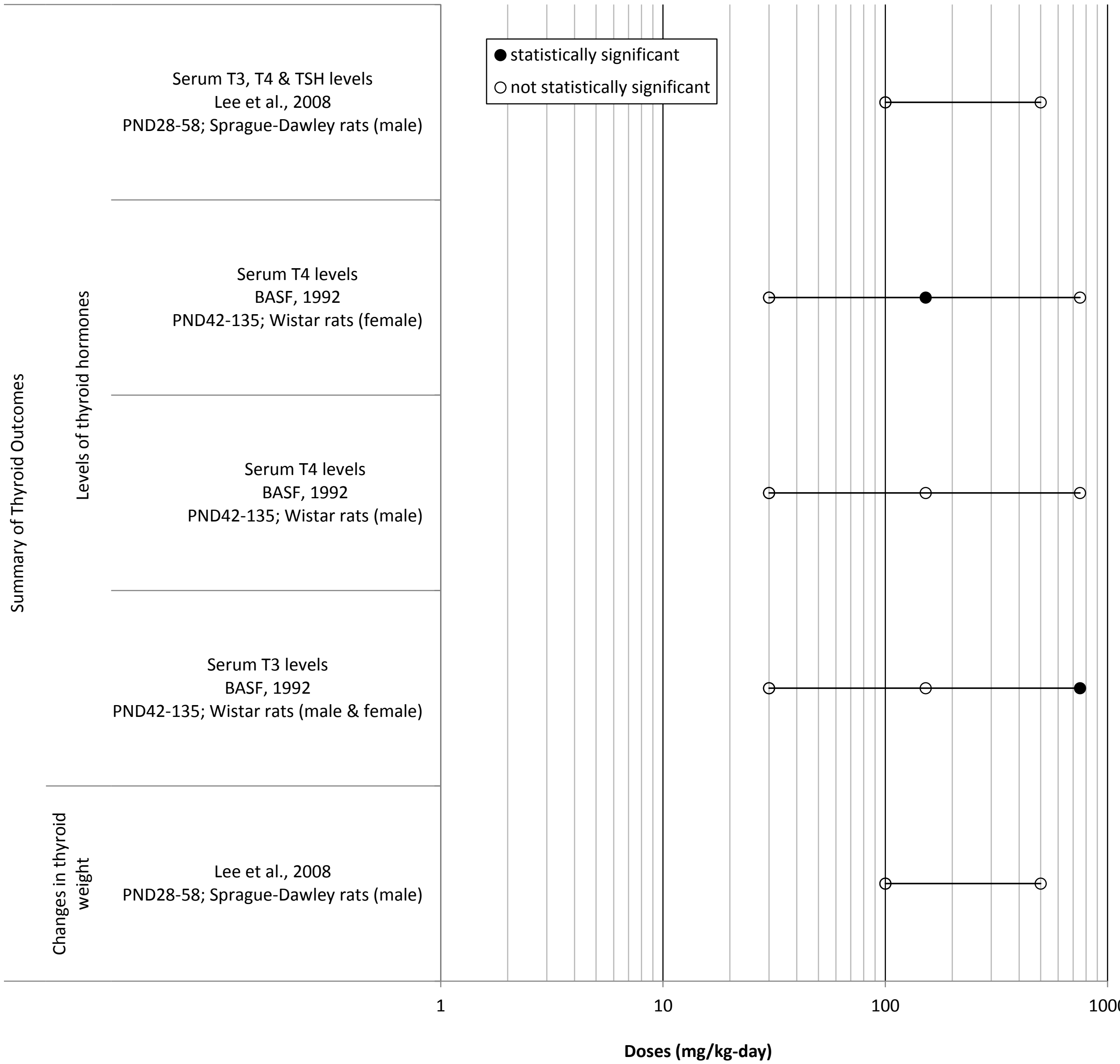

Figure 3-24. Exposure-response array of thyroid outcomes following oral exposure to DBP.

3.3.8. Immune Effects

Table 3-34. Evidence pertaining to immune effects in animals following oral exposure to DBP

Reference and study design	Results						
Changes in thymus weight							
Salazar et al. (2004) Rat (Long Evans); 15 dams/group; organ weights assessed in 6 male offspring/group 0, 12, 50 mg/kg-day[c] Diet 2.5 months before mating to PND 22	*response relative to control*						
	Doses (M)	0	12	50			
	Thymus weight in F1 rats						
	PND 14	0%	1%	-10%			
NTP (1995) Rat (F344); up to 24 dams/treatment group and 48 control dams; assessed in 10 offspring/sex/group 0, 1,250, 2,500, 5,000, 7,500, 10,000, 20,000 ppm (Gestation-lactation doses[a]: 0, 138, 275, 550, 825, 1,100, 2,200 mg/kg-day; Postweaning doses: 0, 143, 284, 579, 879, 1,165 mg/kg-day in males; 0, 133, 275, 500, 836, 1,104 mg/kg-day in females) Diet GD 1-PND 56	*response relative to control*						
	Doses (M)	0	143	284	579	879	1,165
	Thymus weight in F1 males *(PND 56)*						
	Absolute	0%	5%	7%	2%	6%	4%
	Relative	0%	6%	8%	7%	17*%	9*%
	Doses (F)	0	133	275	500	836	1,104
	Thymus weight in F1 females *(PND 56)*						
	Absolute	0%	1%	-2%	2%	-3%	-1%
	Relative	0%	2%	-1%	0.4%	1%	4%
	Note: no pups survived postpartum in 20,000 ppm treatment group						
NTP (1995) Mouse ($B6C3F_1$); 10/sex/group 0, 163, 353, 812, 1,601, 3,689 mg/kg-day in males; 0, 238, 486, 971, 2,137, 4,278 mg/kg-day in females Diet 13 weeks	*response relative to control*						
	Doses (M)	0	163	353	812	1,601	3,689
	Thymus weight						
	Absolute	0%	7%	-4%	-11%	-4%	-4%
	Relative	0%	4%	-2%	-2%	3%	10%
	Doses (F)	0	238	486	971	2,137	4,278
	Thymus weight						
	Absolute	0%	5%	10%	-11%	-11%	-10%
	Relative	0%	2%	5%	-3%	-5%	3%

Reference and study design	Results						
NTP (1995) Rat (F344/N); 10/sex/group 0, 176, 359, 720, 1,540, 2,964 mg/kg-day in males; 0, 177, 356, 712, 1,413, 2,943 mg/kg-day in females Diet 13 weeks	*response relative to control*						
	Doses (M)	0	176	359	720	1,540	2,964
	Thymus weight						
	Absolute	0%	-3%	1%	-1%	-13*%	-48*%
	Relative	0%	-1%	2%	6%	-5%	19*%
	Doses (F)	0	177	356	712	1,413	2,943
	Thymus weight						
	Absolute	0%	9%	18*%	13%	8%	-7%
	Relative	0%	12*%	14*%	15*%	17*%	27*%
NTP (1995) Mouse ($B6C3F_1$); up to 20 dams/group; assessed in 10 offspring/sex/group 0, 1,250, 2,500, 5,000, 7,500, 10,000, 20,000 ppm (Gestation-lactation doses[b]: 0, 244, 488, 975, 1,463, 1,950, 3,900 mg/kg-day; Postweaning doses: 0, 199, 437, 750, 1,286, 3,804 mg/kg-day in males; 0, 170, 399, 714, 1,060, NA mg/kg-day in females) Diet GD 1-PND 56	*response relative to control*						
	Doses (M)	0	199	437	750	1,286	3,804
	Thymus weight in F1 mice *(PND 56)*						
	Absolute	0%	6%	9%	38*%	30*%	-23%
	Relative	0%	8%	17%	55*%	48*%	6%
	Doses (F)	0	170	399	714	1,060	NA
	Thymus weight in F1 mice *(PND 56)*						
	Absolute	0%	0%	0%	0%	-9%	-
	Relative	0%	-6%	1%	1%	1%	-
	Note: no pups survived postpartum in 20,000 ppm treatment group. One male and no female pups survived postpartum in 10,000 ppm group						

[a]Doses calculated using U.S. EPA (1988) reference subchronic values for food intake (0.014 kg/day) and body weight (0.124 kg) in female F344 rats

[b]Doses calculated using U.S. EPA (1988) reference subchronic values for food intake (0.0048 kg/day) and body weight (0.0065 kg) in female B6C3F1 mice

[c]Doses were 0, 610, 2,500 ppm in diet; details on dose estimation were not provided by the study authors.

*Statistically different from controls ($p < 0.05$), as reported by study authors.

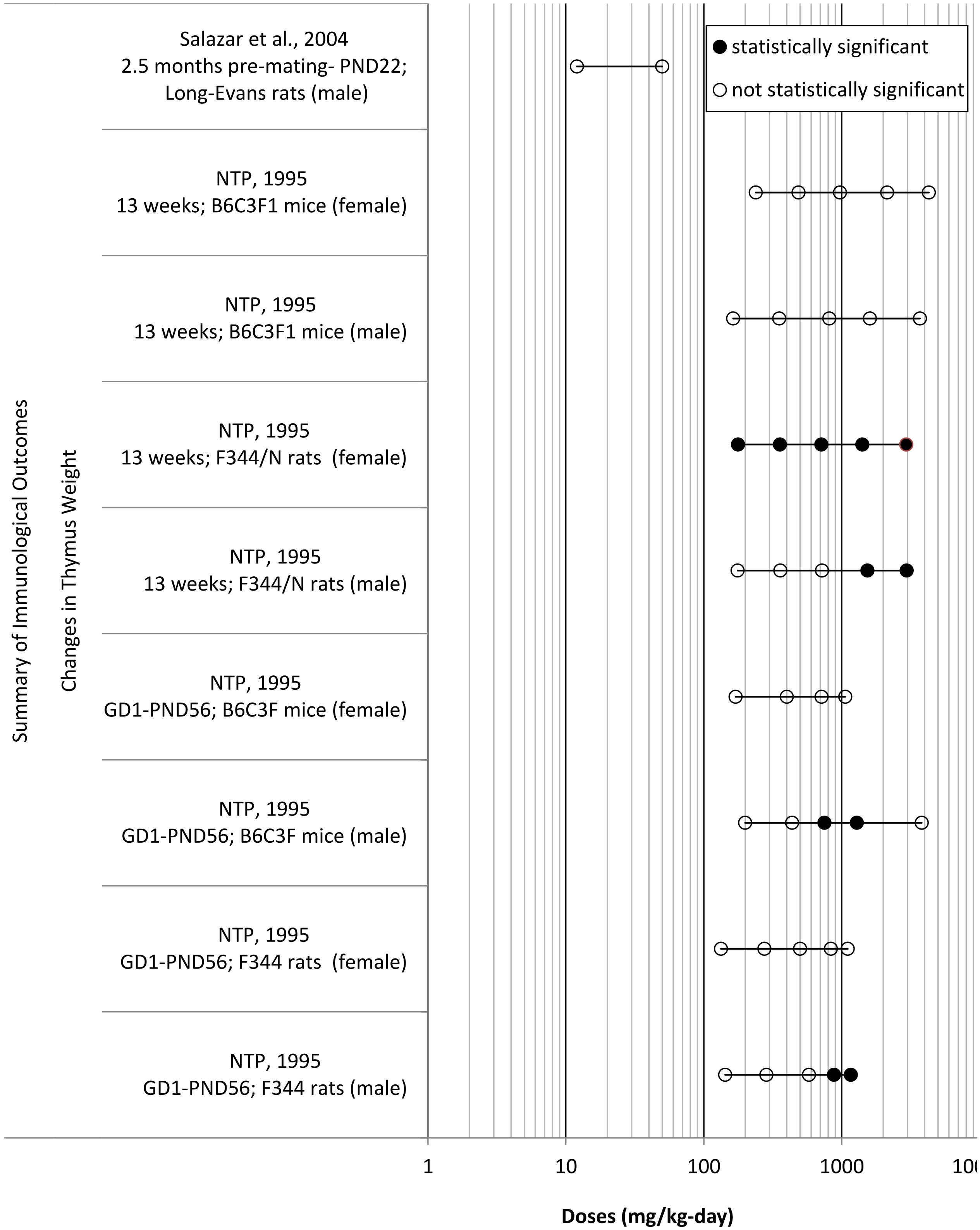

Figure 3-25. Exposure-response array of immunological outcomes following oral exposure to DBP.

3.3.9. Neurological Effects

Table 3-35. Evidence pertaining to neurological effects in animals following oral exposure to DBP

Reference and study design	Results						
Changes in brain weight							
Lee et al. (2004) Rat (Sprague-Dawley); 6-8 dams/group; assessed in 8-10 offspring/sex/group 0, 2-3, 14-29, 148-291, 712-1,372 mg/kg-day Diet GD 15-PND 21 Note: Doses represent a range estimated by the study authors for three different time periods (GDs 15-20, PNDs 2-10, and PNDs 10-21).	*response relative to control*						
	Doses	0	2-3	14-29	148-291	712-1,372	
	Relative brain weight *(PND 77)*						
	M	0%	2%	-6%	0%	-2%	
	F	0%	6%	-3%	3%	0%	
	Relative brain weight *(PND 140)*						
	M	0%	-5%	-10%	-3%	NA[a]	
	F	0%	-2%	-8%	-10%	0%	
BASF (1992) Rat (Wistar); 10/sex/group 0, 30, 152, 752 mg/kg-day Diet 3 months PNDs 42-135	*response relative to control*						
	Doses	0	30	152	752		
	Brain weight (M)						
	Absolute	0%	1%	0.1%	2%		
	Relative	0%	0.5%	3%	-0.5%		
	Brain weight (F)						
	Absolute	0%	1%	2%	2%		
	Relative	0%	3%	2%	6%		
Changes in adrenals weight							
Mylchreest et al. (2000) Rat (Sprague-Dawley); 11-20 dams/group 0, 0.5, 5, 50, 100, 500 mg/kg-day Gavage GDs 12-31	*response relative to control*						
	Doses	0	0.5	5	50	100	500
	Absolute adrenals weight *(PND 110)*						
	F1 (M)	0%	2%	1%	-3%	-4%	-6%
	Note: The litter was the statistical unit of comparison. No treatment-related effects on organ weights were observed in adrenal glands of F0 or adult F1 females (data not reported by study authors).						

<table>
<tr><th>Reference and study design</th><th colspan="6">Results</th></tr>
<tr><td rowspan="9">Lee et al. (2004)
Rat (Sprague-Dawley); 6-8 dams/group; assessed in 8-10 offspring/sex/group
0, 2-3, 14-29, 148-291, 712-1,372 mg/kg-day
Diet
GD 15-PND 21
Note: Doses represent a range estimated by the study authors for three different time periods (GDs 15-20, PNDs 2-10, and PNDs 10-21).</td><td colspan="6">response relative to control</td></tr>
<tr><td>Doses</td><td>0</td><td>2-3</td><td>14-29</td><td>148-291</td><td>712-1,372</td></tr>
<tr><td colspan="6">Relative adrenal weight (PND 77)</td></tr>
<tr><td>M</td><td>0%</td><td>-10%</td><td>0%</td><td>-11%</td><td>-13%</td></tr>
<tr><td>F</td><td>0%</td><td>-7%</td><td>1%</td><td>-8%</td><td>-7%</td></tr>
<tr><td colspan="6">Relative adrenal weight (PND 140)</td></tr>
<tr><td>M</td><td>0%</td><td>-13%</td><td>-7%</td><td>-2%</td><td>NA[a]</td></tr>
<tr><td>F</td><td>0%</td><td>6%</td><td>6%</td><td>-5%</td><td>-8%</td></tr>
<tr><td colspan="6"></td></tr>
<tr><td rowspan="8">BASF (1992)
Rat (Wistar); 10/sex/group
0, 30, 152, 752 mg/kg-day
Diet
3 months PNDs 42-135</td><td colspan="6">response relative to control</td></tr>
<tr><td>Doses</td><td>0</td><td>30</td><td>152</td><td colspan="2">752</td></tr>
<tr><td colspan="6">Adrenals weight (M)</td></tr>
<tr><td>Absolute</td><td>0%</td><td>-5%</td><td>-0.1%</td><td colspan="2">-2%</td></tr>
<tr><td>Relative</td><td>0%</td><td>-6%</td><td>0%</td><td colspan="2">-6%</td></tr>
<tr><td colspan="6">Adrenals weight (F)</td></tr>
<tr><td>Absolute</td><td>0%</td><td>8%</td><td>9%</td><td colspan="2">7%</td></tr>
<tr><td>Relative</td><td>0%</td><td>11%</td><td>8%</td><td colspan="2">11%</td></tr>
<tr><td rowspan="5">Mylchreest et al. (1999a)
Rat (Sprague-Dawley); 10 dams/group
0, 100, 250, 500 mg/kg-day
Gavage
GDs 12-21</td><td colspan="6">response relative to control</td></tr>
<tr><td>Doses</td><td>0</td><td>100</td><td>250</td><td colspan="2">500</td></tr>
<tr><td colspan="6">Absolute adrenals weight (PND 100)</td></tr>
<tr><td>F1 (M)</td><td>0%</td><td>0%</td><td>20%</td><td colspan="2">0%</td></tr>
<tr><td colspan="6">Note: The litter was the statistical unit of comparison.</td></tr>
<tr><td rowspan="6">Lee et al. (2008)
Rat (Sprague-Dawley); 6 males/group
0, 100, 500 mg/kg-day
Gavage
30 days</td><td colspan="6">response relative to control</td></tr>
<tr><td>Doses</td><td>0</td><td colspan="2">100</td><td colspan="2">500</td></tr>
<tr><td colspan="6">Absolute adrenals weight</td></tr>
<tr><td></td><td>0%</td><td colspan="2">-10%</td><td colspan="2">-5%</td></tr>
<tr><td colspan="6">Relative adrenals weight</td></tr>
<tr><td></td><td>0%</td><td colspan="2">-11%</td><td colspan="2">-6%</td></tr>
</table>

Reference and study design	Results					
Gray et al. (2006) Rat (Long Evans); weanling females; 11-13/group 0, 250, 500, 750 mg/kg-day Gavage 5 days/week: PNDs 24-~PND 110 7 days/week: ~PND 110 to GD 13 of F1b litter (F1a litter delivered ~PND 140)	*response relative to control*					
	Doses	0	250	500	750	
	Maternal adrenals weight					
	Absolute	0%	0%	4%	4%	
Mylchreest et al. (1998) Rat (Sprague-Dawley); 10 dams/group; adrenal weights measured in 4-9 dams/group 0, 250, 500, 750 mg/kg-day Gavage GD 3-PND 20 (2-day interruption at parturition, PNDs 1-2)	*response relative to control*					
	Doses	0	250	500	750	
	Absolute adrenals weight *(PND 21)*					
	F0 (F)	0%	-10%	8%	5%	
	Note: Adrenal weights in F1 male and females at ~PND 100 were "comparable to controls" (data not reported by study authors).					
Xiao-Feng et al. (2009) Rat (Sprague-Dawley); 5-week old males, 8/group 0, 250, 500, 1,000, 2,000 mg/kg-day Gavage 30 days	*response relative to control*					
	Doses	0	250	500	1,000	2,000
	Absolute adrenal weight					
		0%	-11%	-6%	0%	28%
Jiang et al. (2007) Rat (Sprague-Dawley); 10 dams/group; organ weights assessed in 21-57 male offspring/group 0, 250, 500, 750, 1,000 mg/kg-day Gavage GDs 14-18	*response relative to control*					
	Doses	0	250	500	750	1,000
	Relative adrenal weight *(F1 males, PND 70)*					
	right adrenal	0%	-2%	13*%	41*%	NA
	left adrenal	0%	5%	17*%	43*%	NA
	Note: No live pups were delivered in the high-dose group.					

Reference and study design	Results					
Pituitary effects						
Lee et al. (2004) Rat (Sprague-Dawley); 6-8 dams/group; assessed in 8-10 offspring/sex/group 0, 2-3, 14-29, 148-291, 712-1,372 mg/kg-day Diet GD 15-PND 21 Note: Doses represent a range estimated by the study authors for three different time periods (GDs 15-20, PNDs 2-10, and PNDs 10-21).	*response relative to control*					
	Doses	0	2-3	14-29	148-291	712-1,372
	Relative pituitary weight *(PND 77)*					
	M	0%	16*%	19*%	22*%	11%
	F	0%	-3%	-7%	-9%	-36*%
	Relative pituitary weight *(PND 140)*					
	M	0%	0.4%	1%	3%	NA[a]
	F	0%	-5%	-16*%	-16*%	-23%
Zhang et al. (2004b) Rat (Sprague-Dawley); 20 dams/group; organ weights assessed in 20 male offspring/group 0, 50, 250, 500 mg/kg-day Gavage GD 1-PND 21	*response relative to control*					
	Doses	0	50	250	500	
	Absolute pituitary weight *(PND 70)*					
	F1 (M)	0%	-4%	-6%	10%	
	Relative pituitary weight *(PND 70)*					
	F1 (M)	0%	-3%	-2%	12*%	
Barlow et al. (2004) Rat (Sprague Dawley);10-11 dams/group; 8-11 litters/group were examined per time-point 0, 100, 500 mg/kg-day Gavage GDs 12-21; F1 males sacrificed at PNDs 180, 370, or 540	Doses	0	100	500		
	Pituitary lesions in F1 males *(adenomas) percent litter incidence*					
	PND 180	0%	0%	0%		
	PND 370	5%	3%	0%		
	PND 540	14%	31%	31%		
Gray et al. (2006) Rat (Long Evans); weanling females, 11-13/group 0, 250, 500, 750 mg/kg-day Gavage 5 days/week: PNDs 24-~PND 110 7 days/week: ~PND 110 to GD 13 of F1b litter (F1a litter delivered ~PND 140)	*response relative to control*					
	Doses	0	250	500	750	
	Maternal pituitary weight					
	Absolute	0%	11%	17*%	-8%	
	response relative to control					
	Doses	0	250	500	750	1,000
	Relative pituitary weight *(PND 70)*					
	F1 (M)	0%	4%	22*%	59*%	NA

Reference and study design	Results
Jiang et al. (2007) Rat (Sprague-Dawley); 10 dams/group; organ weights assessed in 21-57 male offspring/group 0, 250, 500, 750, 1,000 mg/kg-day Gavage GDs 14-18	Note: No live pups were delivered in the high-dose group.

[a]NA = Not available; a sufficient number of male animals could not be obtained.
*Statistically different from controls ($p < 0.05$), as reported by study authors

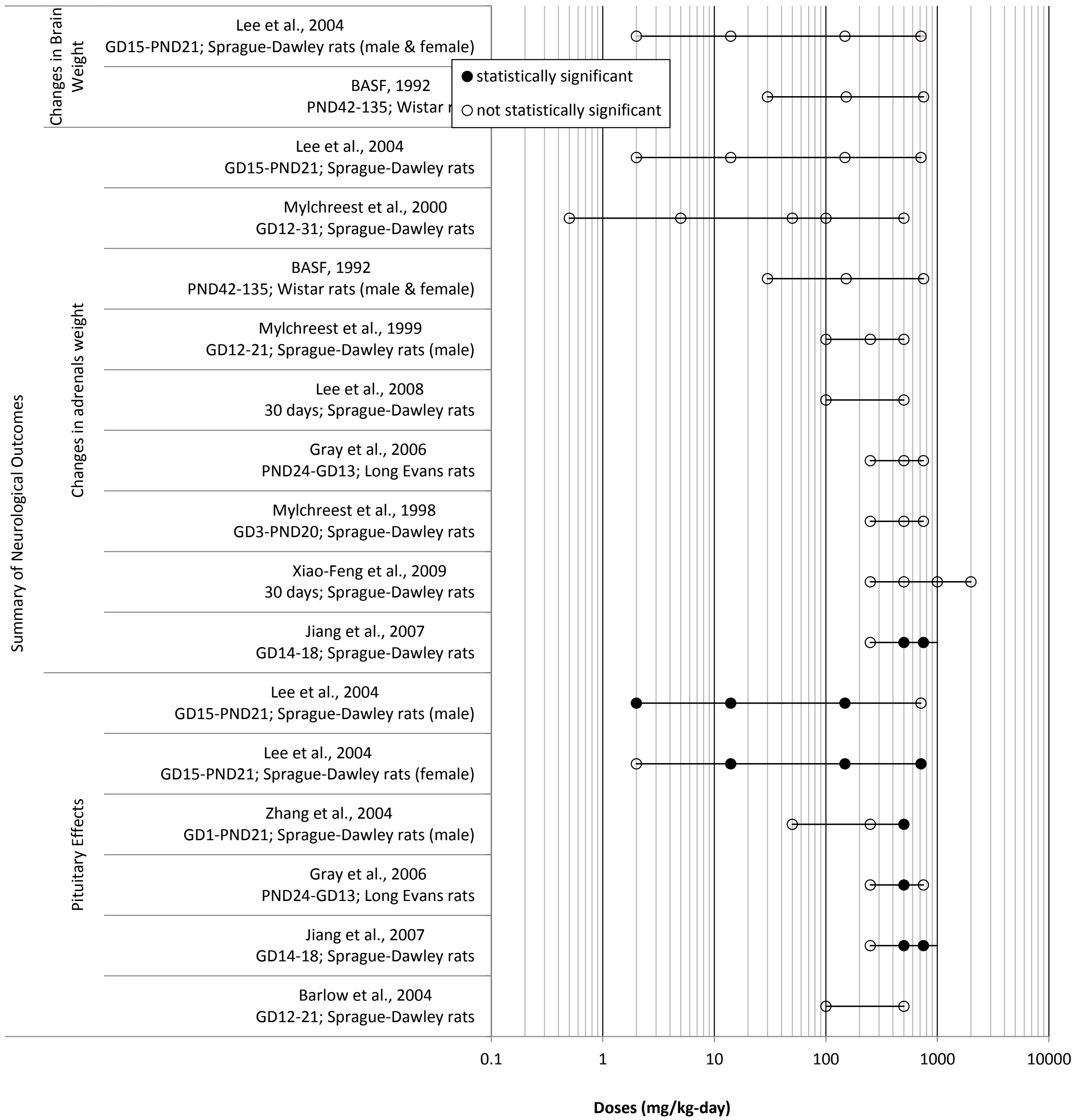

Figure 3-26. Exposure-response array of neurological outcomes following oral exposure to DBP.

3.3.10. Other Toxicity Effects

Table 3-36. Evidence pertaining to other toxicity effects in animals following oral exposure to DBP: alterations in body weight in animals

Reference and study design	Results						
Changes in body weight							
BASF (1992) Rat (Wistar); 10/sex/group 0, 30, 152, 752 mg/kg-day Diet 3 months (PNDs 42-135)	*response relative to control*						
	Doses	0	30	152	752		
	Body weight at study termination						
	M	0%	1%	-1%	3%		
	F	0%	-1%	1%	-3%		
NTP (1991) Rat (Sprague-Dawley); 20/sex/treatment group; 40/sex/control group 0, 0.1, 0.5, 1% (0, 66, 320, or 651 mg/kg-day) continuous breeding protocol Diet 17 weeks (119 days; 7-day pre-cohabitation; 112 days cohabitation)	*response relative to control*						
	Doses	0	66	320	651		
	Body weight (M)						
	Week 17	0%	-1%	-2%	-4%		
	Body weight (F)						
	Week 17	0%	-4%	-2%	-11*%		
	Body weight (M+F)						
	Week 17	0%	-2%	-2%	-7%		
NTP (1995) Mouse ($B6C3F_1$); 10/group Males: 0, 163, 353, 812, 1,601, 3,689 mg/kg-day; Females: 0, 238, 486, 971, 2,137, 4,278 mg/kg-day Diet 91 days	*response relative to control*						
	Doses	0	163	353	812	1,601	3,689
	Body weight at necropsy						
	M	0%	1%	-2%	-9*%	-8*%	-13*%
	Doses	0	238	486	971	2,137	4,278
	Body weight at necropsy						
	F	0%	4%	4%	-8%	-6%	-13*%
NTP (1995) Rat (F344); 10/group Males: 0, 176, 359, 720, 1,540, 2,964 mg/kg-day; Females: 0, 177, 356, 712, 1,413, 2,943 mg/kg-day Diet 91 days	*response relative to control*						
	Doses	0	176	359	720	1,540	2,964
	Body weight at necropsy						
	M	0%	-3%	-1%	-8*%	-17*%	-56*%
	Doses	0	177	356	712	1,413	2,943
	Body weight at necropsy						
	F	0%	-2%	2%	-2%	-8*%	-27*%

Reference and study design	Results				
Srivastava et al. (1990b) Rat (Wistar); 6/group 0, 250, 500, 1,000 mg/kg-day Gavage 15 days	*response relative to control*				
	Doses	0	250	500	1,000
	Final body weight				
		0%	-9%	-19*%	-36*%

*Statistically different from controls ($p < 0.05$), as reported by study.

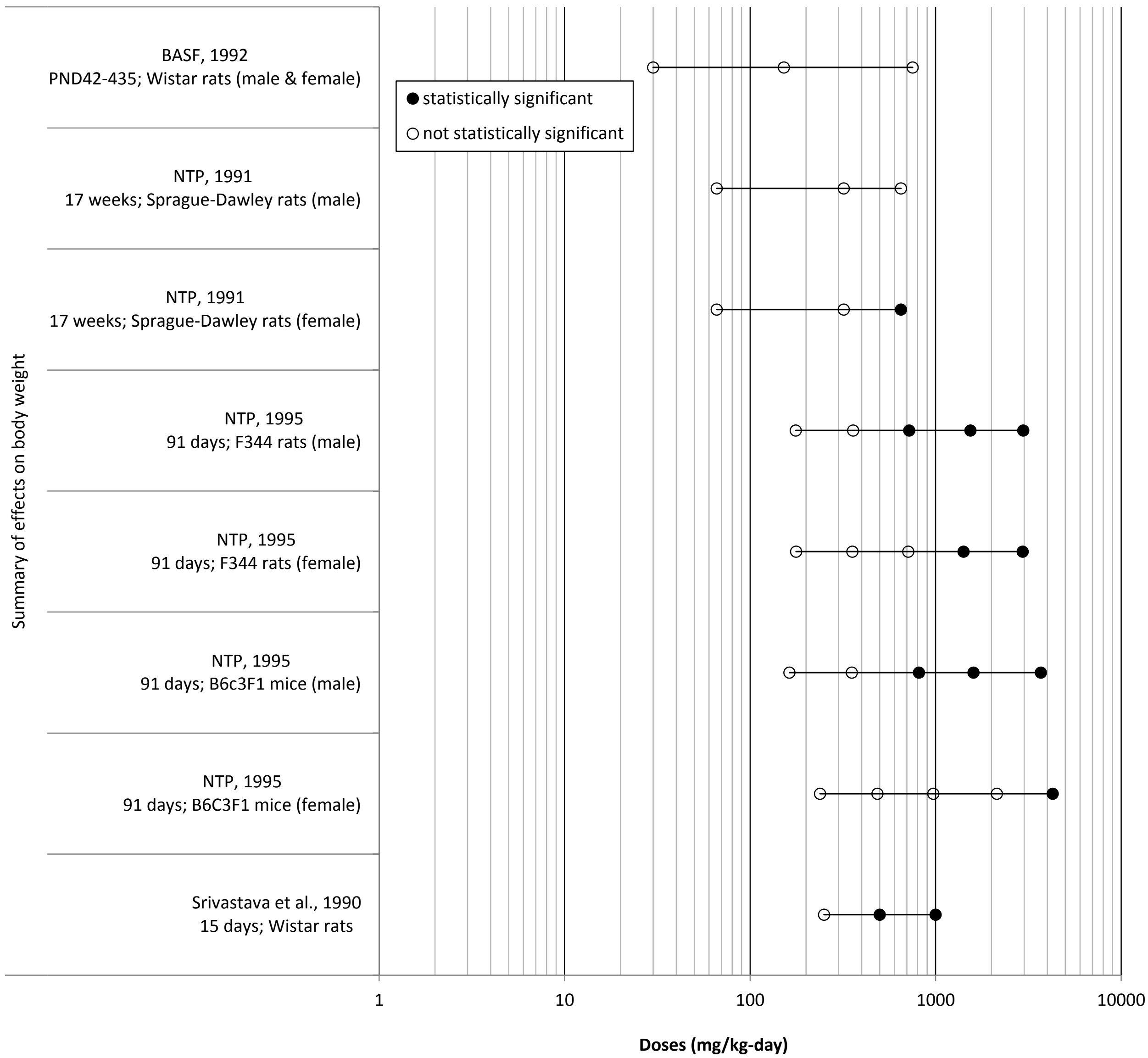

Figure 3-27. Exposure-response array of alterations in body weight following oral exposure to DBP.

Table 3-37. Evidence pertaining to toxicity effects in animals following exposure to DBP metabolites

Reference and study design	Results				
Developmental body weight					
Ema et al. (1996) MBP Rat (Wistar); P0, female (10-11/group) 0, 500, 625, 750 mg/kg-day Gavage GDs 7-9; dams sacrificed on GD 20	Doses	0	500	625	750
	Body weight of live fetuses *(g, litter mean ± SD),* female	3.77 (± 0.16)	3.46 (± 0.09)*	3.26 (± 0.17)*	3.15 (± 0.26)*
	Body weight of live fetuses *(g, litter mean ± SD),* male	4.05 (± 0.16)	3.74 (± 0.13)*	3.58 (± 0.17)*	3.52 (± 0.17)*
Ema et al. (1996) MBP Rat (Wistar); P0, female (10-14/group) 0, 500, 625, 750 mg/kg-day Gavage GDs 10-12; dams sacrificed on GD 20	Doses	0	500	625	750
	Body weight of live fetuses *(g, litter mean ± SD),* female	3.77 (± 0.16)	3.53 (± 0.35)	3.53 (± 0.26)	2.95 (± 0.53)*
	Body weight of live fetuses *(g, litter mean ± SD),* male	4.05 (± 0.16)	3.78 (± 0.3)*	3.81 (± 0.19)	3.1 (± 0.4)*
Ema et al. (1996) MBP Rat (Wistar); P0, female (10-15/group) 0, 500, 625, 750 mg/kg-day Gavage GDs 13-15; dams sacrificed on GD 20	Doses	0	500	625	750
	Body weight of live fetuses *(g, litter mean ± SD),* female	3.77 (± 0.16)	3.77 (± 0.17)	3.68 (± 0.17)	3.5 (± 0.12)
	Body weight of live fetuses *(g, litter mean ± SD),* male	4.05 (± 0.16)	3.97 (± 0.18)	3.9 (± 0.26)	3.81 (± 0.04)
Ema and Miyawaki (2001a) MBP Rat (Wistar); P0, female (16/group) 0, 250, 500, 750 mg/kg-day Gastric intubation GDs 15-17	Doses	0	250	500	750
	Body weight of live fetuses *(g, litter mean ± SD),* female	4.44 (± 0.26)	4.45 (± 0.31)	4.31 (± 0.45)	4.03 (± 0.27*
	Body weight of live fetuses *(g, litter mean ± SD),* male	4.71 (± 0.32)	4.67 (± 0.47)	4.55 (± 0.41)	4.23 (± 0.33)*

Reference and study design	Results					
Ema and Miyawaki (2001b) MBP Rat (Wistar); P0, female (16/group) 0, 250, 500, 750, 1,000 mg/kg-day Gavage GDs 0-8, with outcomes determined on GD 20	Doses	0	250	500	750	1,000
	Body weight of live fetuses *(g, litter mean ± SD),* female	3.17 (± 0.22)	3.15 (± 0.15)	2.8 (± 0.3)*	2.58 (± 0.23)*	2.32 (± 0.29)*
	Body weight of live fetuses *(g, litter mean ± SD),* male	3.35 (± 0.25)	3.42 (± 0.1)	3.01 (± 0.36)*	2.71 (± 0.3)*	2.47 (± 0.29)*
Saillenfait et al. (2003) MBP Rat (Sprague-Dawley); P0, female (14-15/group) 0, 1.8, 3.6, 5.4 mmol/kg (equivalent to 0, 560, 1,120, 1,690 mg/kg as calculated by study authors) Gavage GD 10; dams sacrificed on GD 21	Doses	0		560	1,120	1,690
	Body weight of live fetuses *(g, litter mean ± SE),* male and female	5.28 (± 0.07)		5.15 (± 0.16)	5.19 (± 0.15)	5.25 (± 0.16)
Saillenfait et al. (2003) MBP Mouse (OF-1); P0, female (24-25/group) 0, 0.9, 1.8, 3.6, 5.4 mmol/kg (equivalent to 0, 280, 560, 1,120, and 1,690 mg/kg as calculated by study authors) Gavage GD 8; dams sacrificed on GD 18	Doses	0	280	560	1,120	1,690
	Body weight of live fetuses *(g, litter mean ± SE),* male and female	1.19 (± 0.02)	1.16 (± 0.03)	1.23 (± 0.05)	1.14 (± 0.03)	1.04 (± 0.04)*
Developmental embryotoxic effects						
Ema et al. (1996) MBP Rat (Wistar); P0, female (10-11/group) 0, 500, 625, 750 mg/kg-day Gavage GDs 7-9; dams sacrificed on GD 20	Doses		0	500	625	750
	Adjusted maternal body weight gain		No significant change			
	Maternal food intake during pregnancy *(g, mean ± SD)*		384 (± 22)	366 (± 27)	355 (± 20)*	336 (± 30)*
	Number of litters totally resorbed		0	0	1	3
	Number of live fetuses per litter *(mean ± SD)*		12.3 (± 2.4)	12.1 (± 1.9)	10.3 (± 4.1)	5.9 (± 4.5)*
	Percent postimplantation loss per litter *(mean)*		13.3	18.4	27.8*	57.7*
	Sex ratio of live fetuses *(male/female)*		59/64	53/68	46/66	30/35

Reference and study design	Results				
Ema et al. (1996) MBP Rat (Wistar); P0, female (10-14/group) 0, 500, 625, 750 mg/kg-day Gavage GDs 10-12; dams sacrificed on GD 20	Doses	0	500	625	750
	Adjusted maternal body weight gain	No significant change			
	Maternal food intake during pregnancy *(g, mean ± SD)*	384 (± 22)	387 (± 16)	370 (± 27)	349 (± 28)*
	Number of litters totally resorbed	0	0	0	9*
	Number of live fetuses per litter *(mean ±SD)*	12.3 (± 2.4)	11.2 (± 2.8)	7.5 (± 3.8)*	1.8 (± 3.3)*
	Percent postimplantation loss per litter *(mean)*	13.3	24.6	46.4*	86.9*
	Sex ratio of live fetuses *(male/female)*	59/64	58/54	40/42	15/10
Ema et al. (1996) MBP Rat (Wistar); P0, female (10-15/group) 0, 500, 625, 750 mg/kg-day Gavage GDs 13-15; dams sacrificed on GD 20	Doses	0	500	625	750
	Adjusted maternal body weight gain	No significant change			
	Maternal food intake during pregnancy *(g, mean ± SD)*	384 (± 22)	372 (± 22)	370 (± 18)	350 (± 21)*
	Number of litters totally resorbed *(P0, female)*	0	0	2	12*
	Number of live fetuses per litter *(mean ±SD)*	12.3 (± 2.4)	8.6 (± 3.5)	4.6 (± 3.4)*	0.6 (± 1.5)*
	Percent postimplantation loss per litter *(mean)*	13.3	34.7*	66.8*	95.5*
	Sex ratio of live fetuses *(male/female)*	59/64	55/40	25/26	3/6

Reference and study design	Results					
Ema and Miyawaki (2001a) MBP Rat (Wistar); P0, female (16/group) 0, 250, 500, 750 mg/kg-day Gastric intubation GDs 15-17	Doses	0	250	500	750	
	Adjusted maternal body weight gain *(g, mean ± SD)*	23 (± 11)	23 (± 10)	29 (± 4)	26 (± 9)	
		Note: Maternal weight excluding gravid uterus				
	Number of litters totally dead	0	0	0	3	
	Number of resorptions and dead fetuses per litter *(mean ±SD)*	0.9 (± 0.8)	1.8 (± 2.0)	4.5 (± 3.4)*	7.9 (± 5.1)*	
	Percent postimplantation loss per litter *(mean)*	6.5	12	30.6*	52.7*	
	Number of live fetuses per litter *(mean)*	14 (± 2.6)	13.1 (± 2.2)	9.4 (± 2.5)*	7.1 (± 5.0)*	
	Sex ratio of live fetuses *(male/female)*	117/107	110/100	71/82	54/58	
Ema and Miyawaki (2001b) MBP Rat (Wistar); P0, female (16/group) 0, 250, 500, 750, 1,000 mg/kg-day Gavage GDs 0-8 with outcomes determined on GD 20	Doses	0	250	500	750	1,000
	Adjusted maternal weight gain *(g, mean ± SD)*	33 (± 13)	38 (± 9)	31 (± 10)	37 (± 13)	25 (± 12)
	Number of live fetuses per litter *(mean ±SD)*	14.1 (± 1.6)	13.7 (± 2.7)	13.9 (± 2.4)	12.7 (± 2.7)	10.8 (± 3.7)*
	Number of resorptions and dead fetuses per litter *(mean ±SD)*	1.4 (± 1.5)	1 (± 1)	1.7 (± 1.7)	2.4 (± 2)	3.7 (± 3.1)*
	Percent postimplantation loss per litter *(mean)*[c]	9.1	6.4	11.3	15.9	26.3*
	Percent preimplantation loss per female *(mean)*[d]	5.9	8.7	9.8	19.2	20.2*
	Percent preimplantation loss per litter *(mean)*[e]	5.9	8.7	3.7	7.6	8.7
	Sex ratio of live fetuses *(male/female)*	121/104	120/99	108/100	98/80	77/74

Reference and study design	Results				
Saillenfait et al. (2001) MBP Rat (Sprague Dawley) 0, 1.8, 3.6, 5.4, 7.2 mmol/kg at 5 ml/kg Oral Day 10 11-15 litters/group Second study: 6-8 pregnant dams 0, 5.4, 7.2 mmol oral MBP given on day 10	Doses	0	5.4	7.2	
	Live embryos per litter, Day 12 *(mean ± SEM)*	14.08 (± 0.57)	12.92 (± 0.92)	14 (± 1.15)	
	Live embryos per litter, Day 13 *(mean ± SEM)*	12 (± 0.93)	9.14 (± 0.67)	5.29 (± 1.52)**	
	Live embryos per litter, Day 14 *(mean ± SEM)*	12.57 (± 1.07)	8.87 (± 1.78)	4.33 (± 1.31)**	
	Live embryos per litter, Day 18 *(mean ± SEM)*	12.71 (± 0.81)	7.67 (± 1.2)*	6.67 (± 1.91)**	
	Percent non-live implants per litter, Day 12 *(mean ± SEM)*	4.2 (± 1.5)	9.5 (± 4.3)	4.36 (± 1.3)	
	Percent non-live implants per litter, Day 13 *(mean ± SEM)*	7.7 (± 3)	25.5 (± 6.3)*	57.6 (± 11.9)*	
	Percent non-live implants per litter, Day 14 *(mean ± SEM)*	10.1 (± 5.4)	35.9 (± 8.4)*	66.8 (± 10)*	
	Percent non-live implants per litter, Day 18 *(mean ± SEM)*	2.7 (± 1.9)	37.4 (± 10.4)*	54.5 (± 12.3)*	
	Non-live implants/total implants, Day 12	7/176	15/170	8/176	
	Non-live implants/total implants, Day 13	8/92	24/88*	55/92*	
	Non-live implants/total implants, Day 14	10/98	37/108*	57/83*	
	Non-live implants/total implants, Day 18	3/92	36/105*	46/86*	
Saillenfait et al. (2003) MBP Rat (Sprague-Dawley); P0, female (14-15/group) 0, 1.8, 3.6, 5.4 mmol/kg (equivalent to 0, 560, 1,120, 1,690 mg/kg as calculated by study authors) Gavage GD 10; sacrificed on GD 21	Doses	0	560	1,120	1,690
	Number of live fetuses per litter *(mean ± SD)*	13.46 (± 0.77)	13.92 (± 0.55)	13.5 (± 0.69)	12.77 (± 0.67)
	Percent postimplantation loss per litter *(mean ± SE)*	2.1 (± 1.08)	4.38 (± 1.77)	1.79 (± 1.28)	6.1 (± 1.99)

Reference and study design	Results					
Saillenfait et al. (2003) MBP Mouse (OF-1); P0, female (24-25/group) 0, 0.9, 1.8, 3.6, 5.4 mmol/kg (equivalent to 0, 280, 560, 1,120, and 1,690 mg/kg as calculated by study authors) Gavage GD 8; dams sacrificed on GD 18	Doses	0	280	560	1,120	1,690
	Number of live fetuses per litter *(mean ±SE)*	12.35 (± 0.88)	12.38 (± 0.71)	6.64 (± 0.91)*	2.32 (± 0.69)*	2.33 (± 0.58)*
	Percent postimplantation loss per litter *(mean ± SE)*	9.59 (± 2.76)	11.25 (± 2.5)	40.83 (± 6.22)*	83.31 (± 5.03)*	82.42 (± 4.31)*
	Percent resorptions per litter *(mean ± SE)*	9.3 (± 2.76)	10.21 (± 2.48)	40.15 (± 6.17)*	82.21 (± 4.96)*	80.66 (± 4.45)*
Developmental teratological effects						

Reference and study design	Results				
Ema et al. (1996) MBP Rat (Wistar); P0, female (10-11/group) 0, 500, 625, 750 mg/kg-day Gavage GDs 7-9; dams sacrificed on GD 20	Doses	0	500	625	750
	Number of fetuses with external malformations	0	0	5	4
		Mainly cleft palate and agenesis of the lower body			
	Number of fetuses with internal malformations	0	0	3	0
		Dilation of renal pelvis and hypoplasia of kidney			
	Number of fetuses with skeletal malformations	1	10	10	14
		Mainly fusion and/or absence of cervical vertebral arches			
Ema et al. (1996) MBP Rat (Wistar); P0, female (10-14/group) 0, 500, 625, 750 mg/kg-day Gavage GDs 10-12; dams sacrificed on GD 20	Doses	0	500	625	750
	Number of fetuses with external malformations	0	0	0	1
	Number of fetuses with internal malformations	0	3	1	0
		Dilation of the renal pelvis			
	Number of fetuses with skeletal malformations	1	0	0	0
Ema et al. (1996) MBP Rat (Wistar); P0, female (10-15/group) 0, 500, 625, 750 mg/kg-day Gavage GDs 13-15; dams sacrificed on GD 20	Doses	0	500	625	750
	Number of fetuses with external malformations	0	1	16	9
		Mainly cleft palate			
	Number of fetuses with internal malformations	0	0	0	0
	Number of fetuses with skeletal malformations	1	6	10	5
		Mainly fusion of the sternebrae			

Reference and study design	Results						
Saillenfait et al. (2001) MBP Rat (Sprague-Dawley) 0, 1.8, 3.6, 5.4, 7.2 mmol/kg at 5 ml/kg Oral Day 10 11-15 litters/group	Doses	0	NH_4Cl	1.8	3.6	5.4	7.2
	Total embryos with defects *(% embryos affected/total embryos examined)*	27/8 (16)	25/10 (16.5)	26/7 (16.5)	57/12 (36.8)	136/12 (88.3)	146/12 (86.9)
Saillenfait et al. (2003) MBP Rat (Sprague-Dawley); P0, female (14-15/group) 0, 1.8, 3.6, 5.4 mmol/kg (equivalent to 0, 560, 1,120, 1,690 mg/kg as calculated by study authors) Gavage GD 10; sacrificed on GD 21	Doses	0	560	1,120	1,690		
	Percent of malformed fetuses	0	0	0	0		
		Statistical significance not evaluated					
Saillenfait et al. (2003) MBP Mouse (OF-1); P0, female (24-25/group) 0, 0.9, 1.8, 3.6, 5.4 mmol/kg (equivalent to 0, 280, 560, 1,120, and 1,690 mg/kg as calculated by study authors) Gavage GD 8; sacrificed on GD 18	Doses	0	280	560	1,120	1,690	
	Percent of malformed fetuses	0	0.4	2	9.8	34.7	
		Statistical significance not evaluated					
Female reproductive effects							
Ema et al. (1996) MBP Rat (Wistar); P0, female (10-11/group) 0, 500, 625, 750 mg/kg-day Gavage GDs 7-9; dams sacrificed on GD 20	Doses	0	500	625	750		
	Number of implantations per litter *(mean ± SD)*	14.2 (± 1.1)	15 (± 1.3)	14.2 (± 1.3)	14.5 (± 1.9)		

Reference and study design	Results					
Ema et al. (1996) MBP Rat (Wistar); P0, female (10-14/group) 0, 500, 625, 750 mg/kg Gavage GDs 10-12; dams sacrificed on GD 20	Doses	0	500	625	750	
	Number of implantations per litter *(mean ± SD)*	14.2 (± 1.1)	14.8 (± 0.8)	14.5 (± 1.3)	13.6 (± 2.2)	
Ema et al. (1996) MBP Rat (Wistar); P0, female (10-15/group) 0, 500, 625, 750 mg/kg-day Gavage GDs 13-15; dams sacrificed on GD 20	Doses	0	500	625	750	
	Number of implantations per litter *(mean ± SD)*	14.2 (± 1.1)	14.4 (± 2.4)	14.5 (± 2.3)	14.2 (± 1.7)	
Ema and Miyawaki (2001a) MBP Rat (Wistar); P0, female (16/group) 0, 250, 500, 750 mg/kg-day Gastric intubation GDs 15-17	Doses	0	250	500	750	
	Number of corpora lutea per litter *(mean ± SD)*	16.8 (± 1.8)	16.1 (± 1.3)	16.1 (± 1.6)	16.1 (± 1.3)	
	Number of implantations per litter *(mean ± SD)*	14.9 (± 2.3)	14.9 (± 1.6)	14.1 (± 1.8)	15 (± 1.2)	
	Number of pregnant rats	16	16	16	16	
Ema and Miyawaki (2001b) MBP Rat (Wistar); P0, female (16/group) 0, 250, 500, 750, 1,000 mg/kg-day Gavage GDs 0-8 with outcomes determined on GD 20	Doses	0	250	500	750	1,000
	Number of corpora lutea per litter *(mean ± SD)*	16.5 (± 1.2)	16 (± 1.2)	16.2 (± 1)	16.4 (± 1.8)	15.9 (± 0.9)
	Number of implantations per female *(mean ± SD)*	15.5 (± 1.3)	14.6 (± 2.5)	14.6 (± 4.2)	13.2 (± 5.4)	12.7 (± 5.1)*
	Number of implantations per litter *(mean ± SD)*	15.5 (± 1.3)	14.6 (± 2.5)	15.6 (± 1.5)	15.1 (± 1.8)	14.5 (± 1.3)
Kai et al. (2005) MBP Rat (Sprague Dawley); P0, female 4/group, first study; P0 female 6/control or 8/MBP second study 0, 500 mg/kg-day[b] Gavage GDs 15-18	Dose	0	500			
	Percent pregnant	85.7	46.9*			

Reference and study design	Results					
Saillenfait et al. (2001) MBP Rat (Sprague Dawley) 0, 1.8, 3.6, 5.4, 7.2 mmol/kg at 5 ml/kg Oral Day 10 11-15 litters/group Second study: 6-8 pregnant dams 0, 5.4, 7.2 mmol oral MBP given on day 10	Doses	0	5.4	7.2		
	Implantation sites per litter, Day 12 *(mean ± SEM)*	14.67 (± 0.48)	14.17 (± 0.6)	14.67 (± 1.18)		
	Implantation sites per litter, Day 13 *(mean ± SEM)*	13.14 (± 1.16)	12.57 (± 0.97)	13.14 (± 1.65)		
	Implantation sites per litter, Day 14 *(mean ± SEM)*	14 (± 0.79)	13.5 (± 1.45)	13.83 (± 1.25)		
	Implantation sites per litter, Day 18 *(mean ± SEM)*	13.14 (± 0.96)	11.67 (± 0.94)	14.33 (± 0.49)		
Saillenfait et al. (2003) MBP Rat (Sprague-Dawley); P0, female (14-15/group) 0, 1.8, 3.6, 5.4 mmol/kg (equivalent to 0, 560, 1,120, 1,690 mg/kg as calculated by study authors) Gavage GD 10; sacrificed on GD 21	Doses	0	560	1,120	1,690	
	Number of implantations per litter *(mean ± SE)*	13.73 (± 0.73)	14.62 (± 0.63)	13.75 (± 0.68)	13.62 (± 0.69)	
	Percent pregnant	79	93	86	87	
		Statistical significance not evaluated				
Saillenfait et al. (2003) MBP Mouse (OF-1); P0, female (24-25/group) 0, 0.9, 1.8, 3.6, 5.4 mmol/kg (equivalent to 0, 280, 560, 1,120, 1,690 mg/kg as calculated by study authors) Gavage GD 8; sacrificed on GD 18	Doses	0	280	560	1,120	1,690
	Number of implantations per litter *(mean ± SE)*	13.45 (± 0.89)	13.71 (± 0.65)	11.27 (± 1.04)	12.73 (± 0.72)	13.24 (± 0.75)
	Percent pregnant	83	88	88	96	88
		Statistical significance not evaluated				
Male hormones						
Kai et al. (2005) MBP Rat (Sprague Dawley); P0, female 4/group, first study; P0 female 6/control or 8/MBP second study 0, 500 mg/kg-day[b] Gavage GDs 15-18	Dose	0	500			
	Concentration of testosterone *(pg/mg testis weight ± SE),* 0 day old pups from second study	1.45 (± 0.46)	0.59 (±0.18)*			

Reference and study design	Results		
Shono et al. (2000) MBP Rat (Wistar-King A) Equivalent to 0 and 300 mg/kg-day Gavage GDs 15-18	Dose	0	300
	Testosterone content of the testes *(pg/testis, testis mean ± SE)*	852 (± 80.3)	50.9 (± 3.8)*
Male malformations			
Gray et al. (1982) MBP Mouse (TO); 6/group Hamster (Syrian); 7/group 0, 800 mg/kg-day (Mouse) 0, 1,600 (Hamster) Oral intubation 5 day treatment for mice 9 day treatment for hamster	Dose	0	800
	Testes histology (Mouse), >90% tubular atrophy	-	6
	Doses	0	1,600
	Testes histology (Hamster), normal	-	5
	Testes histology (Hamster), occasional tubular atrophy	-	2
Imajima et al. (2001) MBP Rat (Wistar-King A); 2/group for control and 3/group for MBP 0, 1,923 mg/kg-day[b] Gavage GDs 15-18	Dose	0	1,923
	Degree of transabdominal testicular migration, GD 19 *(number of units from bladder neck where 100 U = distance from bladder neck to lower pole of kidney; mean ± SE)*	15 (± 2.0)	56 (± 3.1)*
Oishi and Hiraga (1980) MBP Rat (Wistar - Male) 2% MBP (equivalent to 1.90 mg/kg-day as calculated by study authors) 5 groups of different metabolites 1 week of treatment Diet n not identified in study	Dose	Control	1.9
	Concentration of testosterone for testes *(% of control ± SD)*[a]	-	220 (± 35.9)*
	Concentration of testosterone for serum *(% of control ± SD)*[a]	-	87 (± 23.1)
Shono et al. (2000) MBP Rat (Wistar-King A) Equivalent to 0 and 300 mg/kg-day Gavage GDs 7-10	Dose	0	300
	Degree of transabdominal testicular migration *(number of units from bladder neck where 100 U = distance from bladder neck to lower pole of kidney; mean ± SE)*	9.3 (± 1.9)	12.3 (± 5.9)

Reference and study design	Results				
Shono et al. (2000) MBP Rat (Wistar-King A) Equivalent to 0 and 300 mg/kg-day Gavage GDs 11-14	Dose	0	300		
	Degree of transabdominal testicular migration *(number of units from bladder neck where 100 U = distance from bladder neck to lower pole of kidney; mean ± SE)*	9.3 (± 1.9)	24.5 (± 5.2)*		
Shono et al. (2000) MBP Rat (Wistar-King A) Equivalent to 0 and 300 mg/kg-day Gavage GDs 15-18	Dose	0	300		
	Degree of transabdominal testicular migration *(number of units from bladder neck where 100 U = distance from bladder neck to lower pole of kidney; mean ± SE)*	9.3 (± 1.9)	57.9 (± 2.6)*		
	Epididymis: nonneoplastic lesions	Poorly developed epididymis			
	Testis: nonneoplastic lesions	No remarkable changes in the morphological features of Sertoli and Leydig cells			
Male puberty, reproductive development					
Cater et al. (1977) MBP Rat (Sprague Dawley); 6/group 0,400, 800 mg/kg-day Oral intubation 4 days or 6 days	Doses	0	400	800	
	Testes weight, 4 days *(mean; percent of control)*	100	78*	66*	
	Testes weight, 6 days *(mean; percent of control)*	100	64*	53*	
Ema and Miyawaki (2001a) MBP Rat (Wistar); P0, female (16/group) 0, 250, 500, 750 mg/kg-day Gastric intubation GDs 15-17	Doses	0	250	500	750
	AGD[a]	4.1	3.7*	2.9*	2.7*
	AGD[a] *(AGD/body weight)*	0.9	0.8	0.6	0.6
	AGD[a] *(AGD/cube root of body weight)*	2.4	2.2	1.7	1.6
	Number of fetuses with undescended testis *(n=litters)*	0	9 (6)*	61 (16)*	53 (13)*

Reference and study design	Results		
Gray et al. (1982) MBP Mouse (TO); 6/group Hamster (Syrian); 7/group 0, 800 mg/kg-day (Mouse) 0, 1,600 (Hamster) Oral intubation 5 day treatment for mice 9 day treatment for hamster	Dose	0	800
	Testes weight, mice *(percent of control)*	-	57 (± 3)*
	Dose	0	1,600
	Testes weight, hamster *(percent of control)*	-	93 (± 6)
Hallmark et al. (2007) MBP Marmosets; 5 pairs co-twins 0, 500 mg/kg-day oral silastic tubing syringe 14 days	Dose	0	500
	Leydig cell volume/testis[a]	0.6	0.9
	Average Leydig cell size[a]	257	301
	Total Leydig cell # per testis[a]	167	235
Imajima et al. (1997) MBP Rat (Wistar); 3 litters 0, 0.3 g/day (0, 1,000 mg/kg-day[b]) GDs 15-18 Gavage	Dose	0	1,000
	Degree of transabdominal testicular ascent, GD 20 *(number of units from bladder neck where 100 U = distance from bladder neck to lower pole of kidney; mean ± SE)*	9.3	57.9
	Incidence of cryptorchidism, unilateral	0	14
	Incidence of cryptorchidism, bilateral	0	8
	Incidence of cryptorchidism, total	0	22
Kai et al. (2005) MBP Rat (Sprague Dawley); P0, female 4/group, first study; P0 female 6/control or 8/MBP, second study 0, 500 mg/kg-day[b] Gavage GDs 15-18	Dose	0	500
	Testes weight *(mean g/100 g body weight)*	0.38 (± 0.03)	0.31 (± 0.09)*

<table>
<tr><th>Reference and study design</th><th colspan="5">Results</th></tr>
<tr><td rowspan="4">Kondo et al. (2006)
MBP
Rat (Wister-King A); 10/group
0, 1,264 mg/kg-day for 30 day rats[b] or 0, 615 mg/kg-day for 90 day rats[b]
Diet
10 days</td><td>Dose</td><td colspan="2">0</td><td colspan="2">1,264</td></tr>
<tr><td>Testes weight, Prepubertal 30 day rats (g/100 g body weight)</td><td colspan="2">4.11</td><td colspan="2">2.52*</td></tr>
<tr><td>Dose</td><td colspan="2">0</td><td colspan="2">615</td></tr>
<tr><td>Testes weight, Prepubertal 90 day rats (g/100 g body weight)</td><td colspan="2">4.07</td><td colspan="2">4.18</td></tr>
<tr><td rowspan="10">Mckinnell et al. (2009)
MBP
Marmosets; First study: P0 female, 9/group
0, 500 mg/kg-day
Oral
GDs 7-15
Second study; 10 newborn marmosets (5 pairs of co-twins)
0, 500 mg/kg-day
Oral
14 days</td><td>Dose</td><td>0 (vehicle control)</td><td>0 (non-vehicle treated)</td><td>0 (combined control)</td><td>500</td></tr>
<tr><td>Testes weight, 1-5 day old pups (mean in mg)</td><td>5.5</td><td>4.7</td><td>4.9</td><td>4.8</td></tr>
<tr><td>Dose</td><td>0 (control 1)[f]</td><td>0 (control 2)[f]</td><td>0 (combined control)</td><td>500</td></tr>
<tr><td>Testes weight (mean in mg)</td><td>522</td><td>516</td><td>518</td><td>605</td></tr>
<tr><td>Dose</td><td colspan="2">0 (vehicle treated)</td><td colspan="2">500</td></tr>
<tr><td>Testes weight, 17-20 days old (mean in mg)</td><td colspan="2">11.5</td><td colspan="2">11</td></tr>
<tr><td>Germ cell proliferation in testes (10^6), 1-5 days old (mean ± SEM)</td><td colspan="2">28 (± 4.9)</td><td colspan="2">33.4 (± 6.8)</td></tr>
<tr><td>Sertoli cell number in testes, 1-5 days old (mean ± SEM)</td><td colspan="2">4.16 (± 0.43)</td><td colspan="2">4.6 (± 0.66)</td></tr>
<tr><td>Germ cell/Sertoli cell ratio in testes (10^6), 1-5 days old (mean ± SEM)</td><td colspan="2">0.09 (± 0.02)</td><td colspan="2">0.12 (± 0.04)</td></tr>
<tr><td>G cell per testis (10^6), 17-20 days old (mean ± SEM)</td><td colspan="2">1.6 (± 0.24)</td><td colspan="2">1.4 (± 0.17)</td></tr>
<tr><td rowspan="2">Oishi and Hiraga (1980)
MBP
Rat (Wistar-Male)
2% MBP (equivalent to 1.90 mg/kg-day as calculated by study authors)
5 groups of different metabolites
1 week of treatment
Diet
n not identified from study</td><td>Dose</td><td colspan="2">Control</td><td colspan="2">1.9</td></tr>
<tr><td>Testicular Weight (absolute) (mean ± SD)</td><td colspan="2">1.73 (± 0.2)</td><td colspan="2">0.76 (± 0.14)*</td></tr>
</table>

Reference and study design	Results					
Shono and Suita (2003) MBP Rat (Wistar-King A); P0, female (6/group) 0, 125, 250, 500, 1,000 mg/kg-day Gavage GDs 15-17; half of sacrificed on GD 20 for fetal examination; remaining offspring examined PNDs 60-70	Doses	0	125	250	500	1,000
	Degree of transabdominal testicular ascent *(number of units from bladder neck where 100 U = distance from bladder neck to lower pole of kidney; mean ± SD)*	8.5 (± 1.3)	9.5 (± 1.4)	18.5 (± 1.9)*	33.7 (± 2.8)*	58.6 (± 2.1)*
	Percent of fetuses with undescended testis	0	0	25*	61.1*	76.9*
Shono et al. (2005) MBP Rat (Sprague Dawley); P0 female 10/group 0, 1% (mean intake 766.2 mg/kg-day) Diet	Dose	0		766.2		
	Degree of transabdominal testicular ascent[a], GD 19 *(number of units from bladder neck where 100 U = distance from bladder neck to lower pole of kidney; mean ± SD)*	13.5 (± 2.2)		54.9 (± 1.7)*		
Shono and Taguchi (2014) MBP Rat; Wistar-King A; 21/group 0, 164 mg/kg-day 156 (plus 250 mg/kg-day Vitamin C and 50 mg/kg-day Vitamin E) mg/kg-day Diet 3 days	Dose	0	156 (+Vitamin C and E)	164		
	Testes weight *(mg/g rat weight)*	3.0 (± 0.3)	2.8 (± 0.12)*	2.5 (± 0.15)*		

[#] Results are presented as the raw data as reported by the study authors.
*Result is statistically significant (p <0.05) based on analysis of data by study authors.
− = for controls, no response relevant; for other doses, no quantitative response reported; (n) = number evaluated from group; NR = not reported
[a]Values reported by the study authors were estimated from published graphs using "Grab It!", a Microsoft Excel based free software application used to digitize data from image files. Publisher: www.datatrendsoftware.com.
[b]Calculated by EPA
[c]Postimplantation loss = (number of resorptions and dead fetuses/number of implantations) × 100
[d]n = number of pregnant females; preimplantation loss = ((number of corpora lutea − number of implantations)/number of corpora lutea) × 100
[e]n = number of litters; preimplantation loss = ((number of corpora lutea − number of implantations)/number of corpora lutea) × 100
[f]control 1 animals are untreated adults most closely age-matched to MBP-exposed animals; control 2 animals are untreated adults showing that quantified adults are representative

3.4. PRELIMINARY MECHANISTIC INFORMATION FOR DBP

The systematic literature search for DBP also identified studies evaluating mechanisms of action considered potentially relevant to effects observed following exposure to DBP. Studies were included if they evaluated mechanistic events following exposure to DBP or metabolites, or contained information relevant to the mechanistic understanding of DBP 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, tissue, cell type, endpoint(s) (i.e., mechanistic outcomes), assay, mechanistic category, and type of hazard. Most of the mechanistic data identified corresponds to noncancer health endpoints including male and female reproductive toxicity, developmental toxicity, immunotoxicity, and hepatotoxicity. The database file is available for download and review via the DBP HERO project page. 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 DBP mechanistic studies consists of 407 mechanistic outcomes from 140 in vivo studies, as well as 461 mechanistic outcomes from 166 in vitro assays. Table 3-38 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) following DBP 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 and molecular adsorption, distribution, metabolism, and excretion (ADME); (11) 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, proteomics and metabolomics arrays, hormone production, and markers of angiogenesis. The ADME category above includes studies reporting the cellular metabolism of DBP, thermodynamics of protein binding, and cellular transport.

Table 3-38. Summary of mechanistic outcomes evaluated following DBP administration

Mechanistic category	Total # outcomes/ # studies	In vivo (# outcomes/# studies)						In vitro (# outcomes/# studies)					
		Total	Human	Primate	Rat	Mouse	Hamster	Total	Human	Primate	Rat	Mouse	Hamster
Mutation	17/12	1/1	0	0	0	1/1	0	16/11	0	0	0	2/2	0
DNA damage	19/9	10/4	0	0	7/2	3/2	0	9/5	7/4	0	0	2/1	0
DNA repair													
Oxidative stress	28/14	20/10	0	0	15/9	0	4/3	8/4	0	0	0	1/1	0
Cell death and division	146/74	22/15	0	1/1	15/12	6/2	0	124/60	62/28	2/1	18/12	37/23	0
Pathology	39/35	31/28	0	1/1	26/23	4/4	0	8/7	1/1	0	4/3	2/2	1/1
Epigenetics	6/4	3/2	0	0	2/1	1/1	0	3/2	2/1	0	0	1/1	0
Receptor-mediated and cell signaling	186/93	51/33	0	0	40/28	9/5	1/1	135/66	47/28	10/5	20/15	22/14	4/3
Immune system	37/13	23/6	0	0	0	23/6	0	14/7	3/2	0	5/2	5/2	0
Cellular & molecular ADME	35/14	26/12	0	0	23/9	3/3	0	9/4	1/1	0	2/1	4/2	0
Cellular differentiation and transformation	21/13	3/3	0	1/1	0	2/2	0	18/12	6/3	0	4/2	8/7	0
Cellular energetics	27/9	0	0	0	0	0	0	27/9	1/1	0	24/7	0	0
Other	311/146	217/99	1/1	1/1	180/40	27/14	0	90/52	31/15	1/1	31/22	20/12	0
Total	872/286	407/140						461/166					

Notes: The number in rows may not sum to "total" amounts as several studies evaluated multiple species or employed both in vivo and in vitro models. The mechanistic categories in italics and in gray shading had no DBP-specific information available. Four endpoints correspond to in-silico analysis and are not classified as in vivo or in vitro.

Information summarized in Table 3-38 and Figure 3-28, 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 which can be used to inform hazard identification and dose-response assessment, specifically addressing questions of human relevance, susceptibility, and dose-response relationships.

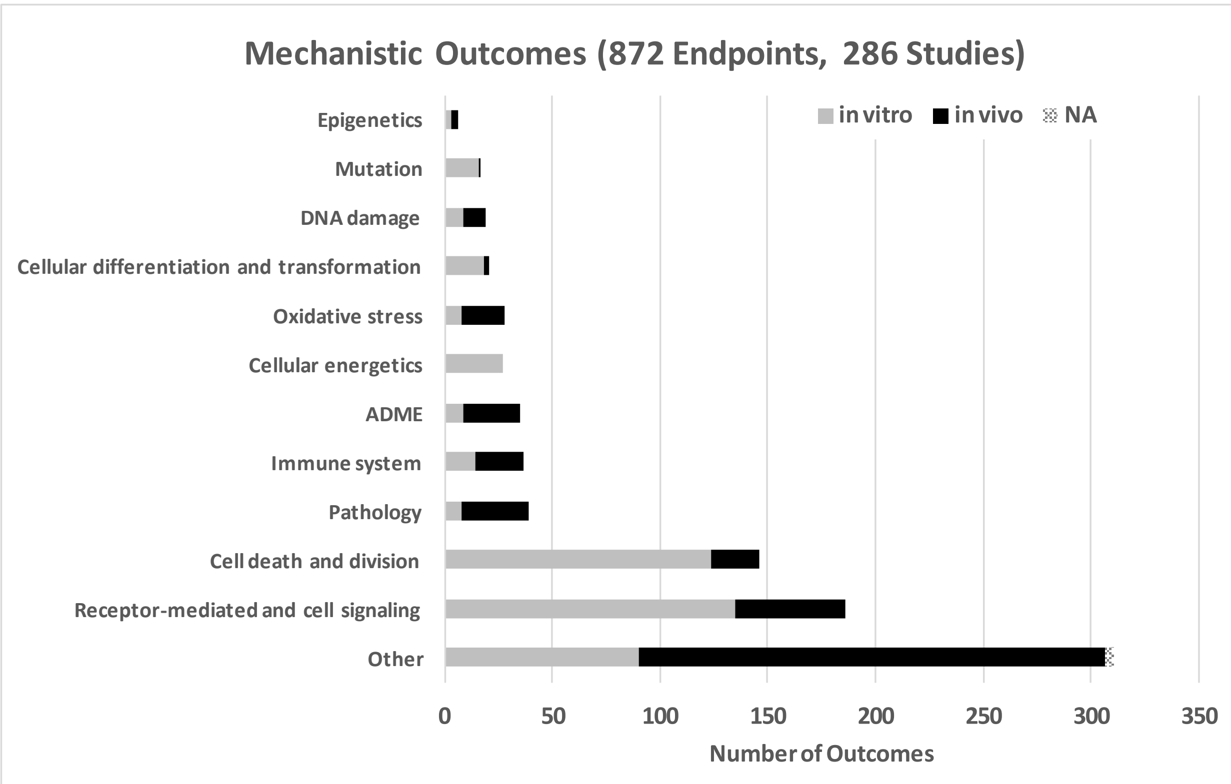

Figure 3-28. Summary of in vivo or in vitro mechanistic data by mechanistic category following oral exposure to DBP.

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