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Preliminary Materials
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Preliminary Materials for the Integrated Risk Information System (IRIS) Toxicological Review of Diisobutyl Phthalate (DIBP)

(CASRN No. 84-69-5)

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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 diisobutyl phthalate (DIBP) prepared by the U.S. Environmental Protection Agency's (EPA's) Integrated Risk Information System (IRIS) Program. These preliminary materials include a planning and scoping summary, information on the approaches used to identify pertinent literature, results of the literature search, approaches for selection of studies for hazard identification, presentation of critical studies in evidence tables and exposure-response arrays, and mechanistic information for DIBP. 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 DIBP, occurrence of DIBP 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 DIBP assessment is in Phase 2 and represents a significant advancement in implementing the NRC recommendations. In the development of this assessment, many of the recommendations are being implemented in full, while others are being implemented in part. Achieving full and robust implementation of certain recommendations will be an evolving process with input and feedback from the public, stakeholders, and independent external peer review. Phase 3 of implementation will incorporate the longer-term recommendations made by the NRC, including the development of a standardized approach to describe the strength of evidence for noncancer effects.

In May 2014, the NRC released their report reviewing the IRIS assessment development process. As part of this review, the NRC reviewed current methods for evidence-based reviews and made several recommendations with respect to integrating scientific evidence for chemical hazard and dose-response assessments. In their report, the NRC states that EPA should continue to improve its evidence-integration process incrementally and enhance the transparency of its process. The committee did not offer a preference but suggests that EPA consider which approach best fits its plans for the IRIS process. The NRC recommendations will inform the IRIS Program's efforts in this area going forward. This effort is included in Phase 3 of EPA's implementation plan.

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

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

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

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

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

1. INTRODUCTION

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

1.1. DIBP IN THE ENVIRONMENT

1.1.1. Production and Use

DIBP (Figure 1-1) is used as a plasticizer (HSDB, 2013) in a wide range of materials including polyvinyl chloride (PVC) formulations; paints; lacquers; varnish; paper, pulp and board industry; as a softener; in viscosity adjustment; nail polish; cosmetics; lubricants; carpets; clothing treatments; rubber dentistry settings; as a fuel stabilizer; as a concrete additive; explosive materials; and printing inks. DIBP has also been classified by the Food and Drug Administration (FDA) as an indirect food additive through its use as a component of adhesives. Because DIBP has similar properties to di-n-butyl phthalate (DBP), it can be used as a substitute for DBP (HSDB, 2013). Approximately 500,000 pounds were manufactured in the United States in 2012 (http://www.epa.gov/oppt/cdr/index.html). In July 2014, the Consumer Product Safety Commission's (CPSC) Chronic Hazard Advisory Panel (CHAP) recommended that DIBP be permanently banned from use in children's toys and child care articles at levels greater than 0.1% (CHAP, 2014).

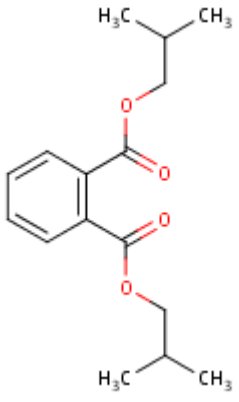


Figure 1-1. Chemical structure of DIBP (HSDB, 2013).

1.1.2. Environmental Fate

If released to air, DIBP will exist in both the vapor and particulate phases in the atmosphere. Vapor-phase DIBP will be photolytically degraded with a half-life of about 1.2 days, and particulate-phase DIBP will be removed from the atmosphere by wet or dry deposition (HSDB, 2013). In soil, DIBP is expected to have low mobility due to a moderately high organic carbon partition coefficient (Koc). Biodegradation in aerobic soil and water is expected to occur over days or weeks. Anaerobic biodegradation rates are expected to be slower. Volatilization from moist soil or water is expected to be an important fate process for DIBP, but volatilization from dry soil is not expected. If released into water, DIBP is expected to adsorb to sediments and solids, and volatilization from water surfaces is expected to be an important process. An estimated bioconcentration factor of 240 suggests that there is a potential for the chemical to concentrate in aquatic organisms, but metabolism in the organisms can reduce accumulation (HSDB, 2013). As noted by Wormuth et al. (2006), the majority of phthalates that are found in the environment come from their slow releases from plastics and other phthalate-containing articles. Certain waste streams, sludges, and industrially contaminated sites, however, may contain higher levels of phthalates than other sites.

1.1.3. Human Exposure Pathways

The routes by which humans are exposed to phthalates and the magnitude of individual phthalate exposures have changed over time as the quantities and uses of the various 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) 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 parent phthalates or their metabolites in a body matrix, such as blood or urine, provides evidence of exposure to that chemical. The predominant metabolite of DIBP in humans is monoisobutyl phthalate (MIBP). Zota et al. (2014) evaluated the prevalence and temporal trends of MIBP in urine samples collected as part of the National Health and Nutrition Examination Survey (NHANES) conducted between 2001 and 2010. MIBP was found in 72% of the samples in the 2001–2002 cycle and 96% of the samples in the 2009–2010 cycle, and increased in concentration over time, starting at about 2.4 ng/mL in the 2001–2002 cycle, and rising to about 7.8 ng/mL in the 2009–2010 cycle.

Intake exposures can be estimated on a pathway-basis by combining exposure media concentrations and contact rates. Using this approach, Clark et al. (2011) estimated median intakes of DIBP for various lifestages as defined by the authors: between 0.75 and 1.0 µg/kg-day for teens (12–19 years of age) and adults (20–70 years of age), based on ingestion of food, drinking water, dust/soil, and inhalation of air; and between 1.3 and 2.6 µg/kg-day for infants (0–0.5 years of age), toddlers (ages 0.5–4 years of age), and children (5–11 years of age). The exposure was found to be

dominated by food, with inhalation of indoor air also important. The intakes determined by Clark et al. (2011) were higher than those found by Wormuth et al. (2006), who determined intakes for these age ranges at about ≤0.5 µg/kg-day. Clark et al. (2011) attributed this difference to use of higher food concentrations in the estimates.

Wittassek et al. (2011) reported median intakes of DIBP in the range of 0.1–1.7 µg/kg-day based on a literature survey of urinary biomonitoring data and intake estimates provided therein. Their review included a single study in the United States of a cohort of pregnant woman that found median intakes at 0.1 µg/kg-day. Three other studies from Germany had median intakes ranging from 1.1 to 1.7 µg/kg-day. Qian et al. (2014) used NHANES 2007–2008 and found a median intake of 0.2 µg/kg-day and a 95th percentile intake of 0.9 µg/kg-day. Christensen et al. (2014b) combined the data from NHANES 2005–2008 and found similar results to Qian et al. (2014), with a median over that time span of 0.2 µg/kg-day and a 95th percentile intake of 0.8 µg/kg-day.

1.2. SCOPE OF THE ASSESSMENT

The National Research Council (NRC) has recommended that, "[c]umulative 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 NHANES that demonstrate exposure to multiple phthalates in most people (NRC, 2008, p23-25). A recent review of human exposure to eight phthalates estimated that indoor air contributed to approximately 25% of DIBP exposure in children (CHAP, 2014, Appendix E1, p35). The unique exposure scenarios and potential sensitivities of children contribute to the need for an assessment of phthalate toxicity. This IRIS assessment will help to inform EPA programs and regions of the potentially unique vulnerabilities of children to DIBP exposure and enable future cumulative risk assessments that assess effects on human health outcomes that might be associated with DIBP and other phthalates. There is currently no IRIS assessment of DIBP.

2. METHODS FOR IDENTIFYING AND SELECTING STUDIES

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

2.1. DRAFT LITERATURE SEARCH AND SCREENING STRATEGY

The literature search for DIBP was conducted in four online scientific databases (PubMed, Web of Science, Toxline, and Toxic Substances Control Act Test Submissions (TSCATS2)) in February of 2013; the search was repeated in March of 2014. This document is complete through March 2014. Additional updates will be performed at regular (e.g., 6-month) intervals. The detailed search approach, including the search strings and number of citations identified per database, is presented in Table 2-1. The search strings and search terms described for DIBP captured studies using the parent compound and metabolites (i.e., the active metabolite, monoisobutyl phthalate [MIBP]). This search of online databases identified 504 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);

343citations were obtained using these additional search strategies. In total, 809 citations were identified using online scientific databases and additional search strategies.

Table 2-1. Database search strategy for DIBP

Database (search date)	Keywords[a]
PubMed 03/2014 02/2013	dibp OR (mibp AND phthalate) OR "diisobutylphthalate" OR "di-isobutyl phthalate" OR "84-69-5" OR "diisobutyl phthalate" OR "di(i-butyl)phthalate" OR "di-iso-butyl phthalate" OR "isobutyl phthalate" OR "phthalic acid diisobutyl ester" OR ("diisobutyl ester" AND phthalate) OR "1,2-benzenedicarboxylic acid bis(2-methylpropyl) ester" OR "1,2-benzenedicarboxylic acid 1,2-bis(2-methylpropyl) ester" OR "monoisobutyl phthalate" OR "mono(i-butyl)phthalate" OR "mono-iso-butyl phthalate" OR "phthalic acid monoisobutyl ester" OR "1,2-benzenedicarboxylic acid, mono(2-methylpropyl) ester" OR "2-[(2-methylpropoxy)carbonyl]benzoic acid" OR "1,2-benzenedicarboxylic acid, mono(2-methylpropyl) ester (9CI)" OR "isobutyl hydrogen phthalate" OR "1,2-benzenedicarboxylic acid 1-(2-methylpropyl) ester"
Web of Science 03/2014 02/2013	TS=dibp OR (TS=mibp AND TS=phthalate) OR TS="diisobutylphthalate" OR TS="di-isobutyl phthalate" OR TS="84-69-5" OR TS="diisobutyl phthalate" OR TS="di(i-butyl)phthalate" OR TS="di-iso-butyl phthalate" OR TS="isobutyl phthalate" OR TS="phthalic acid diisobutyl ester" OR (TS="diisobutyl ester" AND TS=phthalate) OR TS="1,2-benzenedicarboxylic acid bis(2-methylpropyl) ester" OR TS="1,2-benzenedicarboxylic acid 1,2-bis(2-methylpropyl) ester" OR TS="monoisobutyl phthalate" OR TS="mono(i-butyl)phthalate" OR TS="mono-iso-butyl phthalate" OR TS="phthalic acid monoisobutyl ester" OR TS="1,2-benzenedicarboxylic acid, mono(2-methylpropyl) ester" OR TS="2-[(2-methylpropoxy)carbonyl]benzoic acid" OR TS="1,2-benzenedicarboxylic acid, mono(2-methylpropyl) ester (9CI)" OR TS="isobutyl hydrogen phthalate" OR TS="1,2-benzenedicarboxylic acid 1-(2-methylpropyl) ester"
Toxline 03/2014 02/2013	Split into 4 separate search strings: @TERM+@rn+84-69-5 @AND+mibp+phthalate @AND+"diisobutyl ester"+phthalate @OR+(dibp+"diisobutylphthalate"+"di-isobutyl+phthalate"+"diisobutyl+phthalate"+"di(i-butyl)phthalate"+"di-iso-butyl+phthalate"+"isobutyl+phthalate"+"phthalic+acid+diisobutyl+ester"+"1,2-benzenedicarboxylic+acid+bis(2-methylpropyl)+ester"+"1,2-benzenedicarboxylic+acid+1,2-bis(2-methylpropyl)+ester"+"monoisobutyl+phthalate"+"mono(i-butyl)phthalate"+"mono-iso-butyl+phthalate"+"phthalic+acid+monoisobutyl+ester"+"1,2-benzenedicarboxylic+acid,+mono(2-methylpropyl)+ester"+"2-[(2-methylpropoxy)carbonyl]benzoic+acid"+"1,2-benzenedicarboxylic+acid,+mono(2-methylpropyl)+ester+(9CI)"+"isobutyl+hydrogen+phthalate"+"1,2-benzenedicarboxylic+acid+1-(2-methylpropyl)+ester")
TSCATS2 03/2014	(2000-) 84-69-5

[a]The search strings and search terms described above captured studies using the parent compound and the metabolite MIBP.

1 **Table 2-2. Summary of additional search strategies for DIBP**

System used	Selected key reference(s) or sources	Date	Additional references identified
Manual search of citations from regulatory documents	CPSC (2010). Toxicity Review for Diisobutyl phthalate (DIBP). Bethesda, MD: Consumer Product Safety Commission.	3/2014	9 citations added
Web of Science, forward search	Hannas et al. (2011). Dose-response assessment of fetal testosterone production and gene expression levels in rat testes following in utero exposure to diethylhexyl phthalate, diisobutyl phthalate, diisoheptyl phthalate, and diisononyl phthalate. Toxicol Sci. 123(1):206-16.	3/2014	2 citations added
	Saillenfait et al. (2008). Diisobutyl phthalate impairs the androgen-dependent reproductive development of the male rat. Reprod Toxicol. 26(2):107-15.	3/2014	1 citation added
	Ray et al. (2012). Ovarian development in Wistar rat treated prenatally with single dose diisobutyl phthalate. Bratisl Lek Listy. 113(10):577-82.	3/2014	0 citations added
	Kleinsasser et al. (2001a). Genotoxicity of di-butyl-phthalate and di-iso-butyl-phthalate in human lymphocytes and mucosal cells. Teratog Carcinog Mutagen. 21(3):189-96.	3/2014	1 citation added
Web of Science, backward search	Hannas et al. (2011). Dose-response assessment of fetal testosterone production and gene expression levels in rat testes following in utero exposure to diethylhexyl phthalate, diisobutyl phthalate, diisoheptyl phthalate, and diisononyl phthalate. Toxicol Sci. 123(1):206-16.	3/2014	1 citation added
	Saillenfait et al. (2008). Diisobutyl phthalate impairs the androgen-dependent reproductive development of the male rat. Reprod Toxicol. 26(2):107-15.	3/2014	1 citation added
	Ray et al. (2012). Ovarian development in Wistar rat treated prenatally with single dose diisobutyl phthalate. Bratisl Lek Listy. 113(10):577-82.	3/2014	4 citations added
	Kleinsasser et al. (2001a). Genotoxicity of di-butyl-phthalate and di-iso-butyl-phthalate in human lymphocytes and mucosal cells. Teratog Carcinog Mutagen. 21(3):189-96.	3/2014	2 citations added
Snowball search	DIBP references in previous assessment or previously added to the HERO project page	4/2014	45 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)	2/2013, update 3/2014	17 citations added

System used	Selected key reference(s) or sources	Date	Additional references identified
	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) 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)		

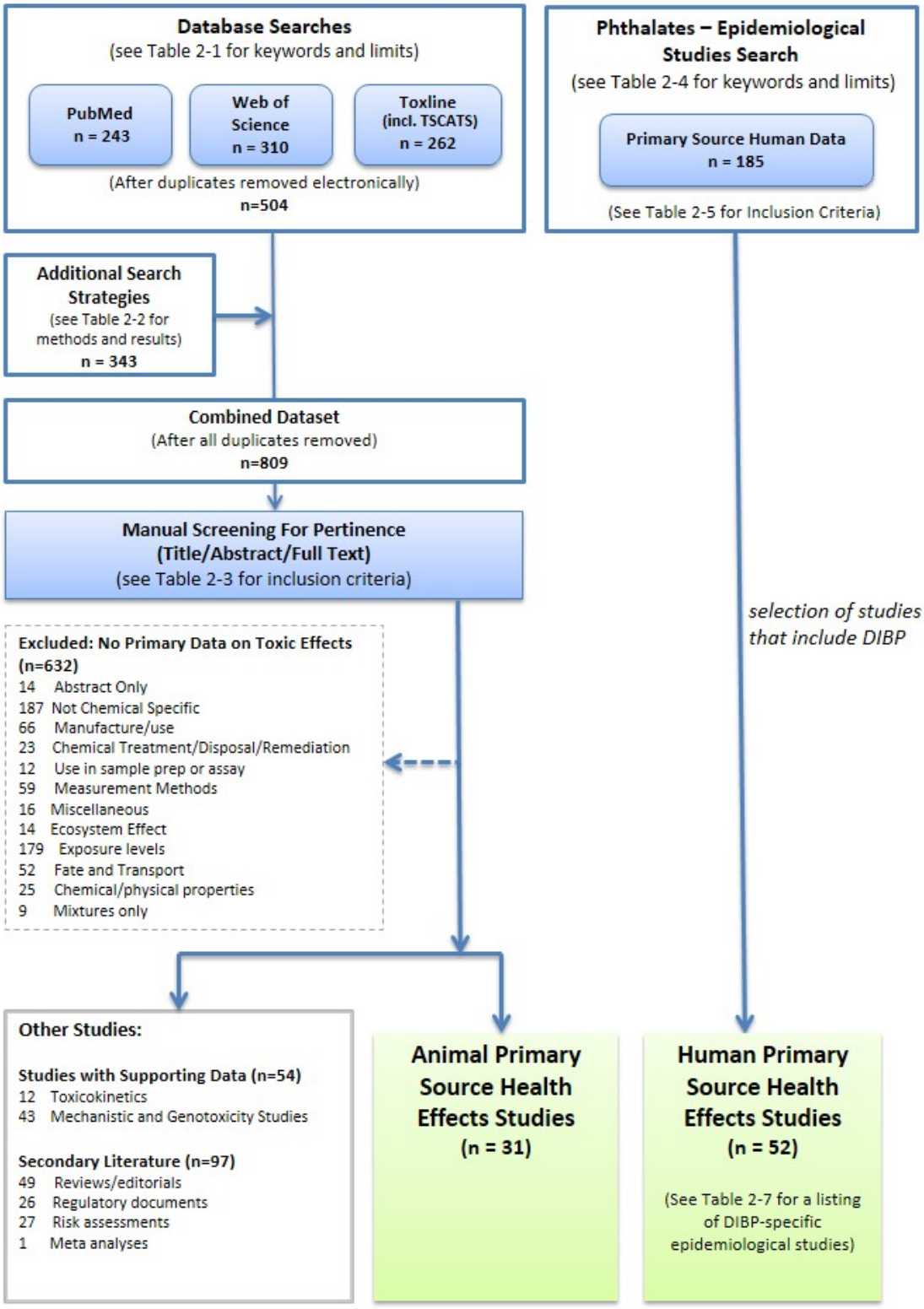
System used	Selected key reference(s) or sources	Date	Additional references identified
	ITER (TERA database) (http://iter.ctcnet.net/publicurl/pub_search_list.cfm) NAP – Search Site (http://www.nap.edu/) NRC – AEGLs via NAP search for "Acute Exposure Guideline Level" and the chemical NCI (http://www.cancer.gov) 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 limited instances, full text for pertinence to examining the health effects of DIBP exposure. The citations were then screened using inclusion criteria (Table 2-3) describing specific information to help identify primary source health effect data and mechanistic and/or genotoxic data, as well as resources useful in preparation of the DIBP package. The process for screening the literature search is described below and is shown graphically in Figure 2-1:

- 31 references were identified as animal studies with health effects data and were considered for data extraction to evidence tables and exposure-response arrays.
- 54 references were identified as supporting studies; of these, 12 were toxicokinetic studies and 43 were mechanistic and genotoxicity studies.
- 97 references were identified as secondary literature (e.g., reviews and editorials, risk assessments, meta analyses, and regulatory documents); these references were kept as additional resources for development of the Toxicological Review.
- 632 references were excluded because these studies did not include primary source data evaluating DIBP 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 (see Figure 2-1 and Table 2-3 for inclusion categories and criteria).

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. For example, the category "Studies with Supporting Data" included one study that contained information relevant to both the toxicokinetics and mechanistic and/or genotoxicity subcategories.

Among the studies identified in the DIBP literature searches, there were a number of foreign language studies. Based on a review of the English titles and, when available, English abstracts, two of the foreign language articles, Ma et al. (2013b) and Iijo (1975), were tagged as toxicity studies and four foreign language articles, Ma et al. (2010), Ma et al. (2013c), Kleinsasser et al. (1999), and Kleinsasser et al. (2001b), were tagged as mechanistic and genotoxicity studies. The other foreign language articles were excluded (tagged to Excluded: No primary data on toxic effects). Ma et al. (2013b) is a report of neurotoxicological effects after DIBP exposure. With the exception of one study (University of Rochester, 1954) that assessed brain weight, the Ma et al. (2013b) article was the only available neurotoxicological study; this article was translated into English (certified translation; Ma et al., 2013a). The remaining five foreign language articles (above), tagged to toxicity studies or mechanistic and genotoxicity studies, have not yet been translated or considered for inclusion in either evidence or mechanistic tables. These studies will be further evaluated and considered during the development of the draft assessment of the available evidence of DIBP-induced health effects.



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 DIBP.

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 DIBP 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 DIBP?

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

Thirty-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 DIBP epidemiology studies was incomplete. Epidemiology studies frequently examine multiple compounds (e.g., metabolites of several different phthalates). The indexing terms and abstracts may not include a comprehensive list of all of the specific phthalates examined, resulting in the inappropriate exclusion of studies and the potential for introduction of bias in the selection process. Specifically, "negative" studies (i.e., studies that did not demonstrate an association between exposure and disease) are potentially more likely to be missed than "positive" studies. This issue did not arise in the search process for experimental (animal toxicology) studies, for which the test compound is virtually always identified through search terms or key word searches of abstracts.

Another issue encountered in the development of the search and screening process for the phthalate epidemiology studies relates to the duplication of efforts involved in the development of EPA's health assessments for several individual phthalates (e.g., dibutyl phthalate [DBP], DIBP, 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 DIBP 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	4,127
	Epidemiology articles meeting inclusion criteria	**127**
December 2013 search	PubMed Web of Science ToxNet Merged Reference Set **Additional epidemiology articles meeting inclusion criteria**	155 249 114 350 **22**
June 2014 search	PubMed Web of Science ToxNet (was not searched because no articles have been found solely through this source in all the previous searches) Merged Reference Set Additional epidemiology articles meeting inclusion criteria	184 409 0 494 **24**

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.

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 DIBP, the primary metabolite of interest is MIBP.

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 were also used to supplement this broad search for epidemiology studies of phthalates), 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, 52 studies analyzed one or more health effects in relation to a measure of DIBP (Table 2-7).

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

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

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

Outcome category	Reference[a]	DIBP measure
Sexual differentiation measures (Table 3-1)	Swan (2008) Swan et al. (2010)	MIBP (maternal urine) MIBP (maternal urine)
Male reproductive (semen parameters, infertility, and hormones) (Tables 3-2 and 3-3)	Buck Louis et al. (2014) Joensen et al. (2012) Kranvogl et al. (2014) Mendiola et al. (2011) Wirth et al. (2008)	MIBP (urine) MIBP (urine) MIBP (urine) MIBP (urine) MIBP (urine)
Male pubertal development (Table 3-4)	Mieritz et al. (2012) Mouritsen et al. (2013b)	MIBP (maternal urine) MIBP (urine) Sum MIBP + MBP (urine)[a]
Female pubertal development (Table 3-5)	Frederiksen et al. (2012) Hart et al. (2013) Lomenick et al. (2010) Mouritsen et al. (2013b)	Sum MIBP + MBP (urine)[a] MIBP (maternal serum) MIBP (urine) Sum MIBP + MBP(urine)[a]

Outcome category	Reference[a]	DIBP measure
Female reproductive (infertility, hormones, gynecological conditions) (Tables 3-6 and 3-7)	Buck Louis et al. (2013) Hart et al. (2013) Sathyanarayana et al. (2014) Upson et al. (2013)	MIBP (urine) MIBP (maternal serum) MIBP (maternal urine) MIBP (urine)
Pregnancy outcomes (fetal growth, preterm birth) (Table 3-8)	Ferguson et al. (2014c) Ferguson et al. (2014a) Huang et al. (2014b) Meeker et al. (2009) Philippat et al. (2012) Wolff et al. (2008)	MIBP (maternal urine) MIBP (maternal urine) DIBP (cord blood) MIBP (maternal urine) MIBP (maternal urine) MIBP (maternal urine)
Immune: allergy (rhinitis, eczema) (Table 3-9)	Ait Bamai et al. (2014) Bornehag et al. (2004) Callesen et al. (2014b) Callesen et al. (2014a) Hoppin et al. (2013) Sun et al. (2009)	DIBP (dust) DIBP (dust) MIBP (urine) DIBP (dust) MIBP (urine) DIBP (dust)
Immune: asthma (Table 3-10)	Ait Bamai et al. (2014) Bertelsen et al. (2013) Callesen et al. (2014b) Callesen et al. (2014a) Hoppin et al. (2013) Sun et al. (2009)	DIBP (dust) MIBP (urine) MIBP (urine) DIBP (dust) MIBP (urine) DIBP (dust)
Neurodevelopment (Table 3-11)	Braun et al. (2014) Engel et al. (2010) Kobrosly et al. (2014) Téllez-Rojo et al. (2013) Whyatt et al. (2012)	MIBP (maternal urine) MIBP (maternal urine) MIBP (maternal urine) MIBP (maternal urine) MIBP (maternal urine)
Thyroid (Table 3-12)	Dirtu et al. (2013) Meeker and Ferguson (2011)	MIBP (urine) MIBP (urine)
Obesity (Table 3-13)	Buser et al. (2014) Dirtu et al. (2013) Hart et al. (2013) Kasper-Sonnenberg et al. (2012) Lind et al. (2012b) Olsén et al. (2012) Svensson et al. (2011) Teitelbaum et al. (2012) Trasande et al. (2013a) Wang et al. (2013)	MIBP (urine) MIBP (urine) MIBP (maternal serum) Sum MIBP + OH-MIBP (urine) MIBP (serum) MIBP (serum) MIBP (urine) MIBP (urine) MIBP (urine) MIBP (urine)
Diabetes and insulin resistance (Table 3-14)	Huang et al. (2014a) James-Todd et al. (2012) Lind et al. (2012a) Olsén et al. (2012) Svensson et al. (2011) Trasande et al. (2013b)	MIBP (urine) MIBP (urine) MIBP (serum) MIBP (serum) MIBP (urine) MIBP (urine)
Other cardiovascular disease risk factors (Table 3-15)	Lind and Lind (2011) Shiue (2014) Trasande et al. (2013c)	MIBP (serum) MIBP (urine) MIBP (urine)

Outcome category	Reference[a]	DIBP measure
	Olsén et al. (2012)	MIBP (serum)
Cancer (Table 3-16)	Lopez-Carrillo et al. (2010)	MIBP (urine)

[a]Included in DIBP tables because in this population, at this time, MIBP concentrations were greater than monobutyl phthalate (MBP) concentrations.

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[1] (http://hero.epa.gov/DIBP and http://hero.epa.gov/phthalates-humanstudies).

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

2.2.1. General Approach

Each study retained following the literature search and screen was evaluated for aspects of design, conduct, or reporting that could affect the interpretation of results and the overall contribution to the synthesis of evidence for determination of hazard potential. Much of the key information for conducting this evaluation can generally be found in the study's methods section and in how the study results are reported. Importantly, this evaluation does not consider study results or, more specifically, the direction or magnitude of any reported effects. For example, standard issues for evaluation of experimental animal data identified by the NRC and adopted in this approach include consideration of the species and sex of animals studied, dosing information (dose spacing, dose duration, and route of exposure), endpoints considered, and the relevance of the endpoints to the human endpoints of concern. Similarly, observational epidemiologic studies in this approach for evaluation should consider the following:

- Approach used to identify the study population and the potential for selection bias.
- Study population characteristics and the generalizability of findings to other populations.

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

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

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

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

2.2.2. Exclusion of Studies

After the literature search was manually screened for pertinence, studies were excluded if fundamental flaws were identified in their design, conduct, or reporting. The DIBP experimental animal database consists of studies designed to examine repeat-dose intraperitoneal or oral toxicity (including subchronic and short-term duration studies) and endpoint-specific toxicities (including reproductive and developmental toxicity). Four studies administered DIBP via the intraperitoneal route of exposure. These studies were excluded from the DIBP evidence tables because the intraperitoneal route of exposure is generally considered less relevant to human health exposure. The remaining studies involved administration of DIBP in the diet or via gavage administration. Acute studies are generally less pertinent for characterizing health hazards associated with chronic exposure. There was one acute study that was excluded from the evidence tables. Two BASF reports identified in the literature searches could not be obtained and thus, could not be evaluated for inclusion in the evidence tables (BASF, 2003, 1961). For these reasons, these studies are not summarized in the preliminary evidence tables. Nevertheless, with the exception of the studies that could not be obtained, the studies will still be evaluated as possible sources of supporting health effects information during assessment development. Experimental animal studies that were sources of short-term, subchronic, or chronic health effects were evaluated for potential flaws in their design, reporting, or conduct. As a result, one study, Ma et al. (2013b) (English translation

cited as Ma et al. (2013a)), was removed from consideration in the assessment because of incomplete description of experimental methods that leads to uncertainty in the results. Another study, Eastman Kodak (1978), a one-page data summary, was excluded because it does not provide detailed data reporting.

The remaining studies are all sources of health effects data that may be used in the assessment. The 20 studies summarized in the evidence tables are considered the "critical" studies from which the study methods and results are presented in preliminary evidence tables and exposure-response arrays (Section 3). There were also a few cases of the same study data being contained in multiple reports; in those cases, the studies are listed together in the evidence tables.

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

Several considerations will be used in EPA's evaluation of epidemiological studies of human health effects of DIBP. 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. A study is externally valid if the study results for the study population can be extrapolated to external target populations. An internally valid study is free from different types of biases, and is a prerequisite for generalizing study results beyond the study population. These issues are outlined in the IRIS Preamble, and are described below.

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 interval validity of a study, resulting in a biased effect estimate.

The general considerations for evaluating issues relating to the study population include adequate documentation of participant recruitment, including eligibility criteria and participation rates, 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 DIBP studies have generally examined metabolites from many different phthalates within the context of research on environmental exposures. Most of these studies rely on objective exposure measures (e.g., biomonitoring data), some of which are collected prior to onset of the outcomes being examined (e.g., in the prospective pregnancy cohort studies). Study participants generally do not have knowledge of the study hypothesis or their exposure to DIBP 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 DIBP, in conjunction with knowledge of specific health outcomes, may motivate people to participate in a study or to continue participation throughout a follow-up period. In the absence of evidence that any of these scenarios is likely to occur in a study, EPA will not consider selection bias as a limitation of a study.

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 DIBP include cosmetics, food, and food packaging (Zota et al., 2014) 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 DIBP is typically from multiple sources, and occurs episodically on a daily basis. Exposure to DIBP may be increasing; a recent study of the U.S. general population found that urinary concentrations of the DIBP metabolite MIBP have increased over time and were 206% higher in 2009–2010 compared to 2001–2002 (Zota et al., 2014).

Urine provides an integrated measure of phthalate exposure from all sources. Measurement of DIBP 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, monoisobutyl phthalate (MIBP) is the most commonly

measured DIBP metabolite in epidemiologic studies. MIBP accounts for an estimated 70.3% of the urinary excretion of DIBP; this value is based on human data from a controlled dosing study of a single volunteer (Koch et al., 2012). EPA considers the use of MIBP to be a good proxy for total DIBP exposure.

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 DIBP metabolites in breast milk or serum have generally reported low levels of detection. One study in Taiwan reported that MIBP 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 MIBP measured in cord blood and maternal urine was −0.11 (Pearson correlation of log-transformed levels) (Lin et al., 2011). Hogberg et al. (2008) reported that few breast milk (2 out of 42) or serum (3 out of 36) samples in a study in Sweden had detectable MIBP concentrations. Another study conducted among 60 men ages 18−26 years found that 33.3% of serum samples and 16.9% of seminal plasma samples had MIBP concentrations above the limit of detection (Frederiksen et al., 2010). The Spearman correlation coefficient between urine and serum concentrations was 0.39; the correlation between urine and seminal plasma concentrations was not calculated because of the low detection rate for the latter samples (Frederiksen et al., 2010). The lower detection rate in tissues other than urine reduces EPA's confidence in DIBP metabolite measures in these biological matrices.

Given their first-order kinetics with half-lives on the order of hours [3.9 hours for MIBP in (Koch and Angerer, 2007)], 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 MIBP found that specific gravity adjusted concentrations were lower in samples collected from 9 am to noon (geometric mean 9.4) compared with samples collected in early morning, early afternoon, or evening (geometric means 13−14) (Cantonwine et al., 2014). Urinary measures of DIBP 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 MIBP (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 DIBP 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 DIBP metabolites as continuous measures.

Another potential limitation of measurement of DIBP 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). An ICC of 0.51 for MIBP was reported in a study of 25 Hmong women ages 19–51 years with samples collected 2-4 weeks apart (Peck et al., 2010). In studies of reproducibility of measures during pregnancy, Cantonwine et al. (2014) reported ICCs of 0.35 and 0.34 (unadjusted and specific gravity adjusted) when comparing urine samples taken at approximately 18, 22, and 26 weeks of gestation. ICCs of 0.36 and 0.38, respectively, were seen before pregnancy and in early pregnancy (Braun et al., 2012), and an ICC of approximately 0.5 was seen over a 6-week period in the last trimester (Adibi et al., 2008). Among women participating in the Nurses' Health Study (NHS) (in 2000–2001 for NHS and in 1996-1999 for NHS II), the ICC for samples collected 1-3 years apart was 0.30 for all samples, and was 0.29 for first-morning samples (Townsend et al., 2013). Data for children are sparse, limiting the ability to examine this source of uncertainty in this population. One study evaluated variability in children aged 6–10 years old over a 6-month period (Teitelbaum et al., 2008) and found a relatively low ICC (0.21 unadjusted, 0.28 creatinine-adjusted). 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 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), and about measurements taken in children.

Some studies present analyses using a combined measure based on summation of MIBP and monobutyl phthalate (MBP), as a measure of both DIBP and DBP, respectively. The relative contribution of DIBP 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). EPA includes studies in the DIBP evidence tables using this summed exposure measure in situations in which the concentration of MIBP is greater than that of MBP, but recognizes that this measure introduces an additional source of exposure misclassification. 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 MIBP does not represent a major contributor to this summation measurement, EPA has not included data from these studies in the DIBP 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 DIBP exposure. This type of scenario adds an additional challenge to the interpretation of the DIBP 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.

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 DIBP. 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 DIBP 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 DIBP 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 DIBP 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 DIBP 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 10th 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 DIBP 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. Studies in older age groups have also shown a very high correlation ($r = 0.99$) between thyroid hormone levels measured in dried blood spots and levels in serum (Hofman et al., 2003).

With respect to thyroid hormones, time of day and season of sampling are two main potential sources of variability. For example, serum TSH measured shortly after midnight may be as much as twice as high as the value measured in late afternoon (Brabant et al., 1991; Weeke and Gundersen, 1978). The evidence with respect to seasonal variability is mixed (Plasqui et al., 2003; Nicolau et al., 1992; Simoni et al., 1990; Behall et al., 1984; Postmes et al., 1974) and this effect is

likely to be smaller than that of time of day. The impact of these sources of variation will depend on whether they are also related to DIBP (i.e., whether DIBP 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 DIBP. If this is not the case, the lack of consideration of time of day or seasonality would result in greater variability in the hormone measures, and would thus result in more imprecise (but not biased) estimates was located. EPA has not found studies examining seasonal variation in DIBP levels. With respect to variability relating to time of day, as noted previously, one study of 139 pregnant women in Puerto Rico reported lower concentrations of specific gravity-adjusted MIBP in samples collected from 9 am to noon (geometric mean of 9.4) compared with samples collected in early morning, early afternoon, or evening (geometric means of 13–14) (Cantonwine et al., 2014). 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.

Obesity

Most of the studies of obesity measures in the DIBP 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 DIBP 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 strongly related to both the exposure and the outcome under consideration, and are not intermediaries on a causal pathway), adequate control for these potential confounders in the study design or analysis, and where appropriate, quantification of the potential impact of mismeasured or unmeasured confounders. Uncontrolled confounding by factors that are positively associated with both the exposure (e.g., DIBP) 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

Few studies have reported results of analyses evaluating the correlation between MIBP and metabolites of other phthalates. 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 MIBP and MEP (the primary metabolite of DEP) was low (0.33). A more moderate correlation was seen with the DEHP metabolites (correlations of approximately 0.5); higher correlations were seen with MBzP (the primary metabolite of BBP, correlation coefficient = 0.58) and MBP (the primary metabolite of DBP; correlation = 0.72). Similar or somewhat lower correlations were seen between MIBP and other phthalate metabolites in a small study (n = 45) of men seen in an infertility clinic (Wirth et al., 2008), in 319 pregnancy women (Whyatt et al., 2012), and in 600 reproductive age women in a study of endometriosis (Buck Louis et al., 2013). EPA will evaluate the potential for confounding by

examining the similarity of the results seen with 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 MIBP 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 of metabolites.

Potential Confounding by Demographic Factors

Age, race/ethnicity, and sex are considered important explanatory factors for most types of outcomes measured in epidemiological research. In NHANES 2009–2010 data, urinary MIBP levels decreased with age (geometric means of 13.2, 8.63, and 7.45 μg/g-creatinine, respectively, in ages 6–11, 12–19 and ≥20 years) (CDC, 2013). Concentrations were lower levels in males compared with females (geometric means of 6.99 and 9.05 μg/g-creatinine, respectively, in males and females), and variability by ethnicity was also observed, with lower levels in non-Hispanic whites (geometric mean of 7.12 μg/g-creatinine) compared with non-Hispanic blacks and Mexican Americans (geometric means of 10.1 and 9.27 μg/g-creatinine, respectively). EPA will consider these differences in assessing the potential influence of demographic factors on observed effect estimates for DIBP.

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 DIBP (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 much of the DIBP 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., 2014a). 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 DIBP 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 DIBP 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 CRITICAL EXPERIMENTAL STUDIES FOR DIBP

Beyond the initial methodological screening described above in Section 2.2.2, methodological aspects of a study's design, conduct, and reporting will be considered again in the overall evaluation and synthesis of the pertinent data that will be developed for each health effect. Some general questions that will be considered in evaluating experimental animal studies are presented in Table 2-9. 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 critical studies will be performed as part of the critical review and synthesis of evidence for hazard identification for each of the health endpoints identified in the evidence tables presented in Section 3.

3. PRELIMINARY EVIDENCE TABLES AND EXPOSURE-RESPONSE ARRAYS

3.1. DATA EXTRACTION FOR EPIDEMIOLOGICAL AND 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 DIBP during the analysis of hazard potential and utility of the data for dose-response evaluation. For each critical study selected, key information on the study design, including characteristics that inform study quality, and study results pertinent to evaluating the health effects from subchronic and chronic oral exposure to DIBP are summarized in preliminary evidence tables.

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

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

3.2. EPIDEMIOLOGICAL STUDIES

3.2.1. Sexual Differentiation Measures

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

Reference and study design	Results
Anogenital distance (AGD)	
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 MIBP in urine (ng/mL): Median 75th percentile Unadjusted 2.5 5.1 **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)	Percent change in AGD per interquartile increase in MIBP concentration (*p*-value) MIBP −3.5 (0.097)
Cryptorchidism or testicular position	
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 (10% prevalence) **Exposure:** Maternal urine sample, 3rd trimester MIBP in urine (ng/mL): Median 75th percentile Unadjusted 2.5 5.1 **Analysis:** Logistic regression, adjusting for age and weight percentile **Related references:** Swan et al. (2005) (exposure data)	MIBP reported as not associated with testicular position (quantitative results not reported)

Reference and study design	Results
Gender-related play	
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 Unadjusted MIBP in urine (ng/mL): Boys: Median 2.4, 75th percentile 5.1 Girls: Median 2.8, 75th percentile 5.0 **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)	Regression coefficient (95% CI) for pre-school activities index scores and log-transformed MIBP (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) Masculine: Boys −1.65 (−4.57, 1.28); Girls 1.04 (−1.75, 3.82) Composite: Boys −4.53 (−8.12, −0.94); Girls 0.38 (−3.86, 4.63)

CI = confidence interval; MIBP = monoisobutyl phthalate

3.2.2. Male Reproductive Effects in Humans

Table 3-2. Evidence pertaining to DIBP and semen parameters or infertility in adult men or couples

Reference[a] and study design	Results
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 MIBP in urine: Median Maximum Unadjusted (µg/L) 21.6 161.8 Cr-adjusted (µg/g Cr) 20.8 119.2 **Analysis:** Spearman correlation	Spearman correlation coefficient, MIBP and sperm parameters: Sperm concentration −0.044 Sperm motility −0.075 (p > 0.05 for both parameters)
Joensen et al. (2012) (Denmark) **Population:** 881 men from general population, assessed at military conscript exam*, 2007–2009, median age 19.1 yrs (5th–95th percentile: 18.4–22.0 yrs) **Outcome:** Semen analysis **Exposure:** Urine sample, collected at same time as semen sample MIBP in urine (ng/mL): Median 95th percentile Unadjusted 58 173 **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 MIBP) reported as "few significant associations" with sperm volume, count, or percentage progressively motile sperm (quantitative results not reported). Sperm concentration analysis adjusted for abstinence time (volume, concentration, and count); sperm motility analysis adjusted for time from ejaculation to analysis (progressively motile); analysis of percent of morphologically normal sperm was unadjusted
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) MIBP in urine (ng/mL) (percentile): Median 75th percentile 95th percentile 5.8 10.0 17.9 **Analysis:** Dichotomized outcomes (above and below WHO reference values), MIBP dichotomized at median; age, education (three levels), income (three levels), race, BMI (three levels), current smoking status, and alcohol use (two levels) considered as potential confounders;	The combined measure for MIBP and MBP was not associated with any sperm parameter, nor was MIBP when analyzed individually (data not shown)

Reference[a] and study design	Results
specific gravity also included in all models	
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, home-fertility monitoring to detect ovulation, and home pregnancy tests **Exposure:** Urine samples from both partners, collected at enrollment (beginning of pregnancy attempt) Unadjusted MIBP in urine (ng/mL) among couples achieving pregnancy: Geometric mean (95% CI) Women 5.11 (4.58–5.70) Men 3.44 (3.09–3.83) **Analysis:** Fecundability OR calculated using Cox models, adjusting for variables shown in results column	Fecundability OR (95% CI) for increase in log-transformed MIBP scaled by standard deviation (adjusted for female age, difference in couple's 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 0.97 (0.80, 1.18) Men 0.91 (0.76, 1.09)

BMI = body mass index; MBP = monobutyl phthalate; OR = odds ratio; WHO = World Health Organization

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

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 MIBP in urine (ng/mL): Median 95^{th} percentile Unadjusted 58 173 **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)	Results for individual phthalate metabolites (including MIBP) reported as "few significant associations" with free testosterone, estradiol, SHBG, LH, inhibin-B, or FSH (quantitative results not reported); analyses adjusted for age, BMI, smoking, alcohol consumption, and time of blood sampling (and assay type for inhibin-B only)
Mendiola et al. (2011) (United States; Minnesota, Missouri, California, Iowa, New York) **Population:** 425 men whose partners enrolled in birth cohort study (Study for Future Families), 1999–2005, mean age 32 yrs **Outcome:** Serum steroidal and gonadotropin hormones **Exposure:** Urine sample, collected at same time as serum sample for hormone analysis MIBP in urine (ng/mL) (distribution not reported) **Analysis:** Pearson correlation of log(10)-transformed MIBP and hormone measures; linear regression considering age, age square, BMI, smoking status, ethnicity, urinary creatinine concentration, time of sample collection, time of collection squared, season, educational level, center, and stressful life events)	Authors reported "little or no association with metabolites of phthalate other than DEHP" [including MIBP] with testosterone, estradiol, SHBG, LH, inhibin-B, or FSH (quantitative results not reported)

DEHP = diethylhexyl phthalate; FSH = follicle-stimulating hormone; LH = luteinizing hormone; MOINP = oxo-(mono-oxoisononyl) phthalate; SD = standard deviation; SHBG = sex hormone binding globulin

3.2.3. Male Pubertal Development in Humans

Table 3-4. Evidence pertaining to DIBP and the timing of male puberty or sex hormones in boys

Reference and study design	Results
Ferguson et al. (2014b) (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 MIBP in urine (ng/mL): Median; 95th percentile Maternal sample: 1.83; 6.64 Child's sample: 9.61; 36.1 **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 as potential covariates	OR (95% CI) for adrenarche or puberty per interquartile increase in ln-transformed MIBP (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): 0.29 (0.07, 1.30); 0.76 (0.32, 1.81) Genitalia (stage ≥2): 0.71 (0.37, 1.35); 0.76 (0.39, 1.49) Testicular volume (>3 mL): 1.60 (0.70, 3.65); 2.17 (0.81, 5.82) Percent change (95% CI) in serum hormone level per interquartile increase in ln-transformed MIBP (adjusted for urine specific gravity, child age, and BMI z-score) Exposure basis Serum hormone: Maternal urine (prenatal); Child urine Testosterone: 5.12 (−23.3, 44.0); −26.2 (−45.6, 0.16) Free testosterone: 1.69 (−26.7, 41.1); −27.9 (−47.8, −0.60) SHBG: 5.72 (−5.18, 17.9); 2.20 (−8.41, 14.1) DHEAS: −2.02 (−15.9, 14.1); 3.02 (−11.4, 19.8) Estradiol: −1.94 (−11.2, 8.23); −12.3 (−20.2, −3.54) Inhibin B: −1.98 (−12.7, 10.1); 2.73 (−8.24, 15.0)
Mouritsen et al. (2013b) (Denmark) **Population:** Boys from population-based cohort (COPENHAGEN Puberty Study), 2006–2010; age 11 yrs (53 boys) or 13 yrs (31 boys) **Outcome:** Adrenarche or puberty, based on Tanner staging by physician (pubarche = pubic hair stage ≥2 and testicular volume >3 mL); serum hormone level **Exposure:** Urine sample, first morning sample; data reported in Mouritsen et al. (2013a), Supplemental Material MIBP + MBP in urine (ng/mL)[a]: Geometric mean; Maximum 118; 676	Median age (yrs) at development by ΣMIBP + MBP level (evaluation at 11 yrs) Low; High Pubarche: 12.3; 11.0 ($p < 0.05$) Testicular volume >3 mL: 11.5; 11.1 Median hormone concentration by MIBP + MBP level (evaluation at 11 yrs) Low; High Testosterone (nmol/L): <0.23; <0.23 DHEAS (µmol/L): 2.02; 1.61

Reference and study design	Results
(based on larger sample of 84 boys) **Analysis:** Two-tailed Mann-Whitney U-test for comparisons between groups, comparing median hormone levels and pubertal stage in "high" and "low" phthalate groups (based on above or below group mean excretion)	Adione (nmol/L) 1.28 1.22 Estradiol (pmol/L) <18 <18 FSH (IU/L) 1.28 1.68 LH (IU/L) 0.28 0.27 Median age (yrs) at development by MIBP + MBP level (evaluation at 13 yrs) Low High Pubarche 12.5 12.1 Testicular volume >3 mL 11.6 11.6 Median age (yrs) at development by MIBP + MBP level (evaluation at 13 yrs) Low High Testosterone (nmol/L) 5.1 7.7 DHEAS (µmol/L) 2.61 3.64 Adione (nmol/L) 2.96 3.85 Estradiol (pmol/L) 19 37 FSH (IU/L) 2.4 2.5 LH (IU/L) 1.8 1.4
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 MIBP in urine (ng/mL): Median 95th percentile Group 3 74.88 229.1 (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	MIBP concentration (ng/mL) by group Group 1 (n = 38) Group 2 (n = 189) Group 3 (n = 517) Median 68.50 73.96 74.88 95th percentile 178.8 199.5 229.1 Group 1 = boys with palpable gynecomastia Group 2 = boys without palpable gynecomastia (age-matched) Group 3 = boys without palpable gynecomastia (all ages) No association between MIBP concentration and timing of puberty or serum testosterone level (quantitative results not reported)

[a]In this population at this time, MIBP tended to be present at higher concentrations than MBP; EPA includes these studies in the DIBP tables, but recognizes the exposure misclassification introduced by the use of the summed concentration exposure measure.

DHEAS = dehydroepiandrosterone; EPA = Environmental Protection Agency

3.2.4. Female Pubertal Development in Humans

Table 3-5. Evidence pertaining to DIBP and timing of female puberty or sex hormones in girls

Reference and study design	Results
Precocious puberty and premature thelarche	
Frederiksen et al. (2012) (Denmark) **Population:** 24 girls with precocious puberty (n = 13 with central precocious puberty, n = 6 with early normal puberty, n = 5 with premature thelarche) from outpatient clinic, 2008–2009 and 184* age-matched controls from population-based cohort (COPENHAGEN Puberty Study), recruited from high schools 2006–2008; age 7.4–9.9 yrs **Outcome:** Precocious puberty, early normal puberty, or premature thelarche based on Tanner staging by physician **Exposure:** Urine sample (child's), first morning sample collected at clinical evaluation MIBP and MBP in urine (ng/mL)[a], controls (analysis based on sum of these two metabolites): Median 95th percentile MIBP 81 241 MBP 51 153 (based on larger sample of 725 controls) **Analysis:** Urine concentrations in cases and controls compared with Mann-Whitney U test *Study reports number of controls inconsistently; text reports 164 controls, while Table 4 reports 184	Median (range) ΣMIBP and MBP metabolites in urine (ng/mL) in cases and controls Controls: 147 (22–2,195) Precocious puberty: 94 (32–383) (*p*-value): (*p* < 0.01)
Lomenick et al. (2010) (United States, Ohio and 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 development); no cases had received medical treatment prior to urine sample collection **Exposure:** Urine sample (child's), collected at clinical evaluation MIBP in urine of controls: Mean ± SE Unadjusted (ng/mL) 22.6 ± 7.6 Cr-adjusted (µg/g Cr) 20.2 ± 4.9 **Analysis:** MIBP concentrations in cases and controls compared with Wilcoxon rank-sum test	Controls / Central precocious puberty / (*p*-value) Unadjusted (ng/mL): 22.6 ± 7.6 / 15.4 ± 2.9 / (0.77) Cr-adjusted (µg/g Cr): 20.2 ± 4.9 / 16.5 ± 2.1 / (0.96)

Reference and study design	Results
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) MIBP in serum (ng/mL): Median 90th percentile Unadjusted 1.77 6.16 **Analysis:** Correlation between log-transformed MIBP and age at menarche	Authors reported no association between MIBP and age at menarche (quantitative results not reported) Authors reported no correlation between MIBP and serum SHBG, FSH, total testosterone, free androgen index, anti-Müllerian hormone, or inhibin B in adolescents (quantitative results not reported by study authors)
Mouritsen et al. (2013b) (Denmark) **Population:** Girls from population-based cohort (COPENHAGEN Puberty Study), 2006–2010; age 10 yrs (47 girls) and 13 yrs (33 girls) **Outcome:** Adrenarche or puberty, based on Tanner staging by physician (pubarche = breast stage ≥2 and pubic hair stage ≥2); serum hormone level **Exposure:** Urine sample, first morning sample; data reported in Mouritsen et al. (2013a), Supplemental Material MIBP + MBP in urine (ng/mL)[a]: Geometric mean Maximum 122 904 (based on larger sample of 84 girls) **Analysis:** Two-tailed Mann-Whitney U-test for comparisons between groups, comparing median hormone levels and pubertal stage in "high" and "low" phthalate groups (based on above or below group mean excretion)	Median age (yrs) at development by MIBP + MBP level (evaluation at 10 yrs) Low High Pubarche (pubic hair stage ≥2) 10.7 11.2 Pubarche (breast stage ≥2) 10.6 10.3 Median hormone concentration by MIBP + MBP level (evaluation at 10 yrs) Low High Testosterone (nmol/L) <0.23 <0.23 DHEAS (µmol/L) 1.1 0.83 Adione (nmol/L) 2.03 1.29 Estradiol (pmol/L) 20 22 FSH (IU/L) 1.86 2.25 LH (IU/L) 0.06 0.1 Median age (yrs) at development by MIBP + MBP level (evaluation at 13 yrs) Low High Pubarche (pubic hair stage ≥2) 10.7 11.2 Pubarche (breast stage ≥2) 10.7 10.5 Median hormone concentration by MIBP + MBP level (evaluation at 13 yrs) Low High Testosterone (nmol/L) 1.1 0.5 ($p < 0.05$) DHEAS (µmol/L) 2.23 1.27 ($p < 0.05$) Adione (nmol/L) 6.40 3.91

<table>
<tr><th>Reference and study design</th><th>Results</th></tr>
<tr><td></td><td>Estradiol (pmol/L) 194 131
FSH (IU/L) 4.9 5.8 ($p < 0.05$)
LH (IU/L) 3.8 3.8</td></tr>
<tr><td>Frederiksen et al. (2012) (Denmark)
Population: 725 healthy girls ages 5.6−19.1 yrs from COPENHAGEN Puberty Study cohort, recruited from high schools during 2006−2008
Outcome: Stage of breast or pubic hair development based on Tanner staging by physician; Serum steroid and gonadotropin hormones
Exposure: Urine sample (child's), collected at time of pubertal stage assessment
Unadjusted MIBP and MBP in urine (ng/mL)[a], all 725 participants:
Median 95th percentile
MIBP 81 241
MBP 51 153
Analysis: Probit analysis, results verified using Pool-Adjacent-Violators algorithm</td><td>Mean age (95% CI) (yrs) at entry into breast stage 2 or pubic hair stage 2, by quartile of ∑MIBP + MBP metabolites:
∑MIBP + MBP quartile | Breast stage 2 (n = 394) | Pubic hair stage (n not reported)
1 (low) 10.12 (9.61, 10.62) 10.83 (10.54, 11.12)
2 9.97 (9.48, 10.46) 10.97 (10.67, 11.28)
3 9.89 (9.40, 10.37) 11.22 (10.93, 11.52)
4 (high) 9.79 (9.30, 10.30) 11.54*(11.21, 11.88)
*Significantly different from quartile 1; $p < 0.05$

Levels of FSH, LH, estradiol, and testosterone were similar across ∑MIBP + MBP metabolite exposure groups when adjusted for age distribution (quantitative results not reported)</td></tr>
</table>

[a]In this population at this time, MIBP tended to be present at higher concentrations than MBP; EPA includes these studies in the DIBP tables, but recognizes the exposure misclassification introduced by the use of the summed concentration exposure measure.

3.2.5. Female Reproductive Effects in Humans

Table 3-6. Evidence pertaining to DIBP and reproductive hormones in adult women

Reference and study design	Results
Maternal hormones during pregnancy	
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 MIBP in urine (ng/mL): Median 75th percentile Unadjusted 2.7 4.85 **Analysis:** Linear regression, log-transformed MIBP and log-transformed hormone level	Regression coefficient (95% CI) for change in maternal log-transformed serum hormone level with unit increase in log-transformed MIBP, stratified by sex of fetus Mothers with male fetus (n = 94) / Mothers with female fetus (n = 86) Testosterone (total): −0.03 (−0.18, 0.13) / −0.10 (−0.28, 0.07) Testosterone (free): −0.03 (−0.20, 0.14) / −0.11 (−0.30, 0.08) Estradiol: 0.003 (−0.12, 0.12) / 0.03 (−0.14, 0.20)
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) MIBP in serum (ng/mL): Median 90th percentile MIBP 1.77 6.16 **Analysis:** Correlation between quartiles of serum MIBP and log-transformed hormone levels	Correlation coefficient between log-transformed maternal serum hormone level and quartiles of MIBP in maternal serum At 18 wks of gestation (n = 119) / At 34–36 wks of gestation (n = 114) Androstenedione (nmol/L): 0.023 / −0.060 DHEAS (µmol/L): −0.042 / −0.084 Testosterone (pmol/L): 0.003 / −0.101 SHBG (nmol/L): 0.108 / −0.020 Free testosterone (pmol/L): −0.061 / −0.063 Free testosterone index: −0.051 / −0.064 $p > 0.10$ for all correlations

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

Reference and study design	Results
Endometriosis	
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 MIBP in urine (ng/mL), unadjusted: Geometric mean Operative cohort-controls 6.82 Population cohort-controls 7.59 **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-MIBP, by cohort (adjusted for age, BMI, and creatinine) Operative cohort 1.02 (0.80, 1.29) Population cohort 2.22 (0.98, 5.04) Adjusted OR (95% CI) for endometriosis per unit increase in ln-MIBP in operative cohort (sensitivity analysis) Endometriosis stage 3 and 4 (n = 339) 0.96 (0.67, 1.38) Visual/histological confirmed endometriosis (n = 473) 1.08 (0.77, 1.51) Comparison with women with postoperative diagnosis normal pelvis (n = 320) 1.09 (0.82, 1.46) 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) MIBP in urine, controls: Median 75th percentile Unadjusted (ng/mL) 1.5 3.1 **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 MIBP (adjusted for ln-transformed urinary creatinine, age, and reference yr) MIBP quartile (ng/mL) OR (95% CI) 1 (≤0.7) 1.0 (referent) 2 (0.7–1.5) 0.9 (0.4, 2.0) 3 (1.5–3.1) 0.8 (0.3, 2.2) 4 (>3.1) 0.8 (0.3, 2.6) (trend *p*-value) (0.84) Adjustment for education, smoking status and alcohol consumption did not alter the results; similar results in analyses based on summation of MIBP and MBP
Polycystic ovarian syndrome	
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	Correlation coefficient (*p*-value) between log-transformed MIBP and pubertal development parameter

Reference and study design	Results
	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 MIBP and polycystic ovarian syndrome using either definition (quantitative results not reported).

PCO = polycystic ovarian morphology; PCOS = polycystic ovarian syndrome

3.2.6. Pregnancy Outcomes in Humans

Table 3-8. Evidence pertaining to DIBP 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 one hospital in Chongqing between 2011 and 2012, aged 18–35 yrs and with no history of tobacco or alcohol use; mean age 28 yrs **Outcome:** Standard clinical measures at birth **Exposure:** Cord blood sample DIBP in cord blood (µg/L) Median 75th percentile 95th percentile All samples 16.7 26.9 114 **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 DIBP (µg/L) (adjusted for gestational age): Girls / Boys Birth weight (g): −27 (−90, 36) / −87 (−195, 200) Birth length (cm): −0.06 (−0.45, 0.33) / −0.75 (−1.35, −0.15) Head circumference (mm): −3.85 (−9.47, 1.76) / −2.76 (−7.62, 2.11)
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 MIBP in urine (ng/mL): Median 95th percentile Measured 45.9 219.0 Standardized* 64.7 365.3 **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 MIBP tertile and per unit change in ln-MIBP (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) MIBP tertile (µg/L) / Birth weight (g) / Birth length (cm) / Head circumference (cm) 1 (<48.2): 0 (referent) / 0 (referent) / 0 (referent) 2 (48.2–97.9): 61 (−77, 200) / 0.4 (−0.3, 1.1) / −0.1 (−0.6, 0.4) 3 (≥97.9): −31 (−190, 129) / 0.3 (−0.4, 1.0) / 0.2 (−0.5, 0.9) (trend *p*-value): (0.48) / (0.54) / (0.40) ln (MIBP): −44 (−110, 23) / 0.0 (−0.3, 0.3) / −0.1 (−0.4, 0.1)
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 MIBP in urine (ng/mL): Median 75th percentile Unadjusted 6.2 12 **Analysis:** Linear regression, adjusting for variables shown in results column	Regression coefficient (95% CI) for change in birth outcome with unit increase in ln-MIBP (ng/mL) (adjusted for race/ethnicity, infant sex, gestational age at delivery, ln-creatinine, prenatal smoking, pre-pregnancy BMI, maternal education, and marital status) Birth weight (g): −14 (−57, 28) Birth length (cm): 0.04 (−0.19, 0.28) Head circumference (cm): 0.05 (−0.11, 0.21) Restricted to observations with creatinine ≥20 mg/dL

Reference and study design	Results
Preterm birth (<37 wks) and gestational age	
(Ferguson et al. (2014a); Ferguson et al. (2014c)) (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) **Exposure:** Maternal urine sample, one to three samples collected at median times of 9.7, 17.9, or 26.0 wks of gestation; geometric mean of results from visits 1–3 used in analyses. MIBP in urine, SG-adjusted (µg/L): Controls: Geometric mean 6.71; 75th percentile 10.3 All cases: Geometric mean 6.85; 75th percentile 10.5 **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 **Related reference:** Ferguson et al. (2014c) (analysis by individual sample results for the four visits)	OR (95% CI) for preterm birth per unit increase in ln-transformed MIBP (adjusted for average specific gravity, maternal age, race/ethnicity, education level, and insurance provider) All preterm: 0.98 (0.72, 1.34) Spontaneous preterm: 1.52 (0.97, 2.38) [Results weaker than those seen with DEHP metabolites] Results by study visit from Ferguson et al. (2014c), all pre-term births Visit 1: 0.92 (0.57, 1.47) Visit 2: 0.88 (0.54, 1.41) Visit 3: 0.75 (0.50, 1.13) Visit 4: 0.66 (0.28, 1.55)
Huang et al. (2014b) (China) **Population:** 207 women delivering at one hospital in Chongqing between 2011 and 2012; aged 18–35 yrs and with no history of tobacco or alcohol use; mean age 28 yrs **Outcome:** Preterm birth (<37 wks of gestation; gestational age estimated from last menstrual period) **Exposure:** Cord blood sample DIBP in cord blood (µg/L) All samples: Median 16.7; 75th percentile 26.9; 95th percentile 114 **Analysis:** Logistic and linear regression, adjusting for variables shown in results column	OR (95% CI) for preterm delivery comparing ln-DIBP 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): 6.01 (3.24, 11.17) No intravenous infusions (n = 154): 4.78 (1.68, 13.57) Intravenous infusions (n = 53): 6.07 (2.66, 13.83) [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 DIBP (µg/L) (adjusted for maternal age, BMI, frequency of prenatal examination, history of intravenous infusions therapy, and pregnancy history) −0.75 (−1.03, −0.46)

Reference and study design	Results
Meeker et al. (2009) (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 MIBP in urine, among term births Median 75th percentile Unadjusted 2.0 4.1 SG-adjusted (µg/L) 2.3 5.0 Cr-adjusted (µg/g Cr) 3.7 6.6 **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	OR (95% CI) for preterm birth by MIBP 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) 3.6 (1.1, 12.2) SG-adjusted (µg/L) 2.0 (0.7, 6.0) Cr-adjusted (µg/g Cr) 1.5 (0.5, 4.5)
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 MIBP in urine (ng/mL): Median 75th percentile Unadjusted 6.2 12 **Analysis:** Linear regression, adjusting for variables shown in results column	Regression coefficient (95% CI) for change in birth outcome with unit increase in ln-MIBP (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) 0.03 (−0.20, 0.14) Restricted to observations with creatinine ≥20 mg/dL

1
2

3.2.7. Immune Effects in Humans

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

Reference and study design	Results
Ait Bamai et al. (2014)[a] (Japan) **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 **Exposure:** Dust samples DIBP in dust (µg/g dust): Floor dust (n = 148) Median 2.4, 75th percentile 5.5 Multi-surface dust (n = 120) Median 1.9, 75th percentile 3.5 **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	OR (95% CI) for allergic condition by tertile of DIBP in floor dust (µg/g dust)(adjusted for adjusted for gender, age strata, smoking status, dampness index, furry pets inside the home, Der 1, and sum of other phthalates) DIBP tertile / Full sample / Children / Adults Allergic rhinitis 1 (low) 1.0 (referent) / 1.0 (referent) / 1.0 (referent) 2 1.87 (0.83, 4.22) / 3.54 (0.86, 14.5) / 0.99 (0.47, 2.05) 3 (high) 1.05 (0.47, 2.32) / 2.30 (0.60, 8.89) / 0.48 (0.22, 1.02) (trend *p*-value) (0.91) / (0.23) / (0.06) Allergic conjunctivitis 1 (low) 1.0 (referent) / 1.0 (referent) / 1.0 (referent) 2 1.07 (0.38, 3.01) / 1.97 (0.35, 11.1) / 0.59 (0.19, 1.8) 3 (high) 1.64 (0.64, 4.18) / 3.27 (0.68, 15.7) / 0.82 (0.31, 2.2) (trend *p*-value) (0.30) / (0.14) / (0.69) Atopic dermatitis 1 (low) 1.0 (referent) / 1.0 (referent) / 1.0 (referent) 2 5.52 (1.68, 18.1) / 11.95 (1.37, 104) / 2.55 (0.89, 7.31) 3 (high) 4.84 (1.46, 16.0) / 15.0 (1.91,118) / 1.56 (0.44, 5.53) (trend *p*-value) (0.01) / (0.01) / (0.49) *p*-value for age interaction >0.05 for all endpoints No increased aORs (either in the full sample or stratified by age) were observed in analyses using DIBP measurements in multisurface dust.

<table>
<tr><th>Reference and study design</th><th>Results</th></tr>
<tr><td>
(Callesen et al. (2014a); Callesen et al. (2014b))[a] (Denmark)
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: DIBP concentrations in dust samples from bedroom and day care centers; total DIBP exposure estimated as a weighted mass fraction
DIBP in dust among controls (µg/g):
Median
Home 27.0
Day care 22.6
Area-weighted 27.2
(weighted by assumed hrs in each environment)
Analysis: Mann-Whitney U-test
Related study: Callesen et al. (2014b) (same study population, with exposure measured in urine sample from participants
MIBP in urine: median 74.2 ng/mL (controls)
</td><td>
Median DIBP in dust (µg/g), by case-control status assessed by clinical examination
<table>
<tr><th></th><th></th><th colspan="2">Cases</th></tr>
<tr><th></th><th>Controls (n = 242)</th><th>Rhinoconjunctivitis (n = 81)</th><th>Atopic dermatitis (n = 88)</th></tr>
<tr><td>Home</td><td>27.0</td><td>30.4</td><td>33.4</td></tr>
<tr><td>Day care</td><td>22.6</td><td>22.3</td><td>22.5</td></tr>
<tr><td>Area-weighted</td><td>27.2</td><td>26.8</td><td>33.1</td></tr>
</table>
Similar results when based on case status defined by parent-questionnaire data (n = 56 rhinoconjunctivitis, n = 83 atopic dermatitis)

Results from Callesen et al. (2014b):
OR (95% CI) by quartile of MIBP (urine sample), adjusting for sex, breastfeeding less than 3 mo, smoking in the home, and single allergic predisposition
<table>
<tr><th></th><th>Rhinoconjunctivitis (76 cases, 222 controls)</th><th>Atopic dermatitis (76 cases, 216 controls)</th></tr>
<tr><td>1</td><td>1.0 (referent)</td><td>1.0 (referent)</td></tr>
<tr><td>2</td><td>1.18 (0.54, 2.55)</td><td>1.11 (0.53, 2.34)</td></tr>
<tr><td>3</td><td>0.89 (0.39, 2.02)</td><td>0.88 (0.41, 1.91)</td></tr>
<tr><td>4</td><td>1.07 (0.52, 2.22)</td><td>0.97 (0.48, 1.94)</td></tr>
</table>
</td></tr>
</table>

Reference and study design	Results
Hoppin et al. (2013)[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 yr; allergic sensitization as measured by serum IgE (19 allergen specific IgEs, ≥0.35kU/L) **Exposure:** Urine sample collected same day as serum sample MIBP in urine (µg/L): Median, 75th, 95th percentile Children 8.93 16.38 45.97 Adults 5.42 10.53 28.98 **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 MIBP level (adjusted for age, race/ethnicity, gender, BMI, creatinine, and cotinine) Children (n = 779) Hay fever (n = 23) 3.6% 0.12(0.04, 0.39) Rhinitis (n = 188) 27.6% 0.84 (0.53, 1.33) IgE sensitization (any) 46.1% 0.93 (0.51, 1.70) Adults (n = 1,546) Hay fever (n = 88) 7.4% 0.93 (0.46, 1.87) Rhinitis (n = 498) 35.4% 0.99 (0.76, 1.29) IgE sensitization (any) 44.0% 1.32 (0.99, 1.76) Authors reported that adjustment for poverty income ratio did not alter ORs.
Sun et al. (2009)[a] (China) **Population:** Cases of rhinitis (n = 240) or eczema (n = 61) and controls (n = 204 and 119 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 rash; controls responded no to questions on asthma/wheeze, rhinitis, and eczema **Exposure:** Surface dust sample in dorm rooms DIBP in dust (µg/g): Median 75th percentile 20.24 34.77 **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 DIBP concentrations of cases and controls;	OR for rhinitis and eczema comparing DIBP 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 DIBP in dust (µg/g dust) Cases Controls Rhinitis 20.17 28.76* Eczema 28.68 22.56 *p = 0.019 by Mann-Whitney test; p = 0.051 by t-test.

Reference and study design	Results
t-test for comparisons between log-transformed concentrations	
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 3–8 yrs **Outcome:** Eczema, wheezing, or rhinitis (Cases report at least two incidents of eczema, or wheezing or rhinitis without a cold, in the preceding yr, and at follow-up 1.5 yrs later) **Exposure:** Surface dust samples from children's bedrooms DIBP in dust (mg/g): Median All homes 0.045 **Analysis:** Mann-Whitney U-test for comparing concentrations in all homes; t-test for comparing log-transformed concentrations in homes with concentrations above detection limit.	Concentration in dust (mg/g dust) Median, all homes (n = 346) / Geometric mean (95% CI), homes with phthalate > detection limit (n = 290) Controls: 0.048 / 0.055 (0.046, 0.065) Cases (all): 0.042 / 0.058 (0.048, 0.070) $p > 0.4$ in both tests

[a]Additional results for this study presented in asthma table.

aOR = adjusted odds ratio; IgE = immunoglobin E; NHANES = National Health and Nutrition Examination Survey; VOC = volatile organic compound

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

Reference and study design	Results
Ait Bamai et al. (2014)[a] (Japan) **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 **Exposure:** Dust samples from floor and other surfaces DIBP (µg/g dust): Floor dust (n = 148): Median 2.4, 75th percentile 5.5 Multi-surface dust (n = 120): Median 1.9, 75th percentile 3.5 **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.	OR (95% CI) for bronchial asthma by tertile of DIBP in floor dust (adjusted for adjusted for gender, age strata, smoking status, dampness index, furry pets inside the home, Der 1, and sum of other phthalate dusts) Full sample / Children / Adults 1 (low): 1.0 (referent) / 1.0 (referent) / 1.0 (referent) 2: 2.25 (0.48, 10.57) / 4.37 (0.36, 53.6) / 1.16 (0.16, 8.17) 3 (high): 5.09 (1.17, 22.15) / 8.94 (0.86, 93.0) / 2.90 (0.52, 16.2) (trend *p*-value): (0.03) / (0.067) / (0.22) *p*-value for age interaction = 0.51 No significantly increased aORs (either in the full sample or stratified by age) were observed in analyses of bronchial asthma using DIBP measurements in multisurface dust.

Reference and study design	Results
(Callesen et al. (2014a); Callesen et al. (2014b))[a] (Denmark) **Population:** 72 asthma 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; 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:** DIBP concentrations in dust samples from bedroom and day care centers; total DIBP exposure estimated as a weighted mass fraction DIBP in dust among controls (µg/g): Median Home 27.0 Day care 22.6 Area-weighted 27.2 (weighted by assumed hrs in each environment) **Analysis:** Mann-Whitney U-test **Related study:** Callesen et al. (2014b) (same study population, with exposure measured in urine sample from participants MIBP in urine: median 74.2 ng/mL (controls)	Median DIBP in dust (µg/g), by case-control status assessed by clinical examination Controls (n = 242) Asthma (n = 72) Home 27.0 25.8 Day care 22.6 21.5 Area-weighted 27.2 25.7 Similar results when based on case status defined by parent-questionnaire data (n = 110 asthma cases) Results from Callesen et al. (2014b): OR (95% CI) by quartile of MIBP (urine sample), adjusting for sex, breastfeeding <3 mo, smoking in the home, and single allergic predisposition Bronchial asthma (60 cases, 216 controls) 1 1.0 (referent) 2 0.49 (0.22, 1.09) 3 0.91 (0.41, 1.69) 4 0.61 (0.27, 1.34)
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 MIBP in urine (µg/L) Percentile Median 75th 95th Unadjusted 49.2 88.4 231.0 SG-adjusted 50.1 90.5 239.6 **Analysis:** Logistic regression, adjusting for variables shown in the results column	OR (95% CI) for current asthma by quartile of MIBP (µg/L) (adjusted for urine specific gravity, sex, parental asthma, and household income) 1: ≤31.4 (referent) 1 (referent) 2: >31.4–49.2 1.3 (0.74, 2.4) 3: >49.2–88.4 1.4 (0.73, 2.5) 4: >88.4 1.5 (0.80, 2.7) Increase in odds of current asthma per $\log_{10}$ IQR MIBP (95% CI) = 1.1 (0.87, 1.5)

Reference and study design	Results
Hoppin et al. (2013)[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 yr) **Exposure:** Urine sample collected same day as serum sample Unadjusted MIBP in urine (µg/L): Median 75th Percentile 95th Percentile Children 8.93 16.38 45.97 Adults 5.42 10.53 28.98 **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 MIBP level (adjusted for age, race/ethnicity, gender, BMI, creatinine, and cotinine) Children (n = 779) Asthma (n = 65) 8.4% 0.92 (0.26, 3.29) Wheeze (n = 80) 10.7% 1.08 (0.49, 2.35) Adults (n = 1,546) Asthma (n = 116) 7.4% 1.39 (0.77, 2.50) Wheeze (n = 219) 16.6% 0.92 (0.57, 1.48) Authors reported that adjustment for poverty income ratio did not alter ORs.
Sun et al. (2009)[a] (China) **Population:** 92 cases asthma/wheezing, cases and 346 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 mos, have you had wheezing or whistling the 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; controls responded no to questions on asthma/wheeze, rhinitis, and eczema **Exposure:** Surface dust sample in dorm rooms DIBP in dust (µg/g): Median 75th percentile 20.24 34.77 **Analysis:** Logistic regression for OR, considering age, gender, passive smoking, smoking, pet raising, atopy, and building age as potential covariates; Mann-Whitney U-test (nonparametric) for comparison between DIBP concentrations of cases and controls; t-test for comparisons between log transformed concentrations	OR for asthma comparing DIBP in dust (µg/g dust) above and below the median (adjusted to age, gender, smoking, atopy, and building age) reportedly did not reach statistical significance (quantitative results not reported) Median concentration DIBP in dust (µg/g dust) Cases Controls Wheezing 23.13 22.73 ($p > 0.46$ by Mann Whitney or t-test)

[a]Additional results for this study presented in allergy/immune table.

IQR = interquartile range

3.2.8. Neurodevelopmental Effects in Humans

Table 3-11. Evidence pertaining to DIBP and neurodevelopmental effects in humans

Reference and study design	Results
Attention and executive function in school-aged children	
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) Unadjusted MIBP in urine (ng/mL): Geometric mean (95% CI) 2.3 (2.0, 2.8) **Analysis:** Linear regression, considering sex, age, mother's education, urinary creatinine, family stress measure, and race/ethnicity, as potential covariates. **Related references:** Swan et al. (2005) (exposure data)	Regression coefficient (95% CI) for change in raw score on child behavior checklist per unit increase in ln-transformed MIBP (adjusted for sex, age, mother's education and urinary creatinine, and family stress score) Boys / Girls Anxiety/ depression: 0.11 (−0.13, 0.34) / −0.03 (−0.29, 0.22) Withdrawn: −0.01 (−0.21, 0.18) / −0.04 (−0.25, 0.17) Somatic complaints: −0.03 (−0.23, 0.16) / −0.07 (−0.28, 0.13) Social problems: 0.18 (−0.02, 0.37) / −0.06 (−0.27, 0.16) Thought problems: 0.15 (−0.05, 0.35) / 0.07 (−0.15, 0.29) Attention problems: 0.27 (0.04, 0.50) / 0.12 (−0.12, 0.36) Rule-breaking behavior *: 0.20 (0.01, 0.38) / −0.04 (−0.23, 0.16) Aggressive behavior: 0.34 (0.09, 0.59) / 0.12 (−0.14, 0.39) Internalizing behavior: 0.09 (−0.18, 0.37) / −0.07 (−0.37, 0.22) Externalizing behavior: 0.32 (0.06, 0.58) / 0.06 (−0.22, 0.34) Total problems: 0.42 (0.05, 0.80) / 0.07 (−0.33, 0.47) *Sex interaction *p*-value = 0.04; all other interaction *p*-values > 0.05

Reference and study design	Results		
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, 7–9 yrs **Outcome:** Behavior assessed by maternal reporting on BRIEF and BASC-PRS **Exposure:** Maternal urine sample, 25–40 wks gestation* Median 75th percentile MIBP (µg/L)* 2.6 12.2 Sum LMW (µM/L) 1.88 4.59 (sum of MBP, MEP, MIBP, and MMP) **Analysis:** Generalized linear regression model, adjusting for variables shown in results column; other variables (not specified) were considered **Related references:** Engel et al. (2009) (exposure data for n = 295 children in the cohort) *MIBP concentrations not reported in (Engel et al., 2010); values reported here are from an earlier analysis of this cohort described in Engel et al. (2009)	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)		
		MIBP	Low molecular weight phthalate sum
	Clinical scales (higher score = more problem behaviors)		
	Aggression	−0.12	1.24*
	Anxiety	−0.25	0.78
	Attention problems	0.66	1.29*
	Atypicality	0.53	0.95
	Conduct problems	0.23	2.40*
	Depression	0.29	1.18*
	Hyperactivity	0.85	1.03
	Somatization	1.04	0.36
	Withdrawal	−0.01	0.46
	Adaptive scales (lower score = more problem behaviors)		
	Adaptability	−1.32*	−1.08*
	Leadership	−1.30	−0.88
	Social skills	−0.93	−1.04
	Composite scales (higher score = more problem behaviors)		
	Externalizing problems	0.33	1.75*
	Internalizing problems	0.46	0.99
	Adaptive skills	−1.17	−0.98
	Behavioral Symptoms Index	0.47	1.55*
	Significant sex-phthalate interactions ($p \leq 0.05$) for aggression, conduct problems, hyperactivity, externalizing problems, and behavioral symptoms index, as reported by study authors.		
	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)		
	Emotional control	0.09	1.33*
	Behavioral	0.30	1.13

Reference and study design	Results
	regulation index Initiate 0.83 0.81 Working memory 1.11 1.03 Plan/organize 0.76 1.02 Metacognition index 0.70 1.05 Global executive composite 0.56 1.23* *$p \leq 0.05$ Study authors reported that there were few significant associations between phthalate concentration and behavior among girls (quantitative results not reported).
Neurobehavioral outcomes in infants and preschool-aged children	
Braun et al. (2014) (United States) **Population:** 175 children from birth cohort in Ohio (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 of gestation MIBP in urine (µg/g Cr): Median 75th Percentile 95th Percentile Cr-adjusted 5.6 8.6 17 **Analysis:** Semi-Bayesian hierarchical regression model	Regression coefficient (95% CI) for change in total score per unit increase in log-transformed Cr-adjusted MIBP (adjusted for maternal demographic and perinatal factors, depressive symptoms, caregiving environment, and serum cotinine): 0.7 (−1.4, 2.8)
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 MIBP in urine (ng/mL): Geometric mean (95% CI) SG-adjusted 2.30 (1.92, 2.76) **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-MIBP (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 0.53 (−0.85, 1.91) 0.32 (−1.62, 2.28) −0.12 (−1.94, 1.69) PDI 0.57 (−0.67, 1.82) 0.63 (−0.68, 1.95) 0.37 (−1.67, 2.43)

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 MIBP in urine (ng/mL): Geometric mean Unadjusted 9.3 **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-MIBP (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: 0.59 (−1.40, 2.58) / −1.33 (−3.20, 0.54) PDI: −2.21 (−4.61, 0.19) / −2.33 (−4.59, −0.08) OR (95% CI) for risk of mental or psychomotor delay (score ≤85) per ln-unit increase in maternal ln-MIBP (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: 0.87 (0.60, 1.28) / 0.98 (0.62, 1.56) PDI: 1.80 (1.13, 2.87) / 1.98 (1.02, 3.83) Regression coefficient (95% CI) for change in neurobehavior per unit increase in maternal ln-MIBP (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: 0.42 (−0.005, 0.85) / 0.34 (−0.11, 0.78) Anxious/depressed: 0.12 (−0.38, 0.61) / 0.16 (−0.34, 0.66) Somatic complaints: 0.31 (−0.18, 0.81) / 0.24 (−0.22, 0.70) Withdrawn behavior: 0.36 (−0.05, 0.77) / 0.47 (−0.007, 0.94) Internalizing behavior: 1.21 (−0.16, 2.56) / 1.20 (−0.15, 2.55) No effect modification by gender was observed (*p*-values >0.7). 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

Reference and study design	Results		
	demoralization and satisfaction during pregnancy, and child's sex and age at testing)		
		Borderline	Clinical
	Somatic complaints	1.29 (0.84, 1.99)	0.76 (0.42, 1.36)
	Withdrawn behavior	0.81 (0.44, 1.51)	1.62 (0.97, 2.73)
	Internalizing behavior	1.98 (1.24, 3.23)	1.41 (0.91, 2.18)

BASC-PRS = Behavior Assessment System for Children—Parent Rating Scales; BPA = bisphenol A; BRIEF = Behavior Rating Inventory of Executive Function; HOME = Health Outcomes and Measures of the Environment; LMW = low molecular weight; MDI = mental delay index; MMP = monomethyl phthalate; PAH = polycyclic aromatic hydrocarbon; PDI = psychomotor delay index

3.2.9. Thyroid Hormone Effects in Humans

Table 3-12. Evidence pertaining to DIBP and thyroid hormones 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) MIBP in urine (ng/mL): Controls: Median 65, 75th percentile 93, 90th percentile 133 Obese (at baseline): Median 58, 75th percentile 89, 90th percentile 129 **Analysis:** Linear regression, adjusting for variables shown in results column	Regression coefficient (*p*-value) for change in hormone level with unit change in ln-MIBP (adjusted for age, weight loss, and sex, or stratified by sex) (0.0 = no effect) Overweight/obese group: Free T4 0.07 (0.41) Full sample; 0.11 (0.47) Men; 0.05 (0.66) Women TSH −0.01 (0.93) Full sample; 0.09 (0.58) Men; −0.01 (0.94) Women Referent group: Free T4 0.24 (0.14) Full sample; 0.49 (0.12) Men; 0.16 (0.44) Women TSH 0.23 (0.16) Full sample; −0.43 (0.19) Men; 0.32 (0.10) Women
Meeker and Ferguson (2011) (United States) **Population:** Participants in population-based survey (NHANES), 2007–2008; 1,346 ages ≥20 yrs and 329 adolescents ages 12–19 yrs **Outcome:** Serum thyroid hormone levels **Exposure:** Urine sample collected same day as serum sample Cr-adjusted MIBP in urine (µg/g Cr): Adults: Median 6.67, 75th percentile 11.1, 95th percentile 24.1 Adolescents: Median 8.24, 75th percentile 13.73, 95th percentile 28.78 **Analysis:** Linear regression adjusting for variables shown in results column.	Regression coefficient (95% CI) for change in hormone level with unit increase in ln-MIBP (adjusted for age, sex, race, BMI, ln-serum cotinine, ln-urinary creatinine, and ln-urinary iodine, and weighted for sampling strategy) Total T3 (ng/dL): Adults 0.77 (−0.59, 2.12); Adolescents 2.30 (−0.81, 0.52) Ln (Free T3) (pg/mL): Adults −0.0012 (−0.0074, 0.0051); Adolescents 0.0083 (−0.0062, 0.023) Total T4 (µg/mL): Adults 0.020 (−0.075, 0.11); Adolescents −0.034 (−0.25, 0.19) Ln (Free T4) (ng/dL): Adults 0.0010 (−0.0094, 0.011); Adolescents −0.0001 (−0.021, 0.021) Ln (TSH) (µIU/mL): Adults −0.013 (−0.054, 0.028); Adolescents 0.003 (−0.076, 0.081) Ln (Tg) (ng/mL): Adults −0.018 (−0.081, 0.045); Adolescents −0.047 (−0.12, 0.074)

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

3.2.10. Obesity and Metabolic Effects in Humans

Table 3-13. Evidence pertaining to DIBP and obesity in humans

Reference and study design	Results
Buser et al. (2014) (United States, NHANES) **Population:** Participants in population-based survey (NHANES), 2007–2010ages ≥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 MIBP in urine (ng/mL) Geometric mean (SE) Ages 6–19 yrs 10.43 (0.39) Ages ≥20 yrs 6.75 (0.23) **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 analysis of ages ≥20 yrs	OR (95% CI) in children (6–19 yrs of age) for obesity or overweight comparing highest quartile urinary MIBP (>20.84 ng/mL) with lowest quartile (≤5.38 ng/mL) (adjusted for age, race/ethnicity, calorie intake, serum cotinine, urinary creatinine, income level) Obese / Overweight All: 1.82 (0.73, 4.57) / 1.85 (0.78, 4.40) Boys: 4.26 (1.32, 13.74) / 2.22 (0.78, 6.28) Girls: 0.57 (0.18, 1.83) / 1.57 (0.58, 4.25) OR (95% CI) in adults (≥20 yrs of age) for obesity or overweight comparing highest quartile urinary MIBP (>14.40 ng/mL) with lowest quartile (≤3.49 ng/mL) (adjusted for age, gender, race/ethnicity, calorie intake, recreational activity, serum cotinine, education level, smoking status, alcohol intake, diabetes) Obese / Overweight All: 1.40 (0.90, 2.16) / 1.18 (0.79, 1.78) Men: 0.98 (0.57, 1.67) / 1.06 (0.60, 1.89) Women: 1.81 (0.94, 3.48) / 1.25 (0.66, 2.36)
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) MIBP in serum (ng/mL): Median 90th percentile Unadjusted 1.77 6.16 **Analysis:** Correlation between log-transformed MIBP and BMI	Authors reported no association between adolescent BMI (either as absolute value or as age- and gender-adjusted z-score) and any phthalate metabolite 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, MIBP, and MCPP
Analysis: Logistic regression for overweight and obese classification; linear regression of BMI z-score as continuous variable; adjusted for variables shown in results column</td><td>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 seen, with associations seen between ln-LMW phthalates and each of the obesity measures in blacks, but not in whites or Hispanics. The patterns seen with ΣLMW phthalates were also seen in analyses for MIBP. Using same adjustment factors as above, the associations with ln-MIBP are:
<table><tr><th></th><th colspan="2">∑LMW phthalates</th><th colspan="2">MIBP</th></tr><tr><th></th><th>Hispanic</th><th>White</th><th>Black</th><th>Black</th></tr><tr><td>Over-weight OR (95% CI)</td><td>0.88 (0.72, 1.08)</td><td>0.97 (0.78, 1.22)</td><td>1.21 (1.05, 1.39)</td><td>1.16 (0.99, 1.37)</td></tr><tr><td>Obese OR (95% CI)</td><td>0.97 (0.83, 1.14)</td><td>0.94 (0.69, 1.29)</td><td>1.22 (1.07, 1.39)</td><td>1.17 (0.97, 1.41)</td></tr><tr><td>BMI z-score β (95% CI)</td><td>−0.04 (−0.15, 0.06)</td><td>0.02 (−0.08, 0.12)</td><td>0.09 (0.003, 0.18)</td><td>0.08 (−0.01, 0.17)</td></tr></table></td></tr>
<tr><td>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
MIBP in urine (ng/mL):
Geometric mean (SD)
38.9 (1.1)
Low molecular weight phthalate metabolites included MMP, MEP, MBP, MIBP, and MHBP
Analysis: Linear regression, sampling weights applied to adjust for sampling strategy; adjusted for variables shown in the results column</td><td>Regression coefficient (95% CI) for change in BMI or waist circumference per unit increase in SG-adjusted lnMIBP (adjusted for age and sex in Model 1; plus sum of DBP, MMP, and MEP in Model 2)
<table><tr><th></th><th>Model 1</th><th>Model 2</th></tr><tr><td>BMI</td><td>0.027 (0.006, 0.048)</td><td>0.020 (−0.005, 0.045)</td></tr><tr><td>Waist circumference</td><td>0.022(0.005, 0.038)</td><td>0.019 (−0.001, 0.038)</td></tr></table></td></tr>
</table>

<table>
<tr><th>Reference and study design</th><th>Results</th></tr>
<tr><td>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) MIBP, in urine (ng/mL):
<table>
<tr><th></th><th>Median</th><th>Percentile
75th</th><th>90th</th></tr>
<tr><td>Controls</td><td>65</td><td>93</td><td>133</td></tr>
<tr><td>Obese (at baseline)</td><td>58</td><td>89</td><td>129</td></tr>
</table>
Analysis: Linear regression, adjusting for variables shown in results column; treatment of repeated urinary phthalate measures was not specified</td><td>Regression coefficient (p-value) for change in waist circumference with unit change in ln-MIBP (adjusted for age, weight loss, and sex, or stratified by sex) (0.0 = no effect)
<table>
<tr><th></th><th>Full sample</th><th>Men</th><th>Women</th></tr>
<tr><td>Overweight/ obese group</td><td>0.07 (0.40)</td><td>−0.16 (0.30)</td><td>0.03 (0.76)</td></tr>
<tr><td>Referent group</td><td>−0.16 (0.30)</td><td>0.07 (0.81)</td><td>−0.01 (0.98)</td></tr>
</table></td></tr>
<tr><td>Lind et al. (2012b) (Sweden)
Population: 1,016 (507 men, 509 women), from population-based cohort (Prospective Investigation of Vasculature in Uppsala Seniors study), 2001–2003; age 70 yrs at enrollment
Outcome: BMI, waist circumference measured at enrollment; DXA (n = 890 participated) and MRI of abdominal region (n = 287 randomly selected) 2 yrs later
Exposure: Serum sample (fasting), collected at baseline
MIBP in serum (ng/mL):
<table>
<tr><th></th><th>Median</th><th>75th percentile</th></tr>
<tr><td>Women</td><td>13.4</td><td>24.5</td></tr>
<tr><td>Men</td><td>13.5</td><td>33.3</td></tr>
</table>
Analysis: Linear regression, adjusted for variables shown in results column
Related reference: Olsén et al. (2012) reports cross-sectional analysis of BMI from this study population, see Table 14</td><td>Regression coefficient (95% CI) for change in body metric per unit increase in ln-MIBP (ng/mL) (adjusted for serum cholesterol and triglycerides, education, exercise, and smoking)
<table>
<tr><th>Outcome</th><th>Males
β (95% CI)</th><th>Females
β (95% CI)</th></tr>
<tr><td>BMI (kg/m2)</td><td>−0.083 (−0.35, 0.19)</td><td>0.39 (0.002, 0.79)</td></tr>
<tr><td>Waist circumference (cm)</td><td>−0.025 (−0.80, 0.75)</td><td>1.3 (0.425, 2.3)</td></tr>
<tr><td>DXA total fat (kg)</td><td>−73 (−754, 608)</td><td>1,079 (283, 1875)</td></tr>
<tr><td>MRI visceral adipose tissue (cm2)</td><td>−5.9 (−24, 13)</td><td>14 (1.4, 26)</td></tr>
</table></td></tr>
</table>

Reference and study design	Results
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: MIBP ∑LMW phthalates Boys 22.7 253.2 Girls 22.2 294.0 Low molecular weight phthalate metabolites included MEP, MBP, MIBP, and MCPP. **Analysis:** Linear regression, considering sex, age at baseline, sedentary hrs, metabolic equivalent hrs, caloric intake, race, ethnicity, season of urine collection, family income, and parent education as potential covariates; restricted to children with creatinine ≥10 mg/dL	Full sample results, regression coefficient (95% CI) for change in body metric per unit change in ln-MIBP (µg/g Cr) (adjusted for creatinine, age, sex, sedentary hrs, metabolic equivalent hrs, Hispanic ethnicity, caloric intake, season, and parental education level) BMI (kg/m^2) −0.27 (−0.73, −0.18) Waist circumference (cm) −0.62 (−1.84, −0.61)
Olsén et al. (2012) (Sweden) **Population:** 1,016 (507 men, 509 women), from population-based cohort (Prospective Investigation of Vasculature in Uppsala Seniors study), 2001–2003; age 70 yrs at enrollment **Outcome:** BMI measured at study visit **Exposure:** Serum sample, collected at time of examination; results not shown **Analysis:** Linear regression, adjusted for the variables shown in results column	Regression coefficient for change in outcome per unit increase in ln-MIBP (adjusted for sex, smoking, diabetes (except for glucose) and the other variables in the table; model for Framingham Risk Score only adjusted for sex) BMI 0.094 (−0.13, 0.32)

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 MIBP and 0H-MIBP in urine (µg/g Cr): Geometric mean (95% CI) Children MIBP 64.6 (55.2, 75.7) OH-MIBP 34.2 (28.5, 41.0) ∑DIBP 101 (87.2, 118) Adults MIBP 37.2 (31.8, 43.5) OH-MIBP 17.4 (15.1, 20.0) ∑DIBP 55.9 (48.4, 64.5) **Analysis:** Spearman's rank correlation analysis	Spearman correlation coefficient between ∑DIBP and BMI in Children −0.035 ($p > 0.05$) Mothers −0.137 ($p > 0.05$)
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 MIBP in urine (µg/g Cr): Geometric mean (SD) No diabetes 9.1 (2.3) **Analysis:** Spearman correlation coefficient **Related references:** Lopez-Carrillo et al. (2010)	Spearman correlation coefficient between anthropometric measure and ln-MIBP in urine (µg/g Cr) BMI (kg/m^2) 0.0457 Waist circumference (cm) 0.0151 Waist/height ratio −0.0156 ($p > 0.05$ for all parameters)

DXA = dual energy x-ray absorptiometry; MCPP = mono-(3-carboxypropyl) phthalate; MHBP = mono-(3-hydroxybutyl)phthalate; MRI= magnetic resonance imaging; SE = standard error

Table 3-14. Evidence pertaining to DIBP and diabetes/insulin resistance in humans

Reference and study design	Results
Diabetes diagnosis	
James-Todd et al. (2012) (United States, NHANES) **Population:** 215 cases, 1,235 controls from population-based survey (NHANES), 2001–2008; women age 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?" **Exposure:** Urine sample, collected at time of survey MIBP in urine (units not reported): Geometric mean Unadjusted 3.7 (based on larger sample of 2,350 women) **Analysis:** Logistic regression, adjusting for variables shown in the results column	OR (95% CI) for diabetes by quartile of MIBP (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) MIBP quartile 1 (low) 1.0 (referent) 2 1.04 (0.66–1.67) 3 1.69 (0.93–3.06) 4 (high) 1.95 (0.99–3.85)
Lind et al. (2012a) (Sweden) **Population:** 1,003 (501 men, 502 women), from population-based cohort (Prospective Investigation of Vasculature in Uppsala Seniors study), 2001–2003; age 70 yrs at enrollment **Outcome:** Diabetes (n = 88; history of diabetes or fasting glucose >7.0 mmol/L, mean duration 8.9 yrs); **Exposure:** Serum sample (fasting), collected at time of clinical assessment MIBP in serum (ng/mL): Median 75th percentile Women 13.4 24.5 Men 13.5 33.3 **Analysis:** Logistic regression for diabetes classification, adjusting for variables shown in results column	OR (95% CI) per unit increase in serum ln-MIBP (adjusted for sex, serum cholesterol and triglycerides, BMI, smoking, exercise, and education) 1.30 (1.10, 1.55) OR (95% CI) by quintile of ln-MIBP (adjusted for sex, serum cholesterol and triglycerides, BMI, smoking, exercise, and education) MIBP quintile 1 (low) 1.0 (referent) 2 1.19 (0.59, 2.38) 3 0.84 (0.41, 1.76) 4 1.37 (0.7, 2.66) 5 (high) 2.00 (1.03, 3.99) (trend *p*) (0.038)

Reference and study design	Results
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 MIBP in urine (µg/g creatinine): Geometric mean (SD) No diabetes 9.1 (2.3) Diabetes 7.9 (2.1) **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-MIBP (adjusted for creatinine and education) 1.01 (0.65, 1.55)
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; HOMA-IR **Exposure:** Urine sample at time of clinical exam Cr-adjusted MIBP in urine (µg/g Cr): Median 75th percentile Men 3.8 6.6 Women 4.9 8.9 **Analysis:** Logistic regression, adjusting for variables shown in the results column	Median change (95% CI) in biomarkers for diabetes by quartile of MIBP (adjusted for age, gender, race/ethnicity, fasting time, urinary creatinine, total caloric intake, triglycerides, education, and poverty and smoking status) MIBP quartile / Fasting glucose / Fasting insulin / HOMA-IR 1 (low) 1.0 (referent) 1.0 (referent) 1.0 (referent) 2 1.87 (0.83, 2.92) 1.45 (0.85, 2.04) 0.38 (0.23, 0.52) 3 2.77 (1.75, 3.80) 1.23 (0.57, 1.89) 0.35 (0.19, 0.51) 4 (high) 3.69 (2.60, 4.78) 1.73 (0.92, 2.54) 0.53 (0.33, 0.72) (*p* for trend) (<0.0001) (0.0028) (0.0002)
Trasande et al. (2013b) (United States, NHANES) **Population:** 766 participants in the 2003–2008 NHANES, 12–19 yrs old **Outcome:** HOMA, 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 MIBP alone not reported. **Analysis:** HOMA-IR assessed as continuous or categorical variable; categorical 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-MIBP 1.57 (1.18, 2.09) 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-MIBP 0.15 (0.04, 0.26) Ln-ΣLMW -0.07 (-0.18, 0.04)

Reference and study design	Results
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.	
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, FBG (n = 985), HOMA-IR (n = 971), glycosolated hemoglobin A1c (n = 2,092) **Exposure:** Urine sample, collected at time of survey MIBP in urine (units not reported): Geometric mean Unadjusted 3.7 **Analysis:** Logistic regression, adjusting for variables shown in the results column	Among women without diabetes, difference (from first quartile) in median value (95% CI) of glucose and insulin parameters by quartile of MIBP (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) MIBP Quartile — Model 1 — Model 2 FBG (mg/dL) 1 (low) — (referent) — (referent) 2 — 3.08 (1.22, 4.93) — 3.03 (1.05, 5.00) 3 — 3.50 (1.45, 5.54) — 3.17 (1.17, 5.17) 4 (high) — 5.86 (3.55, 8.17) — 6.04 (3.81, 8.28) Ln (HOMA) 1 (low) — (referent) — (referent) 2 — 0.13 (−0.02, 0.28) — 0.13 (0.01, 0.25) 3 — 0.08 (−0.08, 0.25) — 0.10 (−0.01, 0.21) 4 (high) — 0.22 (0.06, 0.38) — 0.18 (0.06, 0.31) A1c (%) 1 (low) — (referent) — (referent) 2 — 0.03 (−0.01, 0.08) — 0.03 (−0.01, 0.08) 3 — 0.03 (−0.02, 0.09) — 0.04 (0.00, 0.09) 4 (high) — 0.01 (−0.05, 0.07) — 0.01 (−0.04, 0.07)

Reference and study design	Results
Lind et al. (2012a) (Sweden) **Population:** 1,003 (501 men, 502 women), from population-based cohort (Prospective Investigation of Vasculature in Uppsala Seniors study), 2001–2003; age 70 yrs at enrollment **Outcome:** Ratio of fasting proinsulin to insulin; HOMA **Exposure:** Serum sample (fasting), collected at time of clinical assessment MIBP in serum (ng/mL): Median 75th percentile Women 13.4 24.5 Men 13.5 33.3 **Analysis:** Linear regression for continuous outcomes (proinsulin/insulin and HOMA-IR); adjusting for variables shown in results column **Related reference:** Olsén et al. (2012) presents blood glucose data for this study population; the regression coefficient per unit increase in serum ln-MIBP was 0.024 (0.01, 0.04) (see Table 14)	Regression coefficient (95% CI) for insulin measures per unit increase in serum ln-MIBP (adjusted for sex, serum cholesterol and triglycerides, BMI, smoking, exercise, and education) Proinsulin/insulin 0.06 (0.03, 0.089) HOMA 0.014 (−0.015, 0.043) The magnitude of the association between proinsulin/insulin and MIBP was similar to that for MEHP, but in the opposite direction of MEP and MMP (−0.05 and −0.005, respectively). The magnitude of the association between HOMA-IR and MIBP was lesser than that for MEP and MMP. The magnitude of the association between prevalent diabetes and MIBP was greater than that for MEHP, and less than that for MEP and MMP in the highest quintile.
Olsén et al. (2012) (Sweden) **Population:** 1,016 (507 men, 509 women), from population-based cohort (Prospective Investigation of Vasculature in Uppsala Seniors study), 2001–2003; age 70 yrs at enrollment **Outcome:** Fasting serum sample for glucose **Exposure:** Serum sample, collected at time of examination; results not shown **Analysis:** Linear regression, adjusted for the variables shown in results column.	Regression coefficient for change in outcome per unit increase in ln-MIBP (adjusted for sex, smoking, diabetes (except for glucose), and the other variables in the table; model for Framingham Risk Score only adjusted for sex) Fasting serum glucose 0.024 (0.01, 0.04; p = 0.0001

FBG = fasting blood glucose; HOMA-IR = homeostatic model assessment of insulin resistance

Table 3-15. Evidence pertaining to DIBP 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 MIBP in urine (units not given) Mean ± SD Normal BP 13.13 ± 22.17 High BP 15.71 ± 25.15 **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 with increased log-transformed MIBP (adjusted for urinary creatinine, age, sex, ethnicity, BMI, and sampling weights) 1.14 (0.92, 1.41) Mean ± SD MIBP in urine (units not given) in participants with normal and high BP Normal BP (n = 2,180) 13.13 ± 22.17 High BP (n = 309) 15.71 ± 25.15
Trasande et al. (2013c) (United States, NHANES) **Population:** 2,447 children in population-based survey (NHANES), 2003–2008; ages 8–19 yrs old **Outcome:** Systolic BP and diastolic BP z-score (based on height-, sex-, and age-normalized values); 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 BP ≥90th percentile 1.002 ∑LMW phthalate = sum of MEP, MBP, and MIBP **Analysis:** Logistic regression for pre-hypertension (BP ≥90th percentile) classification; linear regression for systolic BP and diastolic BP 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) ∑LMW phthalates: Systolic BP 0.03 (−0.02, 0.07); Diastolic BP 0.02 (−0.04, 0.07); Triglycerides −0.22 (−4.40, 0.07); HDL 0.13 (−0.60, 0.85) MIBP: Systolic BP 0.03 (−0.02, 0.08); Diastolic BP −0.02 (−0.09, 0.04); Triglycerides not reported; HDL not reported OR (95% CI) for BP ≥90th percentile per unit increase in ln-phthalates ∑LMW phthalates: BP ≥90th percentile 1.19 (0.96, 1.47); High triglycerides 0.85 (0.71, 1.01); Low HDL 1.00 (0.87, 1.15) MIBP: BP ≥90th percentile 1.00 (0.74, 1.35); High triglycerides not reported; Low HDL not reported Interactions with covariates examined in supplemental analyses; stratified analyses showed no statistically significant associations between ∑LMW phthalates and systolic BP for gender, age, race/ethnicity, cotinine level, or BMI

<table>
<tr><th>Reference and study design</th><th>Results</th></tr>
<tr><td>Olsén et al. (2012) (Sweden)
Population: 1,016 (507 men, 509 women), from population-based cohort (Prospective Investigation of Vasculature in Uppsala Seniors study), 2001–2003; age 70 yrs at enrollment
Outcome: Blood pressure measured at study visit; fasting serum sample for LDL and HDL cholesterol, and triglycerides; Framingham risk score
Exposure: Serum sample, collected at time of examination; results not shown
Analysis: Linear regression, adjusted for the variables shown in results column</td><td>Regression coefficient for change in outcome per unit increase in ln-MIBP (adjusted for sex, smoking, diabetes and the other variables in the table; model for Framingham Risk Score only adjusted for sex)
<table><tr><th></th><th>(β [SE])</th></tr><tr><td>LDL</td><td>0.044 (−0.01, 0.09)</td></tr><tr><td>HDL</td><td>0.017 (−0.01, 0.09)</td></tr><tr><td>Triglycerides</td><td>−0.009 (−0.03, 0.01)</td></tr><tr><td>Systolic BP</td><td>−0.05 (−1.28, 1.18)</td></tr><tr><td>Diastolic BP</td><td>0.35 (−0.20, 0.90)</td></tr><tr><td>Framingham risk score</td><td>0.13 (−0.05, 0.31)</td></tr></table></td></tr>
<tr><td>Lind and Lind (2011) (Sweden)
Population: 1,016 (507 men, 509 women), from population-based cohort (Prospective Investigation of Vasculature in Uppsala Seniors study), 2001–2003; age 70 yrs at enrollment
Outcome: Carotid artery intima media thickness (IMT); grey scale media of the intima media complex (IM-GSM); plaque in carotid artery
Exposure: Serum sample (fasting), collected at time of clinical assessment
MIBP in serum (ng/mL):
<table><tr><th>Median</th><th>75th percentile</th></tr><tr><td>13.5</td><td>29.3</td></tr></table>Analysis: Linear regression for continuous outcomes (IMT, IM-GSM) and ordinal logistic regression for number of carotid arteries with plaques (0, 1, 2), adjusted for variables shown in results column</td><td>Median IMT by quintile of MIBP (adjusted for sex, BMI, fasting blood glucose, systolic BP, diastolic BP, HDL and LDL cholesterol, triglycerides, smoking, antihypertensive treatment, statin use)
<table><tr><th rowspan="2">MIBP quintile</th><th colspan="2">IMT</th><th colspan="2">IM-GSM</th></tr><tr><th>Median IMT</th><th>(p-value)</th><th>Median IM-GSM</th><th>(p-value)</th></tr><tr><td>1 (low)</td><td>0.87</td><td>(referent)</td><td>80</td><td>Referent</td></tr><tr><td>2</td><td>0.89</td><td>(0.91)</td><td>72</td><td>(0.0001)</td></tr><tr><td>3</td><td>0.86</td><td>(0.13)</td><td>68</td><td>(0.0001)</td></tr><tr><td>4</td><td>0.89</td><td>(0.91)</td><td>69</td><td>(0.0001)</td></tr><tr><td>5 (high)</td><td>0.85</td><td>(0.074)</td><td>102</td><td>(0.0001)</td></tr></table>Regression coefficient (β [p-value]) per unit increase in serum MIBP (adjusted for sex, BMI, fasting blood glucose, systolic BP, diastolic BP, HDL and LDL cholesterol, triglycerides, smoking, antihypertensive treatment, statin use)
<table><tr><td>IMT</td><td>−0.0045 (0.14)</td></tr><tr><td>IM-GSM</td><td>5.5 (0.0001)</td></tr></table>OR for presence of plaques and median value of plaque GSM by quintile of MIBP (adjusted for sex, BMI, fasting blood glucose, systolic BP, diastolic BP, HDL and LDL cholesterol, triglycerides, smoking, antihypertensive treatment, statin use)
<table><tr><th rowspan="2">MIBP quintile</th><th colspan="2">Plaque prevalence</th><th colspan="2">Plaque GSM</th></tr><tr><th>OR</th><th>(p-value)</th><th>Median</th><th>(p-value)</th></tr><tr><td>1 (low)</td><td>1.0</td><td>(referent)</td><td>65</td><td>(referent)</td></tr><tr><td>2</td><td>0.70</td><td>(0.059)</td><td>69</td><td>(0.37)</td></tr><tr><td>3</td><td>0.74</td><td>(0.17)</td><td>59</td><td>(0.11)</td></tr><tr><td>4</td><td>1.00</td><td>(0.78)</td><td>62</td><td>(0.074)</td></tr></table></td></tr>
</table>

Reference and study design	Results
	5 (high) 0.64 (0.011) 99 (0.0001) OR or regression coefficient per unit increase in serum MIBP Plaque prevalence OR (95% CI) 0.88 (0.79, 0.98) Plaque GSM β (*p*-value) 8.0 (0.0001) The regression models did not show evidence of interaction by gender, except for IMT (interaction term *p*-value = 0.030).

BP = blood pressure; HDL = high-density lipoprotein; IM-GSM = grey scale media of the intima media complex; IMT = intima media thickness; LDL = low-density lipoprotein

Table 3-16. Evidence pertaining to DIBP and cancer in humans

Reference and study design	Results
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) MIBP in urine, controls: Geometric mean Cr-adjusted (µg/g Cr) 8.85 **Analysis:** Logistic regression, adjusting for variables shown in results column	Geometric mean (95% CI) DBP in urine (µg/g Cr), all subjects and by menopausal status Controls / Cases All: 8.85 (7.95, 9.84) / 7.81 (6.93, 8.81) Pre-menopause: 9.99 (8.42, 11.85) / 8.31 (6.85, 10.09) Post-menopause: 8.32 (7.27, 9.52) / 7.53 (6.45, 8.78) OR (95% CI) for breast cancer, by tertile of MIBP (adjusted for current age, age at menarche, parity, menopausal status, and other phthalate metabolites) MIBP tertile (µg/g Cr) 1 (0.23−7.44): 1.0 (referent) 2 (7.45−12.07): 0.59 (0.35, 0.98) 3 (12.08−86.22): 0.73 (0.43, 1.24) (trend *p*): (0.365)

3.3. EXPERIMENTAL STUDIES

3.3.1. Developmental Effects

Table 3-17. Evidence pertaining to developmental effects in animals following oral exposure to DIBP

Reference and study design	Results[a]					
Fetal survival						
See Table 3-19						
Fetal growth						
BASF (2007)	**Fetal body weight** *(percent change compared to control)*					
Rat (Wistar); 22–23 dams/group	Doses	0	88	363	942	
0, 88, 363, 942 mg/kg-day	*M BW*	0%	−3%	−3%	−5%**	
Diet	*F BW*	0%	−3%	−3%	−6%**	
GDs 6–20 (GD 20 c-section)						
Borch et al. (2006)	**Fetal body weight** *(percent change compared to control)*					
Rat (Wistar); 11–12 dams/group	Doses (M)	0		600		
0, 600 mg/kg-day	*BW (GD 19) (data presented in graph[b])*	0%		−27%*		
Gavage	*BW (GD 20/21) (data presented in graph[b])*	0%		−12%		
GDs 7–19 (GD 19 c-section) or GDs 7–20/21 (GD 20/21 c-section); 5–6 dams/group per time point	*Doses (F)*	0		600		
	BW (GD 19) (data presented in graph[b])	0%		−28%*		
	BW (GD 20/21) (data presented in graph[b])	0%		12%		
Saillenfait et al. (2006)	**Fetal body weight** *(mean percent change compared to control)*					
Rat (Sprague-Dawley); 20–22 dams/group	Doses	0	250	500	750	1,000
0, 250, 500, 750, 1,000 mg/kg-day	*M and F (all fetuses) BW*	0%	0%	−7%**	−17%**	−24%**
Gavage	*M BW*	0%	0%	−6%*	−17%**	−25%**
GDs 6–20 (GD 21 c-section)	*F BW*	0%	−1%	−8%**	−18%**	−26%**

Reference and study design	Results[a]				
Postnatal survival					
Saillenfait et al. (2008)	**Pup survival** *(percent change compared to control [litter means])*				
Rat (Sprague-Dawley); 11–14 dams/group	Doses	0	125	250	500	625
0, 125, 250, 500, 625 mg/kg-day	*percentage pup survival PNDs 1–4*	0%	−1%	−1%	−1%	−7%
GDs 12–21 (dams allowed to deliver)	*percentage pup survival PNDs 4–21*	0%	2%	5%	3%	5%
Postnatal and adult growth					
Eastman Kodak (1954)	**Body weight gain** *(percent change compared to control)*				
Rat (no strain designation);	Doses (M)	0	97	1,000	7,800
5 male and 5 females/group	*BW gain (weaning to 4 weeks post-weaning)*	0%	3%	−2%	−61%
0, 0.1, 1, 5% DIBP (0, 97, 1,000, 7,800 mg/kg-day for males; 0, 110, 1,100, 6,400 mg/kg-day for females)[c]	Doses (F)	0	110	1,100	6,400
	BW gain (weaning to 4 weeks post-weaning)	0%	−9%	1%	−34%
	Body weight *(percent change compared to control)*				
Diet	Doses (M)	0	97	1,000	7,800
Weaning to 8 weeks post-weaning	*4 weeks post-weaning BW*	0%	2%	−1%	−41%
	Doses (F)	0	110	1,100	6,400
	4 weeks post-weaning BW	0%	−5%	1%	−19%
	Body weight gain *(percent change compared to control)*				
	Doses (M)	0	97	1,000	7,800
	BW gain (weaning to 8 weeks post-weaning)	0%	3%	−3%	−58%
	Doses (F)	0	110	1,100	6,400
	BW gain (weaning to 8 weeks post-weaning)	0%	−11%	0%	−34%
	Body weight *(percent change compared to control)*				
	Doses (M)	0	97	1,000	7,800
	8 weeks post-weaning BW	0%	2%	−3%	−44%
	Doses (F)	0	110	1,100	6,400
	8 weeks post-weaning BW	0%	−7%	0%	−22%
	Note: Statistical analysis not reported in study.				

Reference and study design	Results[a]					
(Hazleton Laboratories (1992), 1987); NIOSH (1983))	**Body weight change** *(g)*					
Mouse (CD-1); 50 control females; 10 females/treated group (6.5–9 weeks old)	Doses (F)	0	1,000	1,795	3,225	5,790	10,400
	BW change (days 1–8 of study)	0	0	1	0	1	1
0, 1,000, 1,795, 3,225, 5,790, 10,400 mg/kg-day	**Body weight change** *(g)*						
Gavage	Doses (F)	0	1,000	1,795	3,225	5,790	10,400
8 days	*BW change (days 1–12 of study)*	1	1	1	0	1	1
	Body weight change *(g)*						
	Doses (F)	0	1,000	1,795	3,225	5,790	10,400
	BW change (days 1–16 of study)	1	1	1	1	1	1
	Note: Statistical analysis not reported in study.						
Oishi and Hiraga (1980d)	**Body weight and weight gain** *(percent change compared to control)*						
MIBP	Doses (M)	0			1,100		
Rat (Wistar) (JCL); 10 males/group	*BW at 6 weeks*	0%			−10%*		
0, 2% in diet (0, 1,100 mg/kg-day)[d]	*BW gain (5–6 weeks[e])*	0%			−31%		
Diet	Note: Statistical analysis was not performed on BW gain.						
1 week							
Oishi and Hiraga (1980a)	**Body weight and weight gain** *(percent change compared to control)*						
Mouse (JCL:ICR); 10 males/group	Doses (M)	0			2,100		
0, 2% (0, 2,100 mg/kg-day)[d]	*BW at 6 weeks*	0%			−13%*		
Diet	*BW gain (5–6 weeks[e])*	0%			−54%		
1 week	Note: Statistical analysis was not performed on BW gain.						
Saillenfait et al. (2008)	**Body weight** *(percent change compared to control [litter means])*						
Rat (Sprague-Dawley); 11–14 dams/group	Doses	0	125	250	500	625	
	M postnatal (PND 1) BW	0%	−1%	−2%	−2%	−10%**	
0, 125, 250, 500, 625 mg/kg-day	*M postnatal (PND 21) BW*	0%	−1%	−3%	−6%	−10%*	
Gavage	*F postnatal (PND 21) BW*	0%	−3%	−5%	−3%	−10%	

Reference and study design	Results[a]						
GDs 12–21 (dams allowed to deliver)	*M BW at day of PPS*	0%	−8%*	−5%*	7%	2%	
	M adult (PNDs 77–84) BW	0%	−6%	−4%	−7%*	−9%**	
University of Rochester (1953)	**Body weight gain** *(percent change compared to control)*						
Rat (Albino; no other strain designation); 5 males/group	Doses (M)	0	15	140	1,400	3,000	8,900
	BW gain[e] (weaning to 1 month post-weaning)	0%	−22%	−19%	−22%	−27%	−51%
	Note: Statistical analysis was not performed on BW gain.						
0, 0.01, 0.1, 1, 2, 5% (0, 15, 140, 1,400, 3,000, 8,900 mg/kg-day)[f]	**Body weight** *(percent change compared to control)*						
Diet	Doses (M)	0	15	140	1,400	3,000	8,900
Weaning to 1 month post-weaning	*1 month post-weaning BW*	0%	−16%	−14%	−16%	−20%	−38%
	Note: Statistical analysis not reported in study.						
University of Rochester (1953)University of Rochester (1953)University of Rochester (1953)University of Rochester (1953)	**Body weight gain** *(percent change compared to control)*						
	Doses (M)	0	15	140	1,400	3,000	8,900
	BW gain (weaning to PND 49 [~after PPS[g]])	0%	−20%	−18%	−21%	−27%	−49%
	Note: Statistical analysis was not performed on BW gain.						
	Body weight *(percent change compared to control)*						
	Doses (M)	0	15	140	1,400	3,000	8,900
	PND 49 (~after PPS[g]) BW	0%	−14%	−13%	−15%	−19%	−35%
	Note: Statistical analysis not reported in study.						
University of Rochester (1954)	**Body weight gain** *(percent change compared to control)*						
Rat (Albino; no other strain designation); 5 males and 5 females/group	Doses (M)	0	65	710	5,800		
	BW gain (weaning to 1 month post-weaning)[e]	0%	5%	−6%	−60%		
0, 0.1, 1, 5% (0, 65, 710, 5,800 mg/kg-day for males; 0, 82, 770, 4,700 mg/kg-day for females)[h]	Doses (F)	0	82	770	4,700		
	BW gain (weaning to 1 month post-weaning)[e]	0%	−7%	3%	−27%		
Diet	Note: Statistical analysis was not performed on BW gain.						
Weaning to 4 months post-weaning	**Body weight** *(percent change compared to control)*						

Reference and study design	Results[a]				
	Doses (M)	0	65	710	5,800
	BW at 1 month post-weaning	0%	4%	−4%	−42%
	Doses (F)	0	82	770	4,700
	BW at 1 month post-weaning	0%	−4%	2%	−16%
	Note: Statistical analysis not reported in study.				
	Body weight gain *(percent change compared to control)*				
	Doses (M)	0	65	710	5,800
	BW gain (weaning to PND 49 [~after PPS[g]])[e]	0%	3%	−2%	−61%
	Doses (F)	0[y]	82	770	4,700
	BW gain (weaning to PND 49 [~after VO[g]][e]	0%	−8%	3%	−33%
	Note: Statistical analysis was not performed on BW gain.				
	Body weight *(percent change compared to control)*				
	Doses (M)	0	65	710	5,800
	BW at PND 49 (~after PPS[g])	0%	2%	−1%	−41%
	Doses (F)	0	82	770	4,700
	BW at PND 49 (~after VO[g])	0%	−4%	1%	−18%
	Note: Statistical analysis not reported in study.				
	Body weight gain *(percent change compared to control)*				
	Doses (M)	0	65	710	5,800
	BW gain (weaning to 4 months post-weaning)	0%	5%	−11%	−53%
	Doses (F)	0[y]	82	770	4,700
	BW gain (weaning to 4 months post-weaning)	0%	−1%	10%	−19%
	Note: Statistical analysis was not performed on BW gain.				
	Body weight *(percent change compared to control)*				
	Doses (M)	0	65	710	5,800
	BW at 4 months post-weaning	0%	4%	−9%	−43%
	Doses (F)	0	82	770	4,700

Reference and study design	Results[a]				
	BW at 4 months post-weaning	0%	−1%	7%	−13%
	Note: Statistical analysis not reported in study.				
Fetal morphological development					
Saillenfait et al. (2006) Rat (Sprague-Dawley) rats; 20–22 dams/group 0, 250, 500, 750, 1,000 mg/kg-day Gavage GDs 6–20 (GD 21 c-section)	**Malformations**				
	External malformations *(incidence; number of affected fetuses [litters])*				
	Doses	0	250	500	750	1,000
	total fetuses (litters) examined for external malformations	281 (22)	276 (21)	237 (21)	212 (21)	111 (18)
	anasarca	0	0	0	0	1 (1)
	exophthalmos (unilateral) and absence of eyelids (bilateral)	0	0	0	1 (1)	0
	exencephaly	0	0	0	2 (2)	0
	meningoencephalocele	0	0	0	3 (3)	3 (2)
	microstomia	0	0	0	0	1 (1)
	ectopia cordis	0	0	0	0	1 (1)
	omphalocele	0	0	0	0	1 (1)
	Combined total with external malformations *(incidence [percent])*					
	Doses	0	250	500	750	1,000
	total number (%) fetuses with external malformations	0	0	0	5 (2%)*	6 (5%)**
	total number (%) litters with external malformations	0	0	0	4 (19%)	4 (22%)
	mean % fetuses with external malformations/litter	0%	0%	0%	2%	4%
	Visceral malformations *(incidence; number of affected fetuses [litters])*					
	Doses	0	250	500	750	1,000
	total fetuses (litters) examined for visceral malformations	141 (22)	138 (21)	119 (21)	106 (21)	56 (18)
	anophthalmia, uni- or bilateral	0	0	0	6 (4)	4 (3)
	aorta and/or pulmonary artery transposed	0	0	0	6 (5)	3 (3)

Reference and study design	Results[a]				
	diaphragmatic hernia	0	2 (1)	2 (2)	2 (2)	1 (1)
	kidney and ureter, absent, uni- or bilateral	0	0	0	1 (1)	3 (3)
	kidney, small, uni- or bilateral	0	0	0	1 (1)	1 (1)
	Combined total with visceral malformations *(incidence [percent])*					
	Doses	0	250	500	750	1,000
	total number (%) fetuses with visceral malformations	0	2 (1%)	2 (2%)	13 (12%)**	10 (18%)**
	total number (%) litters with visceral malformations	0	1 (5%)	2 (10%)	8 (38%)**	8 (44%)**
	mean % fetuses with visceral malformations/litter	0%	1%	2%	13%*	16%*
	Skeletal malformations *(incidence; number of affected fetuses [litters])*					
	Doses	0	250	500	750	1,000
	total number of fetuses (litters) examined for skeletal malformations	140 (22)	138 (21)	118 (21)	106 (21)	55 (18)
	mandible, small	0	0	0	0	1 (1)
	sternebrae, fused	0	0	0	7 (6)	14 (9)**
	sternebrae, fused and scrambled	0	0	0	5 (3)	12 (7)
	sternebrae, total	0	0	0	12 (7)*	26 (13)**
	cleft sternum	0	0	1 (1)	1 (1)	2 (2)
	sternebrae, checkerboard	0	0	0	2 (2)	0
	ribs, fused	0	0	0	0	2 (2)
	cervical arches, fused	0	0	0	3 (3)	3 (3)
	thoracic or lumbar vertebral arches, fused	0	0	1 (1)	2 (2)	2 (2)
	thoracic or lumbar vertebral centra, fused	0	0	1 (1)	0	4 (3)
	thoracic or lumbar centrum, hemicentric	0	0	1 (1)	4 (3)	3 (3)
	thoracic or lumbar vertebral centra, misaligned	0	0	2 (2)	3 (2)	5 (4)

Reference and study design	Results[a]				
	Combined total with skeletal malformations *(incidence [percent])*				
	Doses	0	250	500	750	1,000
	total number (%) fetuses with skeletal malformations	0	0	4 (3%)	18 (17%)**	34 (62%)**
	total number (%) litters with skeletal malformations	0	0	4 (19%)	11 (52%)**	15 (83%)**
	mean % fetuses with skeletal malformations/litter	0%	0%	3%	18%**	67%**
	Variations					
	External variations *(incidence; number of affected fetuses [litters])*					
	Doses	0	250	500	750	1,000
	total fetuses (litters) examined for external variations	281 (22)	276 (21)	237 (21)	212 (21)	111 (18)
	clubfoot	0	2 (1)	0	0	0
	tail, curly	0	0	0	1 (1)	0
	tail tip, haemorrhage	0	1 (1)	0	0	0
	Visceral variations *(incidence; number of affected fetuses [litters])*					
	Doses	0	250	500	750	1,000
	total fetuses (litters) examined for visceral variations	141 (22)	138 (21)	119 (21)	106 (21)	56 (18)
	dilated cerebral ventricle, slight	0	0	0	1 (1)	0
	dilated renal pelvis	1 (1)	0	0	2 (2)	5(4)
	ureter (all)	3 (3)	0	2 (2)	10 (8)	12 (8)*
	hydroureter	0	0	0	4 (4)	6 (5)
	distended ureter	3 (3)	0	2 (2)	6 (5)	6 (4)
	ovaries, displaced	0	0	0	5 (4)	2 (2)
	testis, ectopic	0	0	3 (2)	30 (16)**	30 (16)**
	degree of trans-abdominal testicular migration (mean)	2.6	3.8	13.6**	42.2**	58.1**

Reference and study design	Results[a]				
	Skeletal variations *(incidence; number of affected fetuses [litters])*				
	Doses	0	250	500	750	1,000
	total fetuses (litters) examined for skeletal variations	140 (22)	138 (21)	118 (21)	106 (21)	55 (18)
	parietals or supraoccipital, incomplete ossification	0	0	0	3 (2)	1 (1)
	hyoid, absent or incomplete ossification	0	0	0	1 (1)	8 (7)
	sternebrae, fused, 1st and 2nd only	1 (1)	0	8 (4)	29 (11)**	5 (4)
	sternebrae, bipartite	0	1 (1)	2 (2)	7 (5)	4 (4)
	sternebrae, incomplete ossification	0	1 (1)	5 (5)	9 (6)	6 (5)
	ribs, cervical, rudimentary	0	0	2 (2)	12 (9)*	9 (6)
	ribs, 14th, any supernumerary	23 (11)	32 (14)	42 (18)	72 (20)**	52 (18)**
	ribs, 14th, long supernumerary	1 (1)	1 (1)	2 (2)	15 (9)*	9 (9)*
	ribs, short or reduced ossification (unilateral)	0	0	0	1 (1)	1 (1)
	thoracic or lumbar vertebral centra, incomplete ossification	3 (2)	8 (6)	7 (7)	18 (14)**	16 (8)*
	vertebrae, 27 presacral	0	0	0	0	2 (2)
	Note: A single fetus may be represented more than once in the individual variations.					
BASF (2007)[i] Rat (Wistar); 25 dams/group 0, 88, 363, 942 mg/kg-day Diet GDs 6–20 (GD 20 c-section)	**Malformations**				
	External malformations *(incidence; number of affected fetuses [litters])*				
	Doses	0	88	363	942
	total fetuses (litters) examined for external malformations and variations	208 (23)	197 (22)	182 (22)	211 (23)
	malformed head	0	1 (1)	0	0
	anophthalnia	0	1 (1)	0	0
	Combined total with external malformations *(incidence [percent])*				
	Doses	0	88	363	942
	fetuses	0	1 (1%)	0	0

Reference and study design	Results[a]			
	litters	0	1 (5%)	0	0
	Combined total with soft tissue malformations				
	No fetuses affected at any dose				
	Skeletal malformations *(incidence; number of affected fetuses [litters])*				
	Doses	0	88	363	942
	total fetuses (litters) examined for skeletal malformations/ variations	109 (23)	101 (22)	97 (22)	110 (23)
	severely malformed skull bones	0	1 (1)	0	0
	shortened scapula (cartilage present)	0	0	1 (1)	0
	malpositioned and bipartite sternebral (unchanged cartilage)	1 (1)	1 (1)	0	0
	branched rib	1 (1)	0	0	0
	misshapen humerus	0	2 (2)	0	2 (2)
	shortened humerus	0	0	2 (1)	0
	Combined total with skeletal malformations *(incidence [percent])*				
	fetuses	1 (1%)	4 (4%)	2 (2%)	2 (2%)
	litters	1 (4%)	4 (18%)	1 (5%)	2 (9%)
	Variations				
	Combined total with external variations				
	No fetuses affected at any dose				
	Soft tissue variations *(incidence; number of affected fetuses [litters])*				
	Doses	0	88	363	942
	total fetuses (litters) examined for external soft tissue malformations and variations	99 (23)	96 (22)	85 (22)	101 (23)
	dilated renal pelvis	10 (7)	7 (5)	9 (8)	7 (5)
	dilated ureter	2 (2)	2 (1)	1 (1)	1 (1)
	Combined total with soft tissue variations *(incidence (percent))*				
	Doses	0	88	363	942
	fetuses	10 (10%)	7 (7%)	9 (11%)	7 (7%)
	litters	7 (30%)	5 (23%)	8 (36%)	5 (22%)

Reference and study design	Results[a]			
	Skeletal variations *(incidence; number of affected fetuses [litters])*			
	Doses	0	88	363	942
	supraoccipital hole(s)	31 (15)	23 (13)	15 (12)	38 (19)
	incomplete ossification of basisphenoid	7 (3)	2 (2)	6 (5)	8 (4)
	incomplete ossification of interparietal (unchanged cartilage)	24 (15)	11 (7)	22 (12)	13 (9)
	incomplete ossification of parietal (unchanged cartilage)	16 (10)	13 (9)	22 (13)	13 (7)
	incomplete ossification of supraoccipital (unchanged cartilage)	9 (7)	14 (11)	14 (12)	13 (6)
	incomplete ossification of skull (unchanged cartilage)	5 (4)	2(1)	7 (4)	2 (2)
	incomplete ossification of hyoid (cartilage present)	1 (1)	0	1 (1)	1 (1)
	incomplete ossification of cervical arch (cartilage present)	1 (1)	0	0	0
	incomplete ossification of thoracic centrum (unchanged cartilage)	0	3 (3)	3 (3)	0
	dumbbell ossification of thoracic centrum (unchanged cartilage)	4 (3)	3 (3)	2 (2)	9 (7)
	dumbbell ossification of thoracic centrum (dumbbell-shaped cartilage of centrum)	14 (9)	13 (9)	13 (13)	17 (14)
	bipartite ossification of thoracic centrum (dumbbell-shaped cartilage of centrum)	2 (2)	2 (2)	0	1 (1)
	supernumerary thoracic vertebra	1 (1)	2 (1)	1 (1)	3 (2)
	unossified thoracic centrum (dumbbell-shaped cartilage of centrum)	1 (1)	0	0	0

Reference and study design	Results[a]			
	dumbbell ossification of lumbar centrum (dumbbell-shaped cartilage of centrum)	1 (1)	0	0	0
	incomplete ossification of lumbar arch (cartilage present)	0	0	1 (1)	0
	misshapen sacral vertebra	1 (1)	1 (1)	1 (1)	4 (4)
	fused sacral centrum and arch (unchanged cartilage)	3 (2)	7 (3)	5 (4)	5 (3)
	incomplete ossification of sacral arch (cartilage present)	5 (4)	2 (2)	0	0
	unossified sternebra (unchanged cartilage)	4 (4)	11 (7)	1 (1)	6 (4)
	incomplete ossification of sternebra (unchanged cartilage)	42 (17)	44 (17)	44 (19)	75 (22*)
	misshapen sternebral (unchanged cartilage)	32 (19)	26 (17)	20 (12)	28 (16)
	unilateral ossification of sternebra (unchanged cartilage)	0	0	0	4 (4)
	extra sternebral ossification site (unchanged cartilage)	0	0	1 (1)	0
	bipartite ossification of sternebral (unchanged cartilage)	1 (1)	0	0	2 (2)
	supernumerary rib (14^{th}) (cartilage present)	6 (5)	1 (1)	6 (6)	6 (5)
	supernumerary rib (14^{th}) (cartilage not present)	50 (15)	33 (15)	40 (17)	62 (22*)
	cervical rib (cartilage present)	0	1 (1)	0	0
	cervical rib (cartilage not present)	5 (5)	5 (4)	5 (3)	4 (4)
	wavy rib	6 (5)	2 (2)	10 (4)	9 (9)
	incomplete ossification of pubis (cartilage present)	0	1 (1)	0	0

Reference and study design	Results[a]			
	Combined total with skeletal variations *(incidence (percent))*			
	Doses	0	88	363	942
	fetuses	101 (93%)	87 (86%)	85 (88%)	107 (97%)
	litters	23 (100%)	22 (100%)	22 (100%)	23 (100%)
	Unclassified observations				
	Unclassified external observations *(incidence; number of affected fetuses [litters])*				
	Doses	0	88	363	942
	total fetuses (litters) examined for unclassified observations	208 (23)	197 (22)	182 (22)	211 (23)
	discolored amniotic fluid	0	0	0	1 (1)
	Combined total with external unclassified observations *(incidence [percent])*				
	Doses	0	88	363	942
	fetuses	0	0	0	1 (1%)
	litters	0	0	0	1 (4%)
	Combined total with unclassified soft tissue observations				
	No fetuses affected at any dose				
	Skeletal unclassified cartilage observations *(incidence; number of affected fetuses [litters])*				
	Doses	0	88	363	942
	total fetuses (litters) examined for skeletal unclassified observations	109 (23)	101 (22)	97 (22)	110 (23)
	notched cartilage between basiphenoid and basioccipital	2 (2)	0	0	1 (1)
	fused cervical arch cartilage	1 (1)	0	0	0
	dumbbell-shaped cartilage of cervical centrum	0	1 (1)	0	0
	hole in processus coracoideus	0	1 (1)	0	0
	bipartite processus xiphoideus	36 (14)	30 (15)	30 (15)	40 (14)

Reference and study design	Results[a]				
	notched manubrium	5 (5)	7 (5)	3 (3)	1 (1)
	fused rib cartilage	0	0	1 (1)	0
	branched rib cartilage	0	0	1 (1)	0
	Combined total with skeletal unclassified cartilage observations *(incidence [percent])*				
	Doses	0	88	363	942
	fetuses	39 (36%)	35 (35%)	32 (33%)	41 (37%)
	litters	16 (70%)	17 (77%)	16 (73%)	15 (65%)
Borch et al. (2006)	**AGD change in females** *(percent change compared to control)*				
Rat (Wistar); 11–12 dams/group	Doses	0		600	
0, 600 mg/kg-day	*AGD at GD 19 (data shown in graph[b])*	0%		16%	
Gavage	*AGD at GD 20/21) (data shown in graph[b])*	0%		26%*	
GDs 7–19 (GD 19 c-section) or GDs 7–20/21 (GD 20/21 c-section); 5–6 dams/group per time point	**AGD/cubic root of BW change in females** *(percent change compared to control)*				
	Doses	0		600	
	at GD 19 (data shown in graph[b])	0%		27%**	
	at GD 20/21 (data shown in graph[b])	0%		27%*	

[a]Response is % control (indicated by %) or in cases when % control was not possible to present (e.g., if control value was 0), response levels are presented. Equation used to calculate percent change compared to control:

$$\frac{\text{treated value} - \text{control value}}{\text{control value}} \times 100$$

[b]GrabIt Software used to estimate % control from graph.

[c]Dose conversions were performed using this information: For the Eastman Kodak (1954) study, average BWs were 183, 186, 180, and 115 g for males, and 132, 126, 133, and 110 g for females at 0, 0.1, 1.0, and 5.0%, respectively. Reference values for food consumption of 0.018 and 0.014 kg/day for male and female rats of an unspecified species (U.S. EPA, 1988) were used.

[d]Dose conversions were performed using this information: In Oishi and Hiraga (1980d), average BWs for rats and mice in these studies were 145 and 25 g, respectively, and the default food consumption rates of 0.008 kg/day for male Wistar rats and 0.0025 kg/day for male B6C3F$_1$ mice (U.S. EPA, 1988) were applied. In Oishi and Hiraga (1980a), average BWs over the week-long studies were 132 and 24 g for rats and mice, respectively, and the default food consumption rates of 0.008 kg/day for male Wistar rats and 0.0025 kg/day for male B6C3F$_1$ mice were applied (U.S. EPA, 1988).

[e]Change in body weight was calculated by EPA.

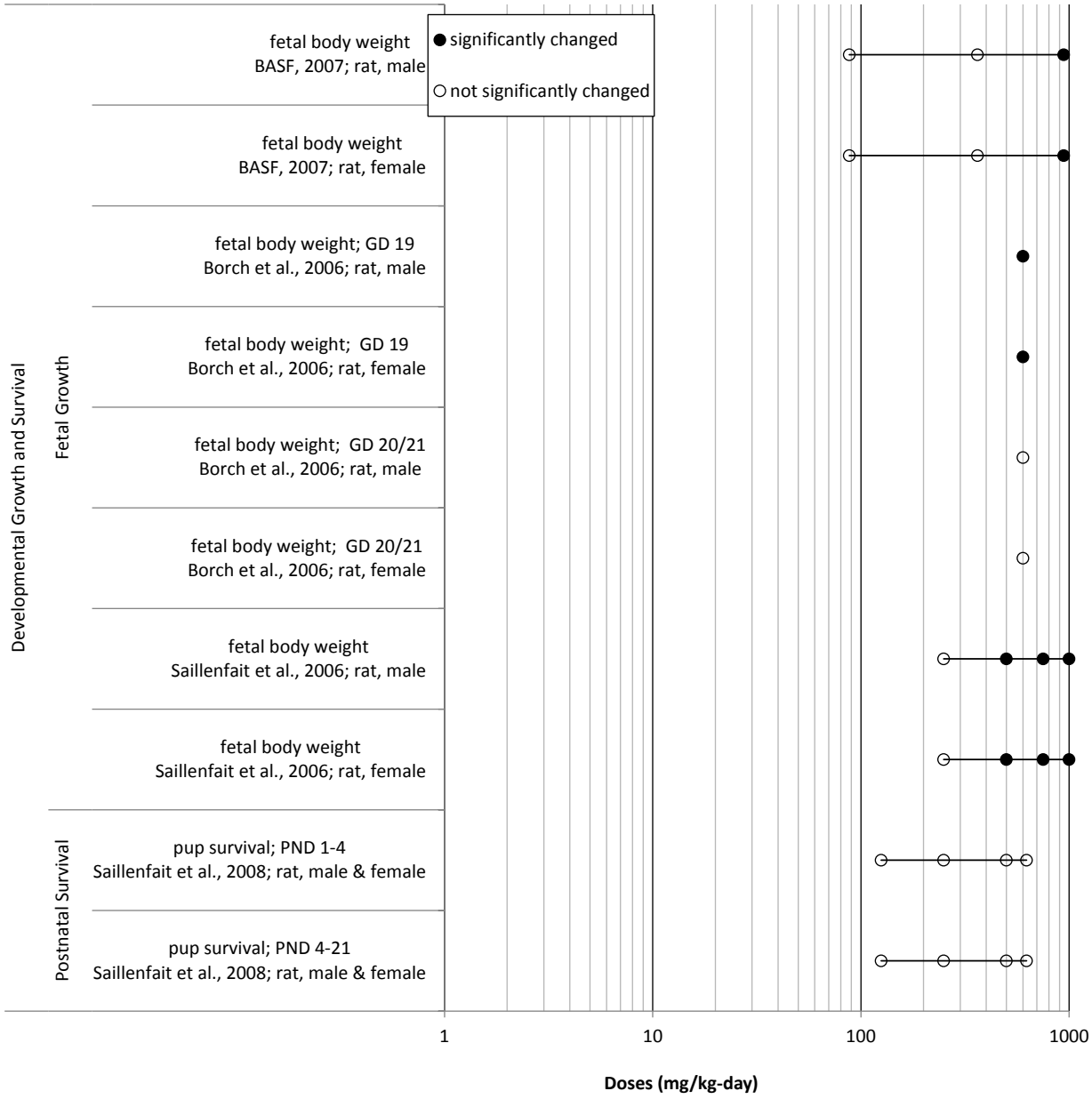
[f]Dose conversions were performed using this information: For University of Rochester (1953), average BWs were 139, 124, 127, 127, 121, and 101 g at 0, 0.01, 0.1, 1.0, 2.0, and 5.0%, respectively). Reference values for food consumption of 0.018 and 0.014 kg/day for male and female rats of an unspecified strain (U.S. EPA, 1988) were used.

[g]PND 49 was selected among the periodic weight measurement ages to present in this table because it corresponds to the age when VO and PPS, the developmental markers of puberty, would be expected to have completed in the male and female rat.

[h]Dose conversions were performed by EPA using this information: For University of Rochester (1954), average BWs were 269, 277, 252, and 155 g for males, and 178, 170, 182, and 148 g for females at 0, 0.1, 1.0, and 5.0%, respectively. Reference values for food consumption of 0.018 and 0.014 kg/day for male and female rats of an unspecified species (U.S. EPA, 1988) were used.

[i]Male reproductive organs were not evaluated in the BASF study.

* = Statistically significant difference at $p < 0.05$ from control value, as reported by study authors; ** = Statistically significant difference at $p < 0.01$ from control value, as reported by study authors; *** = Statistically significant difference at $p < 0.001$ from control value, as reported by study authors; BW = body weight; GD = gestation day; PND = postnatal day; PPS = preputial separation; VO = vaginal opening



1

2 **Figure 3-1. Exposure-response array of effects on developmental growth and**
3 **survival following developmental oral exposure to DIBP.**

4

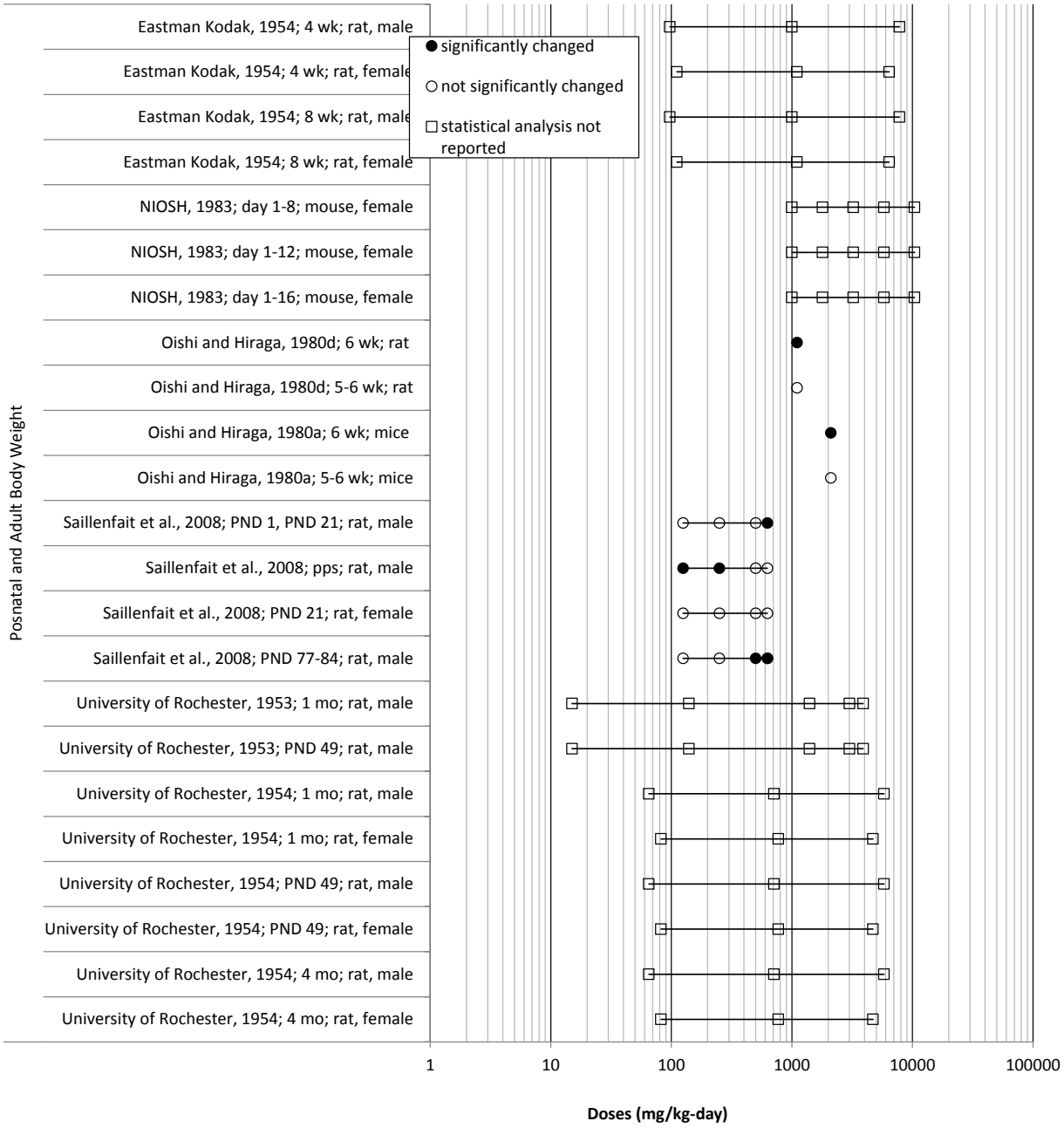
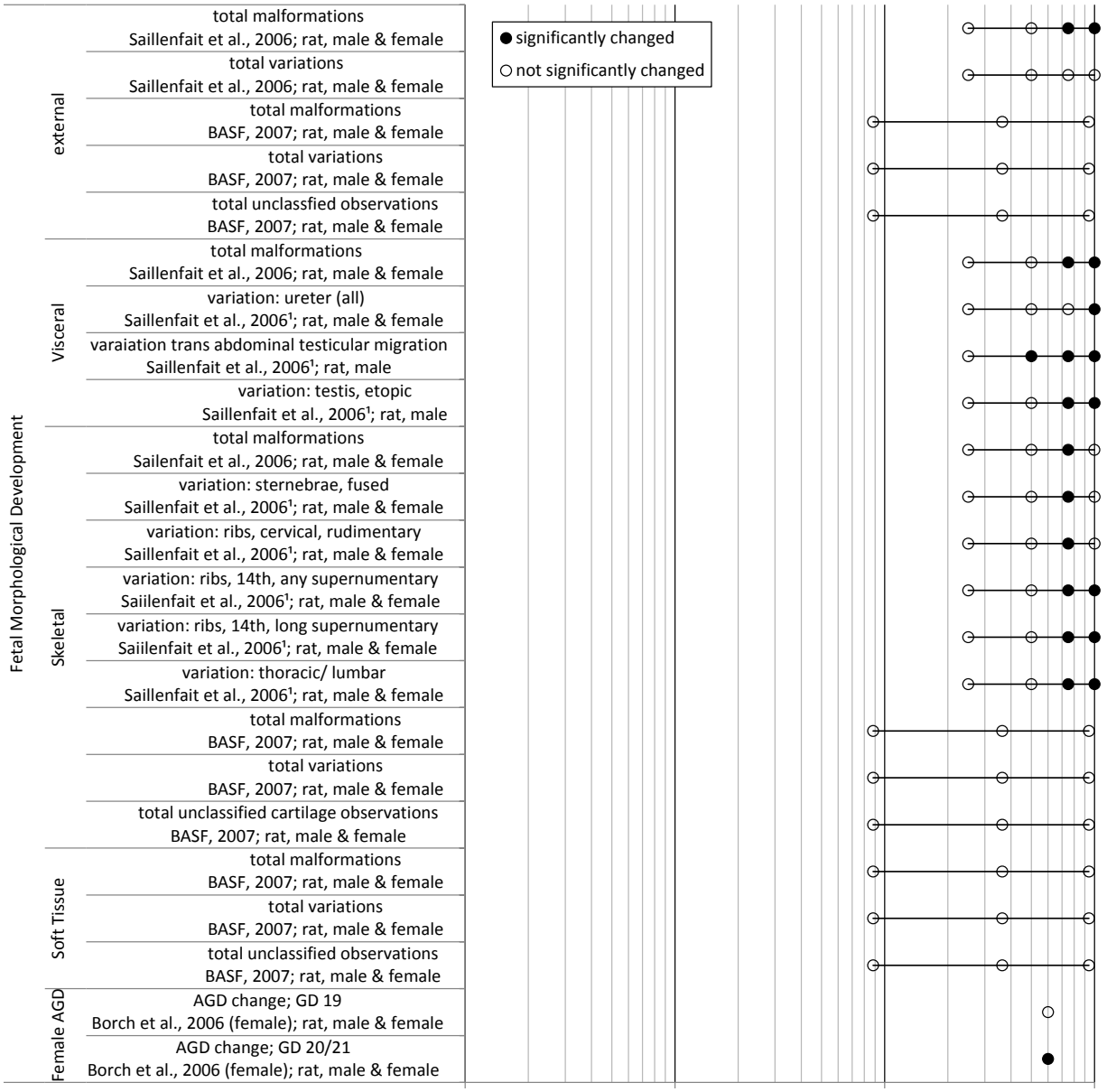


Figure 3-2. Exposure-response array of effects on postnatal and adult body weight following developmental oral exposure to DIBP.



1 Individual variation incidences shown here were included because statistical significance was reported. Incidence for other individual malformations and variations are shown in Table 3-1 (Saillenfait et al., 2006).

Figure 3-3. Exposure-response array of effects on fetal morphological developmental following developmental oral exposure to DIBP.

3.3.2. Male Reproductive Effects

Table 3-18. Evidence pertaining to male reproductive effects in animals following oral exposure to DIBP

Reference and study design	Results[a]		
Morphological development (assessed in fetal or postnatal development or adults)			
Borch et al. (2006)	**AGD change in fetus** *(percent change compared to control)*		
Rat (Wistar); 11–12 dams/group	Doses	0	600
0, 600 mg/kg-day	*At GD 19 (data shown in graph[b])*	0%	−15%**
Gavage	*At GD 20/21 (data shown in graph[b])*	0%	−11%**
GDs 7–19 (GD 19 section) or GDs 7–20/21 (GD 20/21 c-section); 5–6 dams/group per time point	**AGD/cubic root BW change in fetus** *(percent change compared to control)*		
	Doses (M)	0	600
	GD 19 (data shown in graph[b])	0%	−5%
	GD 20/21 (data shown in graph[b])	0%	−9%**
Histologic lesions in fetal testis			
Borch et al. (2006)	**Testicular histological changes** *(incidence; percentage incidence in fetuses)*		
Rat (Wistar); 11–12 dams/group	Doses	0	600
0, 600 mg/kg-day	**Fetuses GD 19**		
Gavage	*clustering of small Leydig cells*	2/13	9/9***
GDs 7–19 (GD 19 section) or GDs 7–20/21 (GD 20/21 c-section); 5–6 dams/group per time point; 1–3 males/litter		15%	100%***
	Sertoli cell vacuolization	0/13	1/9
		0%	11%
	central localization of gonocytes	0/13	2/9
		0%	22%
	multinucleated gonocytes	1/13	0/9
		8%	0%
	Fetuses GD 20/21		

Reference and study design	Results[a]				
	clustering of small Leydig cells	0/10			13/15***
		0%			87%***
	Sertoli cell vacuolization	0/10			14/16***
		0%			88%***
	central localization of gonocytes	0/10			14/16***
		0%			88%***
	multinucleated gonocytes	1/10			10/16*
		10%			63%*
Fetal testicular testosterone production					
Borch et al. (2006) Rat (Wistar); 11–12 dams/group 0, 600 mg/kg-day Gavage GDs 7–19 (GD 19 c-section) or GDs 7–20/21 (GD 20/21 c-section); 5–6 dams/group per time point	**Testicular testosterone (T) content** *(percentage change compared to control)*				
	Doses	0			600
	T content (GD 19 M) (data shown in graph[b])	0%			−70%
	T content (GD 20/21 M) (data shown in graph[b])	0%			−90%***
	Testicular testosterone (T) production *(percentage change compared to control)*				
	Doses	0			600
	testicular T production ex vivo (GD 19 M) (data shown in graph[b])	0%			−21%
	testicular T production ex vivo (GD 20/21 M) (data shown in graph[b])	0%			−96%***
Hannas et al. (2011) Rat (Harlan Sprague-Dawley); 3 dams/group; 3 males/dam 0, 100, 300, 600, 900 mg/kg-day Gavage GDs 14–18	**Fetal testicular testosterone (T) production** *(percentage change compared to control)*				
	Doses	0	100	300	600	900
	T production	0%	10%	−56%**	−80%**	−87%**

Reference and study design	Results[a]					
Hannas et al. (2012) Rat (Sprague-Dawley); 3 dams/group; 3 males/dam 0, 500 mg/kg-day Gavage GDs 14–18	**Fetal testicular testosterone (T) production** *(percentage change compared to control)*					
	Doses	0			500	
	T production (data shown in graph[b])	0%			-73%**	
Howdeshell et al. (2008) Rat (Sprague-Dawley); 5–8 dams/group; 3 males/dam 0, 100, 300, 600, 900 mg/kg-day Gavage GDs 8–18; c-section on GD 18	**Fetal testicular testosterone (T) production** *(percentage change compared to control)*					
	Doses	0	100	300	600	900
	T production (litter mean)	0%	−5%	−40%**	−59%**	−63%**
Morphological development assessed in postnatal development and adults						
Saillenfait et al. (2008) Rat (Sprague-Dawley); 11–14 dams/group 0, 125, 250, 500, 625 mg/kg-day Gavage GDs 12–21 (dams allowed to deliver)	**Postnatal effects** *(percent change in litter mean compared to control)*					
	Doses	0	125	250	500	625
	AGD (PND 1)	0%	−4%	−11%*	−21%**	−22%**
	age at PPS	0%	−4%*	−1%	10%**	6%*
	Postnatal effects *(incidence; percentage incidence)*					
	Doses	0	125	250	500	625
	retained nipples or areolas at PNDs 12–14	0/76	0/78	8/96	47/79	56/76
		0%	0%	8%	59%	74%
	Note: No statistical analysis was reported by the authors for this endpoint.					
	Male adult effects at necropsy *(PNDs 77–84 or 112–119; percentage incidence)*					
	Doses	0	125	250	500	625
	retained nipples or areolas	0/46	0/40	4/55	24/44	29/38
		0%	0%	7%	55%	76%
	hypospadias	0/46	0/40	0/55	5/44	22/39
		0%	0%	0%	11%	56%

Reference and study design	Results[a]					
	exposed os penis	0/46	0/40	0/55	4/44	11/39
		0%	0%	0%	9%	28%
	cleft prepuce	0/46	0/40	0/55	0/44	10/39
		0%	0%	0%	0%	26%
	nonscrotal testis	0/46	0/40	0/55	11/44	30/39
		0%	0%	0%	25%	77%
	Note: No statistical analysis was reported by the authors for this endpoint.					
Histopathologic lesions in adult testis and epididymis						
Saillenfait et al. (2008)	**Adult effects**[c] *(PNDs 77–84; incidence)*					
Rat (Sprague-Dawley); 11–14 dams/group	Doses	0	125	250	500	625
0, 125, 250, 500, 625 mg/kg-day	*number of males (litters) examined*	24 (12)	20 (10)	28 (14)	22 (11)	20 (10)
Gavage	**Epididymides** *(number of males with effect)*					
GDs 12–21 (dams allowed to deliver)	Doses	0	125	250	500	625
	oligospermia	0	1	3	2	1
	azoospermia	0	1	3	10	18
	granulomatous inflammation	0	0	0	4	3
	Testes *(number of males with effect)*					
	Doses	0	125	250	500	625
	tubular degeneration-atrophy/ hypoplasia	2	2	7	16	20
	tubular necrosis	0	0	1	3	5
	interstitial cell hyperplasia	0	0	0	1	9
	Note: No statistical analysis was reported by the authors for these endpoints.					

Reference and study design	Results[a]					
Testes weight						
Zhu et al. (2010) Rat (Sprague-Dawley) Mouse (C57Bl/6N) (number of animals not specified) 0, 100, 300, 500, 800, 1,000 mg/kg-day Gavage 7 days	**Testes weight at 7 days** *(percent change compared to control)*					
	Doses	0	100	300	500	800	1,000
	Rat, *absolute weight (data shown in graph[b])*	0%	−3%	−10%	−22%***	−32%***	−44%***
	Mouse, *absolute weight(data shown in graph[b])*	0%	0%	10%	6%	4%	−22%**
	Note: Relative weight not reported by study authors.						
(Foster et al. (1982); Foster et al. (1981)) MIBP Rat (Sprague-Dawley); 6 males/group 0, 800 mg/kg-day Gavage 6 days	**Testes weight** *(percent change compared to control)*		
	Doses	0	800
	absolute weight	0%	−28%***
	relative weight	0%	−27%***
Oishi and Hiraga (1980c) Rat (JCL:Wistar); 10 males/treated group; 20 control males 0, 2% (0, 1,200 mg/kg-day)[d] Diet 1 week	**Testes weight** *(percent change compared to control)*		
	Doses	0	1,200
	absolute weight	0%	−37%*
	relative weight	0%	−33%*
Oishi and Hiraga (1980d) MIBP Rat (JCL:Wistar); 10 males/group 0, 2% in diet (0, 1,100 mg/kg-day)[d] Diet 1 week	**Testes weight** *(percent change compared to control)*		
	Doses	0	1,100
	absolute weight	0%	−47%*
	relative weight	0%	−40%*
Oishi and Hiraga (1980a) Mouse (JCL:ICR); 10 males/group 0, 2% (0, 2,100 mg/kg-day)[d] Diet 1 week	**Testes weight** *(percent change compared to control)*		
	Doses	0	2,100
	relative weight	0%	29%*

Reference and study design	Results[a]					
Oishi and Hiraga (1980b)	**Testes weight** *(percent change compared to control)*					
MIBP Mouse (JCL:ICR); 10 males/group	Doses			0		2,000
0, 2% (0, 2,000 mg/kg-day)[d]	*relative weight*			0%		45%*
Diet						
1 week						
Saillenfait et al. (2008)	**Male reproductive organ weights** *(percent change compared to control)*					
Sprague-Dawley rats; 11–14 dams/group	Doses	0	125	250	500	625
0, 125, 250, 500, 625 mg/kg-day	*right testis weight*	0%	1%	0%	−22%	−52%**
Gavage	*right epididymal weight*	0%	−2%	−6%	−22%**	−49%**
GDs 12–21 (dams allowed to deliver)	*left testis weight*	0%	−2%	−1%	−13%	−59%**
Assessed PNDs 77–84 (adults) after in utero exposure	*left epididymal weight*	0%	−4%	−8%	−16%**	−49%**
	seminal vesicles	0%	1%	−6%	−18%**	−33%**
	prostate	0%	−10%	−11%*	−16%**	−30%**
University of Rochester (1954)	**Testes weight at 4 months** *(percent change compared to control)*					
Rat (Albino; no other strain designation); 5 males/group	Doses		0[h]	65	710	5,800
0, 0.1, 1, 5% (0, 65, 710, 5,800 mg/kg-day)[e]	*absolute weight*		0%	2%	−1%	−70%
	relative weight		0%	1%	12%	−45%
Diet	Note: Statistical analysis not reported in study.					
Weaning to 4 months post-weaning						
Seminal vesicle weight						
(Foster et al. (1982); Foster et al. (1981))	**Seminal vesicle weight** *(percent change compared to control)*					
MIBP Rat (Sprague-Dawley); 6 males/group	Doses			0		800
0, 800 mg/kg-day	*absolute weight*			0%		−18%
Gavage	*relative weight*			0%		−11%
6 days						

Reference and study design	Results[a]		
Prostate weight			
(Foster et al. (1982); Foster et al. (1981)) MIBP Rat (Sprague-Dawley); 6 males/group 0, 800 mg/kg-day Gavage 6 days	**Prostate weight** *(percent change compared to control)*		
	Doses	0	800
	absolute weight	0%	−13%
	relative weight	0%	4%
Testosterone concentration in adults			
Oishi and Hiraga (1980c) Rat (JCL:Wistar); 10 treated males; 20 control males 0, 2% (0, 1,200 mg/kg-day)[d] Diet 1 week	**Testosterone (T) concentration** *(percent change compared to control)*		
	Doses	0	1,200
	serum T concentration (data shown in graph[b])	0%	19%
	testicular T concentration (data shown in graph[b])	0%	158%*
	Dihydrotestosterone (DHT) concentration *(percent change compared to control)*		
	Doses	0	1,200
	serum DHT concentration (data shown in graph[b])	0%	40%
Oishi and Hiraga (1980d) MIBP Rat (JCL:Wistar); 10 males/group 0, 2% (0, 1,100 mg/kg-day)[d] Diet 1 week	**Testosterone (T) concentration** *(percent change compared to control)*		
	Doses	0	1,100
	serum T concentration (data shown in graph[b])	0%	61%*
	testicular T concentration (data shown in graph[b])	0%	161%*
Oishi and Hiraga (1980a) Mouse (JCL:ICR); 10 males/group 0, 2% (0, 2,100 mg/kg-day)[d] Diet 1 week	**Testicular testosterone (T) concentration** *(percent change compared to control)*		
	Doses	0	2,100
	T concentration	0%	7%
Oishi and Hiraga (1980b) MIBP Mouse (JCL:ICR); 10 males/group 0, 2% (0, 2,000 mg/kg-day)[d]	**Testicular testosterone (T) concentration** *(percent change compared to control)*		
	Doses	0	2,000
	T concentration	0%	−83%*

Reference and study design	Results[a]		
Diet 1 week			
Testes histology in adults			
(Foster et al. (1982); Foster et al. (1981)) MIBP Rat (Sprague-Dawley); 6 males/group 0, 800 mg/kg-day Gavage 6 days	**Number of animals with atrophy of seminiferous tubules**		
	Doses	0	800
	0% atrophic tubules	6/6	0/6
	<50% atrophic tubules	0/6	3/6
	>50% atrophic tubules	0/6	3/6
	The study authors noted marked atrophy of the majority of the seminiferous tubules with decreased spermatocytes and decreased spermatogonia (data not shown).		
Oishi and Hiraga (1980c) Rat (JCL:Wistar); 10 treated males; 20 control males 0, 2% (0, 1,212 mg/kg-day)[d] Diet 1 week	The testes showed decreased spermatocytes and decreased spermatogonia compared to control (quantitative results not provided).		

[a]Percent change compared to control = $\frac{\text{treated value} - \text{control value}}{\text{control value}} \times 100$

[b]GrabIt Software used to estimate % change from graph.

[c]PNDs 112−119 males were also evaluated for these endpoints (see Saillenfait et al., 2008, Table 4).

[d]Dose conversions were performed by EPA using this information: (Oishi and Hiraga (1980a), 1980c)) average BWs over the week-long studies were 132 and 24 g for rats and mice, respectively, and the default food consumption rates of 0.008 kg/day for male weanling Wistar rats and 0.0025 kg/day for male weanling B6C3F$_1$ mice were applied (U.S. EPA, 1988). (Oishi and Hiraga (1980b), 1980d)) average BWs for rats and mice in these studies were 145 and 25 g, respectively, and the default food consumption rates of 0.008 kg/day for male weanling Wistar rats and 0.0025 kg/day for male weanling B6C3F$_1$ mice (U.S. EPA, 1988) were applied. Note that Table 1-6 of U.S. EPA (1988) listed the default food consumption rate for male weanling Wistar rats as 0.080 kg/day. However, it was later determined using an equation in Table 1-3 of the document that this value was actually supposed to be 0.008 kg/day.

[e]Dose conversions were performed by EPA using this information: University of Rochester (1954) average BWs (measured at least once weekly) of the rats were 269, 277, 252, and 155 g for males, and 178, 170, 182, and 148 g for females at 0, 0.1, 1.0, and 5.0%, respectively; and the default food consumption rates of 0.018 kg/day for male rats and 0.014 kg/day for female rats (U.S. EPA, 1988) for an unspecified strain in a sub-chronic study were applied.

* = Statistically significant difference at $p < 0.05$ from control value, as reported by study authors; ** = Statistically significant difference at $p < 0.01$ from control value, as reported by study authors; *** = Statistically significant difference at $p < 0.001$ from control value, as reported by study authors.

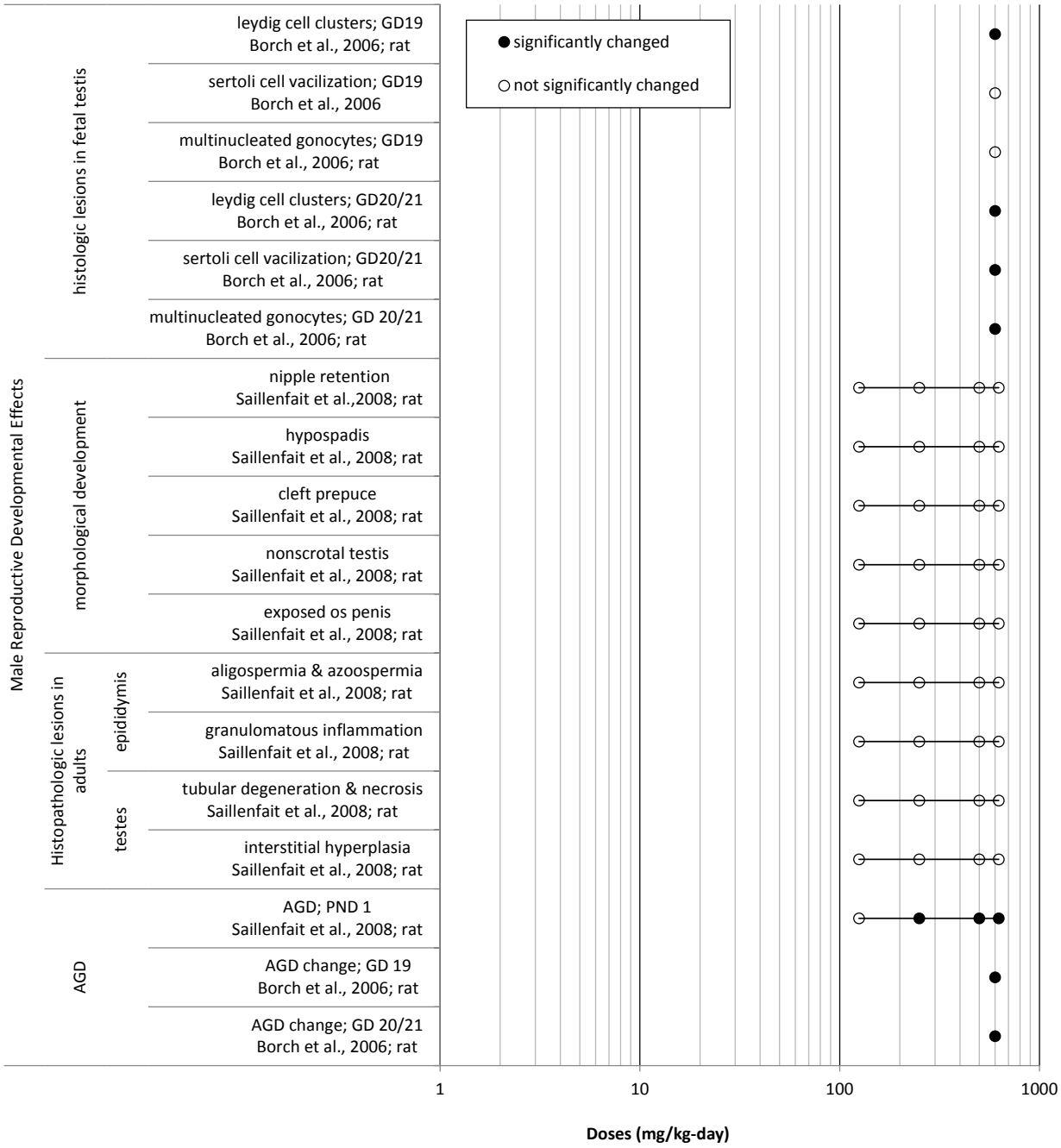


Figure 3-4. Exposure-response array of effects on male reproductive development following developmental oral exposure to DIBP.

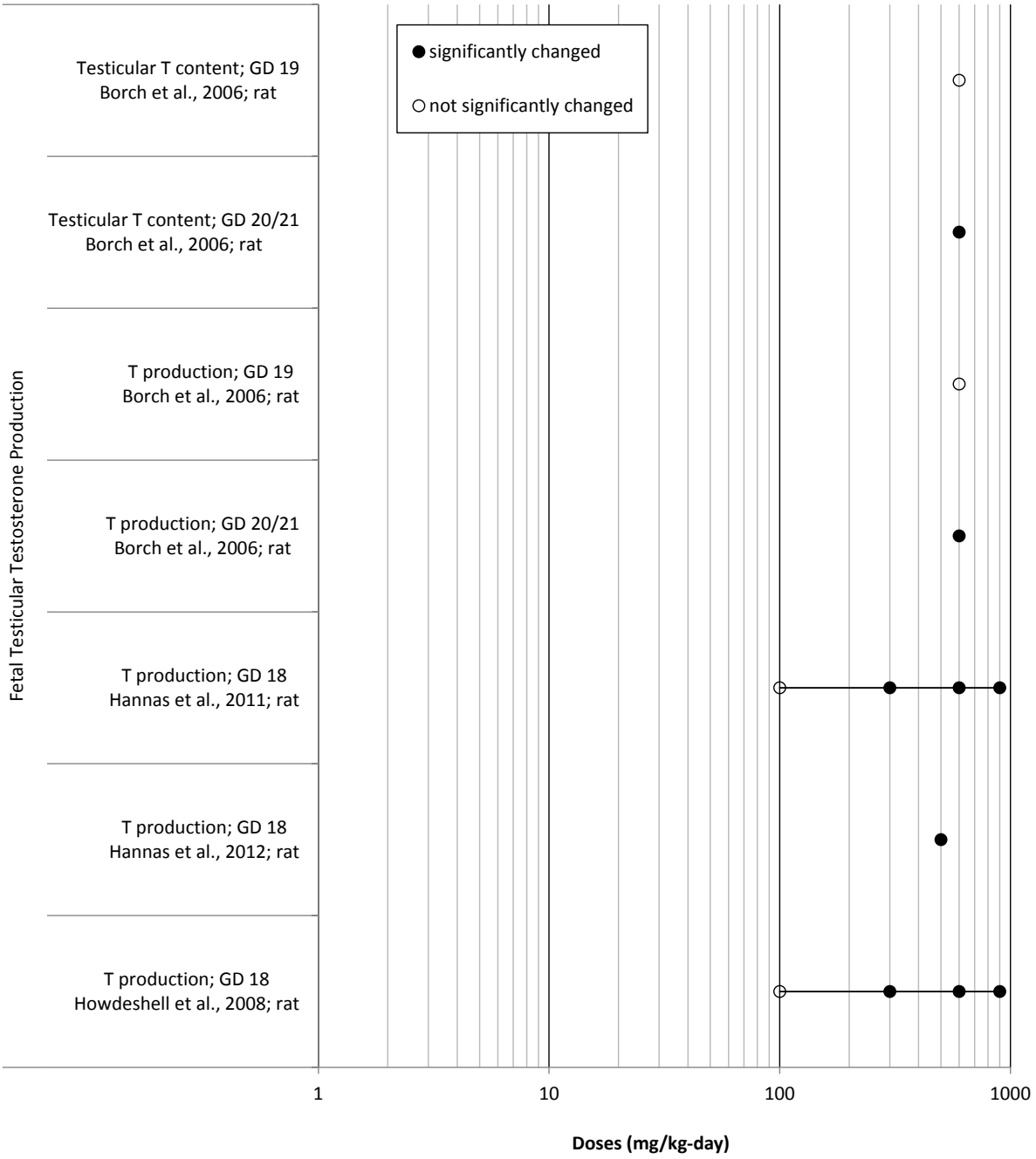


Figure 3-5. Exposure-response array of effects on fetal testosterone (T) following developmental oral exposure to DIBP.

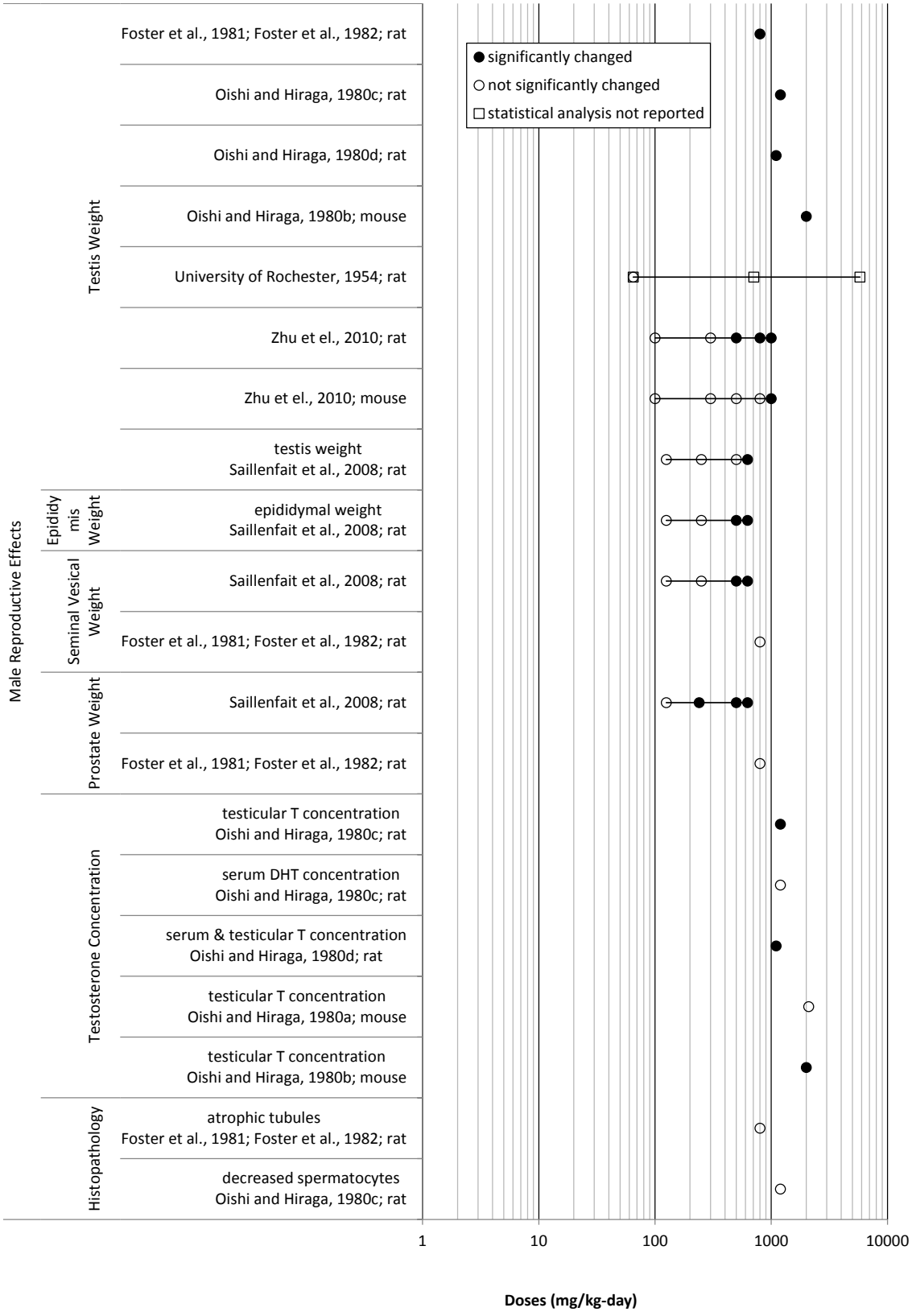


Figure 3-6. Exposure-response array of male reproductive effects following oral exposure to DIBP.

3.3.3. Female Reproductive Effects

Table 3-19. Evidence pertaining to female reproductive effects in animals following oral exposure to DIBP

Reference and study design	Results					
Maternal weight[a]						
Howdeshell et al. (2008) Rat (Sprague-Dawley); 5–8 dams/group 0, 100, 300, 600, 900 mg/kg-day Gavage GDs 8–18 (GD 18 c-section)	**Maternal body weight** *(percent change compared to control[b])*					
	Doses	0	100	300	600	900
	maternal BW gain GDs 8–18	0%	9%	4%	−35%	−42%*
Borch et al. (2006) Rat (Wistar); 11–12 dams/group 0, 600 mg/kg-day Gavage GDs 7–19 (GD 19 c-section) or GDs 7–20/21 (GD 20/21 c-section); 5–6 dams/group per time-point	**Maternal body weight**					
	Doses	0			600	
		—	*No significant effect on maternal weight gain during pregnancy (quantitative data not reported by study authors)*			
BASF (2007)[c] Rat (Wistar); 22–23 dams/group 0, 88, 363, 942 mg/kg-day Diet GDs 6–20 (GD 20 c-section)	**Maternal body weight** *(percent change compared to control[b])*					
	Doses	0		88	363	942
	BW change GDs 6–20	0%		−3%	−6%	−11%*
	gravid uterine weight	0%		−3%	−8%	−3%
	corrected BW gain GDs 6–20[d]	0%		−2%	−2%	−25%*
Saillenfait et al. (2008) Rat (Sprague-Dawley); 11–14 dams/group 0, 125, 250, 500, 625 mg/kg-day Gavage GDs 12–21 (dams allowed to deliver)	**Maternal body weight** *(percent change compared to control[b])*					
	Doses	0	125	250	500	625
	BW gain GDs 12–21	0%	4%	6%	6%	−3%

Reference and study design	Results					
Saillenfait et al. (2006)	**Maternal body weight** *(percent change compared to control[b])*					
Rat (Sprague-Dawley); 20–22 dams/group	Doses	0	250	500	750	1,000
0, 250, 500, 750, 1,000 mg/kg-day	*BW gain GDs 6–21*	0%	−1%	−14%	−14%	−39%**
Gavage	*gravid uterine weight*	0%	−2%	−19%*	−28%**	−61%**
GDs 6–20 (GD 21 c-section)	*corrected BW gain GDs 6–21[e]*	0%	0%	0%	19%	19%
	Maternal food consumption					
	Doses	0	250	500	750	1,000
	food consumption every 4–6 days, GDs 0–21	–	*No statistically significant change from control*			
Maternal toxicity						
BASF (2007)[c]	**Abnormalities in dams examined at necropsy**					
Rat (Wistar); 25 females/group	Doses	0	88	363	942	
0, 88, 363, 942 mg/kg-day	*abnormalities (incidence) Observed: hemorrhagic thymus, diaphragmatic hernia, and dilated renal pelvis*	0/25	2/25	0/25	2/25	
Diet	*abnormalities (percent incidence)*	0%	8%	0%	8%	
GDs 6–20 (GD 20 c-section)	Note: Statistical analysis was not performed on these data					
Fertility/fetal survival						
BASF (2007)[c]	**Fertility** *(percent change compared to control[b])*					
Rat (Wistar); 25 dams/group	Doses	0	88	363	942	
0, 88, 363, 942 mg/kg-day	*percentage pregnant*	23/25	22/25	22/25	23/25	
Diet	**Fetal survival** *(incidence)*					
GDs 6–20 (GD 20 c-section) Note: BW and food consumption measured every 1–3 days through GD 20	Doses	0	88	363	942	
	dams with all resorptions	0/23	0/22	0/22	0/23	
	Fetal survival *(percent change compared to control[b])*					
	Doses	0	88	363	942	
	percentage preimplantation loss/litter	0%	−19%	25%	−30%	
	percentage postimplantation loss/litter	0%	36%	105%	16%	
	percentage resorptions/litter	0%	36%	105%	16%	
	number of live fetuses/litter	0%	0%	−8%	2%	
	number of live male fetuses/litter	0%	5%	2%	−2%	

Reference and study design	Results					
Borch et al. (2006)	**Fertility** *(incidence)*					
Rat (Wistar); 16 dams/group	Doses	0			600	
	number pregnant/dams mated	11/16			12/16	
	Fetal survival					
	Doses	0			600	
0, 600 mg/kg-day Gavage GDs 7–19 (GD 19 c-section) or GDs 7–20/21 (GD 20/21 c-section); 5–6 dams/group per time-point)		—	*No significant effect on litter size, fetal viability, or number of resorptions (quantitative data not reported by study authors)*			
Howdeshell et al. (2008)	**Fetal survival** *(n litters evaluated for endpoint)*					
Rat (Sprague-Dawley); 5–8 dams/group	Doses	0	100	300	600	900
	dams with whole litter loss/total dams	0/5	0/8	0/5	0/5	1/5
0, 100, 300, 600, 900 mg/kg-day	*number of implantations/litter*	13.7 (3)	14.8 (4)	16.0 (3)	12.7 (3)	13.3 (5)
	number of live fetuses/litter	13.3 (3)	13.5 (4)	15.3 (3)	9.3 (3)	5.0* (3)
Gavage	*total resorptions/litter*	0.2 (5)	1.0 (8)	0.4 (5)	2.0 (5)	7.8* (5)
GDs 8–18 (GD 18 c-section)	*percentage fetal mortality per litter*	1.3% (3)	4.6% (4)	2.7% (3)	17.2% (5)	59.0%* (5)
Saillenfait et al. (2006)	**Fertility**					
Rat (Sprague-Dawley); 23–24 dams/group	Doses	0	250	500	750	1,000
0, 250, 500, 750, 1,000 mg/kg-day	*number pregnant/mated dams (percent)*	22/24 (91.7%)	22/24 (91.7%)	22/23 (95.7%)	21/23 (91.3%)	20/24 (83.3%)
Gavage	**Fetal survival** *(percent incidence)*					
GDs 6–20 (GD 21 c-section)	Doses	0	250	500	750	1,000
	percentage postimplantation loss/litter	6.7%	11.0%	13.9%	28.2%**	59.6%**
	percentage dead fetuses per litter	0%	0%	0.3%	0.7%	0.3%
	percentage resorptions/litter	6.7%	11.0%	13.6%	27.6%**	59.3%**
	Fetal survival *(percent change compared to control[b])*					
	Doses	0	250	500	750	1,000
	percentage live litters	0%	−5%	−5%	0%	−10%
	number of live fetuses/litter	0%	2%	−12%	−21%*	−52%**
	percentage male fetuses/litter	0%	−4%	−5%	0%	17%

Reference and study design	Results					
Saillenfait et al. (2008)	**Fetal survival** *(percent change compared to control[b])*					
Rat (Sprague-Dawley); 11–14 dams/group	Doses	0	125	250	500	625
	gestation length	0%	1%	0%	0%	1%
0, 125, 250, 500, 625 mg/kg-day	*percentage postimplantation loss per litter*	0%	41%	−35%	−31%	−13%
Gavage	*percentage pups born alive per litter*	0%	−1%	−4%	−1%	−8%
GDs 12–21 (dams allowed to deliver)	*live pups/litter at PND 1*	0%	5%	0%	8%	1%

[a]Some studies measured BW at multiple timepoints/lifestages and not all of these data are presented here. For the sake of comparability of data across the available studies, BW data measures presented are similar across studies and/or measures of BW change over the dosing period or greatest time period.

[b]Percent change compared to control = $\frac{\text{treated value} - \text{control value}}{\text{control value}} \times 100$

[c]BASF (2007): Dams in the 952 mg/kg-day group showed significantly decreased food consumption on days 10–13 and 15–17 (<10% decreased compared to control); however, overall food consumption did not differ between groups.

[d]Corrected weight gain = carcass weight (GD 20 body weight − gravid uterine weight) − GD 6 body weight.

[e]Corrected weight gain = BW gain GDs 6–21 − gravid uterine weight.

* = Statistically significant difference at $p < 0.05$ from control value, as reported by study authors; ** = Statistically significant difference at $p < 0.01$ from control value, as reported by study authors; *** = Statistically significant difference at $p < 0.001$ from control value, as reported by study authors.

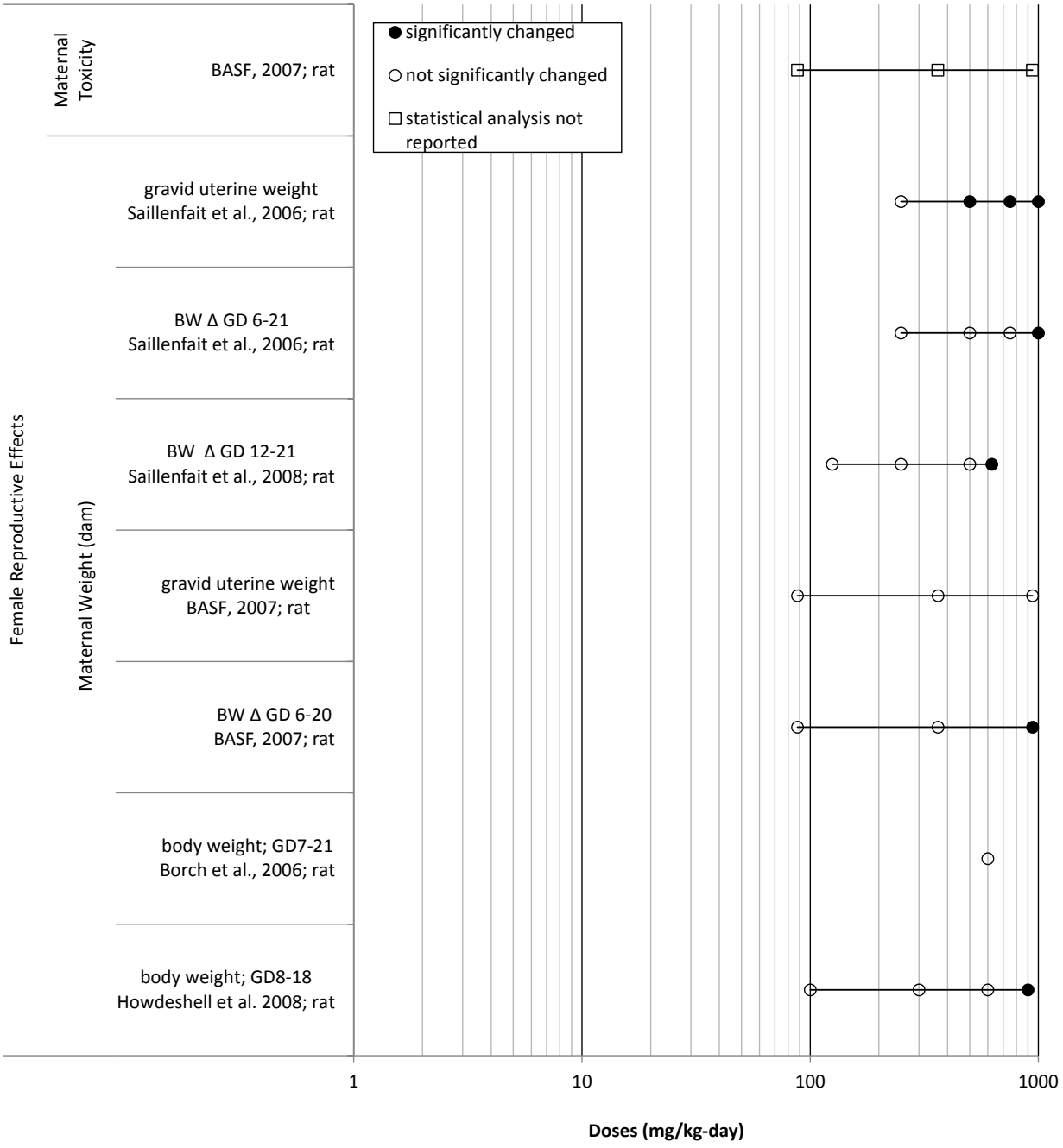


Figure 3-7. Exposure-response array of female reproductive effects, maternal weight and toxicity, following oral exposure to DIBP.

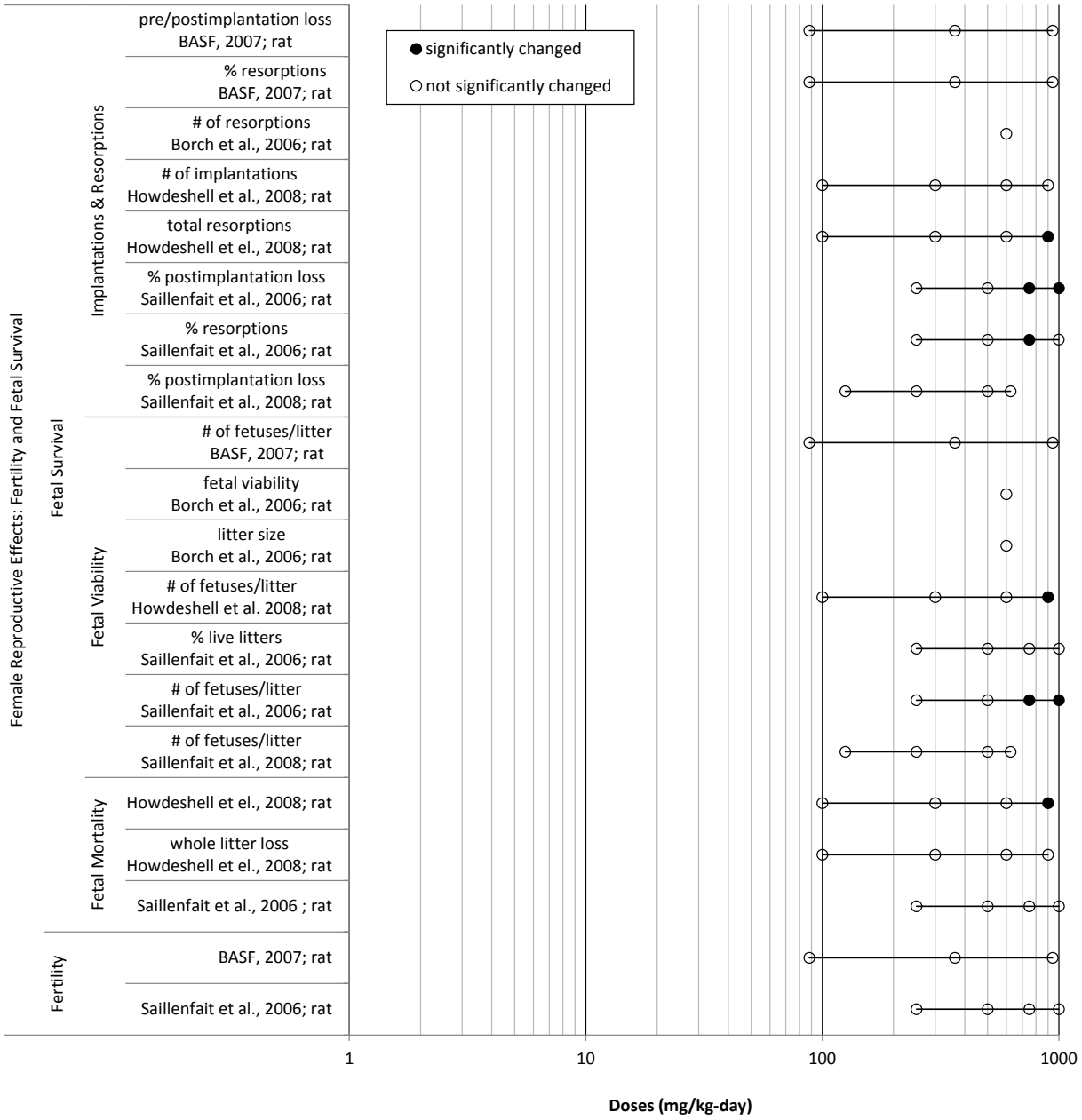


Figure 3-8. Exposure-response array of female reproductive effects, fertility and fetal survival, following oral exposure to DIBP.

3.3.4. Liver Effects

Table 3-20. Evidence pertaining to hepatic effects in animals following oral exposure to DIBP

Reference and study design	Results				
Liver weight					
Foster et al. (1982); Foster et al. (1981) MIBP Rat (Sprague-Dawley); 6 males/group 0, 800 mg/kg-day Gavage 4 days	**Liver weight** *(percent change compared to control[a])*				
	Doses	0			800
	relative weight	0			30%***
Oishi and Hiraga (1980c) Rat (JCL:Wistar); 10 treated males; 20 control males 0, 2% (0, 1,200 mg/kg-day)[b] Diet 1 week	**Liver weight** *(percent change compared to control[a])*				
	Doses	0			1,200
	absolute weight	0%			27%*
	relative weight	0%			35%*
Oishi and Hiraga (1980a) Mouse (JCL:ICR); 10 males/group 0, 2% (0, 2,100 mg/kg-day)[b] Diet 1 week	**Liver (with gallbladder) weight** *(percent change compared to control[a])*				
	Doses			0	2,100
	relative weight			0%	45%*
Oishi and Hiraga (1980b) MIBP Mouse (JCL:ICR); 10 males/group 0, 2% (0, 2,000 mg/kg-day)[b] Diet 1 week	**Liver weight** *(percent change compared to control[a])*				
	Doses			0	2,000
	relative weight			0%	30%*
University of Rochester (1954) Rat (Albino; no other strain designation); 5 males and 5 females/dose 0, 0.1, 1, 5% (0, 65, 710, 5,800 mg/kg-day for males; 0, 82, 770, 4,700 mg/kg-day for females)[c] Diet Weaning to 4 months post-weaning	**Liver weight** *(percent change compared to control[a])*				
	Doses (M)	0	65	710	5,800
	absolute weight	0%	6%	11%	5%
	relative weight	0%	2%	22%	84%
	Doses (F)	0[f]	82	770	4,700
	absolute weight	0%	0%	16%	41%

Reference and study design	Results
	relative weight 0% 0% 8% 62% Note: Statistical analysis not reported in study.
University of Rochester (1953) Rat (Albino; no other strain designation); 5 males/dose 0, 0.01, 0.1, 1, 2, 5% (0, 15, 140, 1,400, 3,000, 8,900 mg/kg-day)[d] Diet Weaning to 1 month post-weaning	**Liver weight** *(percent change compared to control[a])* Doses 0 15 140 1,400 3,000 8,900 *absolute weight* 0% −17% −12% 5% 15% 13% *relative weight* 0% −1% 5% 26% 43% 79% Note: Statistical analysis not reported in study.
Liver histopathology	
University of Rochester (1954) Rat (Albino; no other strain designation); 5 males and 5 females/dose 0, 0.1, 1, 5% (0, 65, 710, 5,800 mg/kg-day for males; 0, 82, 770, 4,700 mg/kg-day for females)[c] Diet Weaning to 4 months post-weaning	**Liver histopathology** *No treatment-related differences from control were observed at any dose group.* Note: 4–5 animals per dose group were assessed. Statistical analysis not reported in study.
University of Rochester (1953) Rat (Albino; no other strain designation); 5 males/dose 0, 0.01, 0.1, 1, 2, 5% (0, 15, 140, 1,400, 3,000, 8,900 mg/kg-day)[d] Diet Weaning to 1 month post-weaning	**Liver histopathology** *Histopathological findings only noted in the control group. No treatment-related differences were observed.* Notes: Number of animals assessed is unclear. Findings limited to "filled with coarse granular cytoplasm." Statistical analysis not reported in study.

[a]Percent change compared to control = $\frac{\text{treated value} - \text{control value}}{\text{control value}} \times 100$

[b]Dose conversions were performed using this information: (Oishi and Hiraga (1980a), 1980c)) average BWs over the week-long studies were 132 and 24 g for rats and mice, respectively, and the default food consumption rates of 0.008 kg/day for male weanling Wistar rats and 0.0025 kg/day for male weanling B6C3F$_1$ mice were applied (U.S. EPA, 1988). Oishi and Hiraga (1980b) average BWs for rats and mice in these studies were 145 and 25 g, respectively, and the default food consumption rates of 0.008 kg/day for male weanling Wistar rats and 0.0025kg/day for male weanling B6C3F$_1$ mice (U.S. EPA, 1988) were applied. Note that Table 1-6 of U.S. EPA (1988) listed the default food consumption rate for male weanling Wistar rats as 0.080 kg/day. However, it was later determined using an equation in Table 1-3 of the document that this value was actually supposed to be 0.008 kg/day.

[c]Dose conversions were performed using this information: University of Rochester (1954) average BWs (measured at least once weekly) were 269, 277, 252, and 155 g for male rats, and 178, 170, 182, and 148 g for female rats at

0, 0.1, 1.0, and 5.0%, respectively; and the default food consumption of 0.018 for male and 0.014 kg/day for female rats (U.S. EPA, 1988) of an unspecified strain in a subchronic study were applied.

[d]Dose conversions were performed using this information: University of Rochester (1953) average BWs (measured weekly) of the rats were 139, 124, 127, 127, 121, and 101 g at 0, 0.01, 0.1, 1.0, 2.0, and 5.0%, respectively; and the default food consumption of 0.018 for male rats and 0.014 kg/day for female rats (U.S. EPA, 1988) of an unspecified strain in a subchronic study were applied.

* = Statistically significant difference at $p < 0.05$ from control value, as reported by study authors; ** = Statistically significant difference at $p < 0.01$ from control value, as reported by study authors; *** = Statistically significant difference at $p < 0.001$ from control value, as reported by study authors.

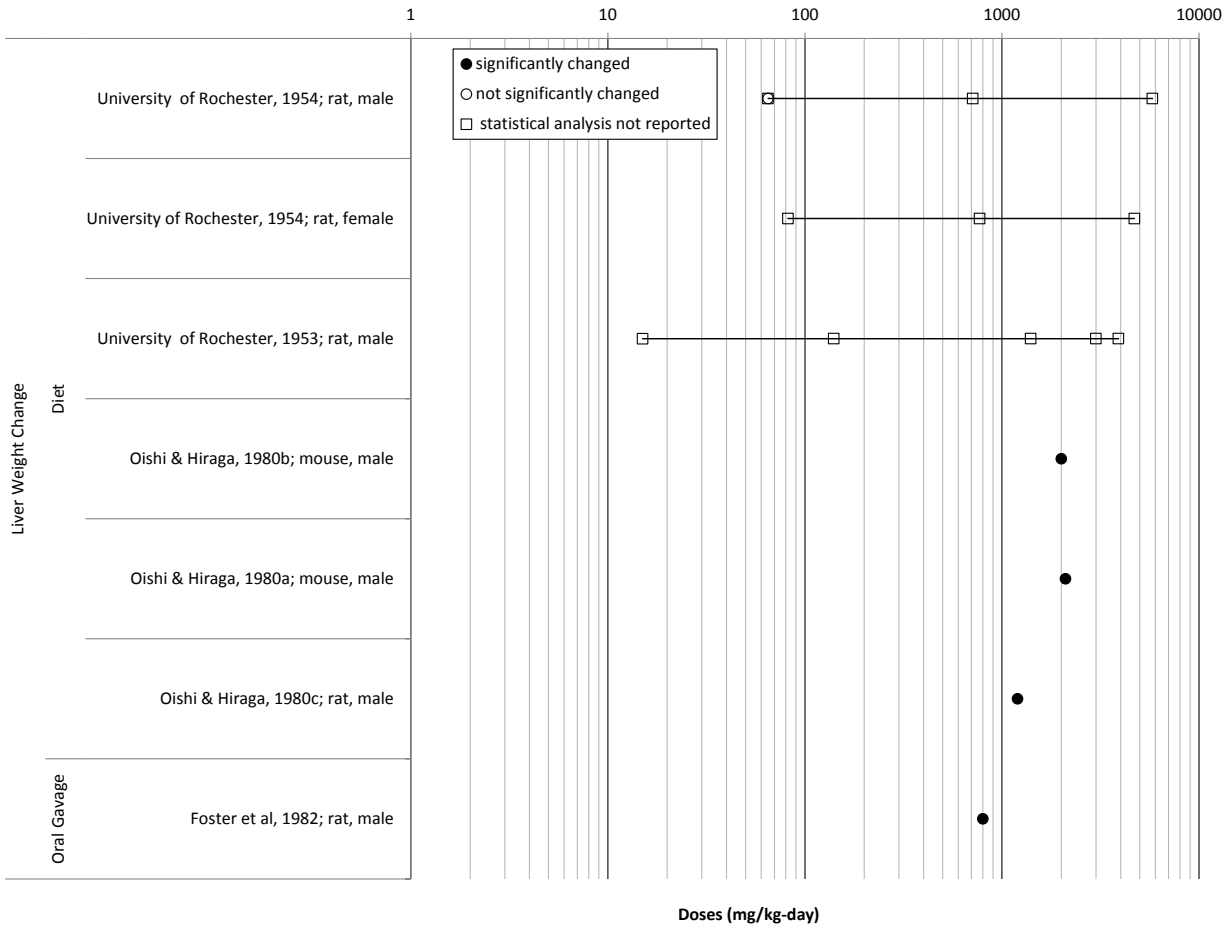


Figure 3-9. Exposure-response array of liver effects following oral exposure to DIBP.

3.3.5. Kidney Effects

Table 3-21. Evidence pertaining to renal effects in animals following oral exposure to DIBP

Reference and study design	Results				
Kidney weight					
Foster et al. (1982); Foster et al. (1981) MIBP Rat (Sprague-Dawley); 6 males/group 0, 800 mg/kg-day Gavage 4 days	**Kidney weight** *(percent change compared to control[a])*				
	Doses	0			800
	relative weight	0			396%***
Oishi and Hiraga (1980c) Rat (JCL:Wistar); 10 treated males; 20 control males 0, 2% (0, 1,200 mg/kg-day)[b] Diet 1 week	**Kidney weight** *(percent change compared to control[a])*				
	Doses			0	1,200
	absolute weight			0%	−5%
	relative weight			0%	2%
Oishi and Hiraga (1980b) MIBP Mouse (JCL:ICR); 10 males/group 0, 2% (0, 2,000 mg/kg-day)[b] Diet 1 week	**Kidney weight** *(percent change compared to control[a])*				
	Doses			0	2,000
	relative weight			0%	−5%
Oishi and Hiraga (1980a) Mouse (JCL:ICR); 10 males/group Diet 0, 2% (0, 2,100 mg/kg-day)[b] 1 week	**Kidney weight** *(percent change compared to control[a])*				
	Doses			0	2,100
	relative weight			0%	−10%*
University of Rochester (1954) Rat (Albino; no other strain designation); 5 males and 5 females/dose 0, 0.1, 1, 5% (0, 65, 710, 5,800 mg/kg-day for males; 0, 82, 770, 4,700 mg/kg-day for females)[c] Diet	**Kidney weight** *(percent change compared to control[a])*				
	Doses (M)	0	65	710	5,800
	absolute weight	0%	10%	9%	−31%
	relative weight	0%	7%	20%	22%

Reference and study design	Results						
Weaning to 4 months post-weaning	Doses (F)	0	82	770	4,700		
	absolute weight	0%	4%	11%	−2%		
	relative weight	0%	5%	4%	13%		
	Note: Statistical analysis not reported in study.						
University of Rochester (1953)	**Kidney weight** *(percent change compared to control[a])*						
Rat (Albino; no other strain designation); 5 males/dose	Doses	0	15	140	1,400	3,000	8,900
0, 0.01, 0.1, 1, 2, 5% (0, 15, 142, 1,417, 2,975, 8,911 mg/kg-day)[d]	*absolute weight*	0%	−14%	−11%	−11%	−11%	−23%
Diet	*relative weight*	0%	3%	7%	7%	12%	23%
Weaning to 1 month post-weaning	Note: Statistical analysis not reported in study.						
Kidney histopathology							
University of Rochester (1954)	**Kidney histopathology**						
Rat (Albino; no other strain designation); 5 males and 5 females/dose	*No treatment-related differences in males or females were observed compared with control.*						
0, 0.1, 1, 5% (0, 65, 710, 5,800 mg/kg-day for males; 0, 82, 770, 4,700 mg/kg-day for females)[c]	Note: 4−5 animals per dose group were assessed. Findings in males limited to pyelitis, granuloma, and pyelonephritis; Findings in females limited to pyelitis and pyelonephritis.						
Diet							
Weaning to 4 months post-weaning							
University of Rochester (1953)	**Kidney histopathology**						
Rat (Albino; no other strain designation); 5 males/dose	*No treatment-related differences were observed.*						
0, 0.01, 0.1, 1, 2, 5% (0, 15, 142, 1,417, 2,975, 8,911 mg/kg-day)[d]	Note: Number of animals assessed is unclear. Findings limited to eosinophils and inflammatory cells. Statistical analysis not reported in study.						
Diet							
Weaning to 1 month post-weaning							

[a]Percent change compared to control = $\frac{\text{treated value} - \text{control value}}{\text{control value}} \times 100$

[b]Dose conversions were performed using this information: (Oishi and Hiraga (1980a), 1980c)) average BWs over the week-long studies were 132 and 24 g for rats and mice, respectively, and the default food consumption rates of 0.008 kg/day for male weanling Wistar rats and 0.0025 kg/day for male weanling B6C3F$_1$ mice were applied (U.S. EPA, 1988). Oishi and Hiraga (1980b) average BWs for rats and mice in these studies were 145 and 25 g, respectively, and the default food consumption rates of 0.008 kg/day for male weanling Wistar rats and 0.0025 kg/day for male weanling B6C3F$_1$ mice (U.S. EPA, 1988) were applied. Note that Table 1-6 of U.S. EPA (1988) listed the default food consumption rate for male weanling Wistar rats as 0.080 kg/day. However, it was later

determined using an equation in Table 1-3 of the document that this value was actually supposed to be 0.008 kg/day.

[c]Dose conversions were performed using this information:University of Rochester (1954) average BWs (measured at least once weekly) were 269, 277, 252, and 155 g for male rats, and 178, 170, 182, and 148 g for female rats at 0, 0.1, 1.0, and 5.0%, respectively; and default food consumption of 0.018 kg/day for male rats and 0.014 kg/day for female rats (U.S. EPA, 1988) of an unspecified strain in a subchronic study were applied.

[d]Dose conversions were performed using this information: University of Rochester (1953) average BWs (measured weekly) were 139, 124, 127, 127, 121, and 101 g at 0, 0.01, 0.1, 1.0, 2.0, and 5.0%, respectively; and default food consumption of 0.018 for male rats and 0.014 kg/day for female rats (U.S. EPA, 1988) of an unspecified strain in a subchronic study were applied.

* = Statistically significant difference at $p < 0.05$ from control value, as reported by study authors.

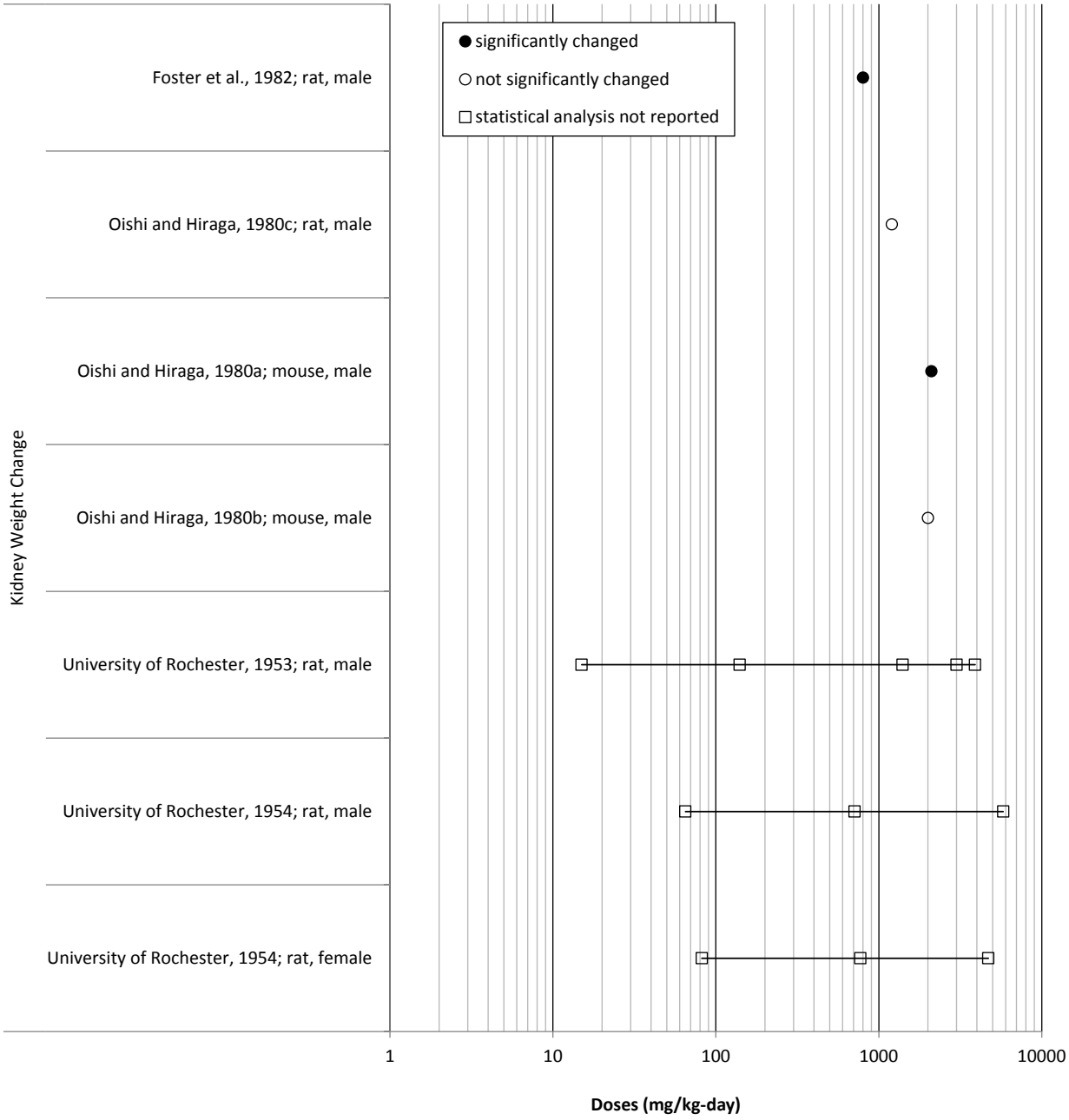


Figure 3-10. Exposure-response array of kidney effects following oral exposure to DIBP.

3.3.6. Hematopoietic Effects

Table 3-22. Evidence pertaining to hematopoietic effects in animals following oral exposure to DIBP

Reference and study design	Results				
Hematology					
University of Rochester (1954) Rat (Albino; no other strain designation); 5 males and 5 females/dose 0, 0.1, 1, 5% (0, 65, 710, 5,800 mg/kg-day for males; 0, 82, 770, 4,700 mg/kg-day for females)[b] Diet Weaning to 4 months post-weaning	**Hematology at 4 months** *(percent change compared to control[a])*				
	Doses (M)	0	65	710	5,800
	RBCs	0%	−1%	−5%	−16%
	WBCs	0%	−37%	−15%	38%
	Hgb	0%	−4%	−5%	−9%
	Doses (F)	0	82	770	4,700
	RBCs	0%	6%	1%	13%
	WBCs	0%	−19%	−8%	29%
	Hgb	0%	0%	3%	−6%
	Note: Statistical analysis not reported in study.				
University of Rochester (1954) Rat (Albino; no other strain designation); 5 males and 5 females/dose 0, 0.1, 1, 5% (0, 65, 710, 5,800 mg/kg-day for males; 0, 82, 770, 4,700 mg/kg-day for females)[b] Diet Weaning to 4 months post-weaning	**Differential counts at 4 months** *(percent of each type of WBC)*				
	Doses (M)	0	65	710	5,800
	neutrophils	20%	18%	19%	17%
	eosinophils	1%	5%	5%	2%
	basophils	0%	0%	1%	1%
	lymphocytes	79%	76%	75%	80%
	monocytes	1%	0%	0%	0%
	myeloids	0%	0%	0%	0%
	blast forms	0%	0%	0%	0%
	plasma cells	0%	0%	0%	0%
	Doses (F)	0	82	770	4,700
	neutrophils	15%	14%	22%	13%
	eosinophils	2%	4%	4%	3%
	basophils	0%	0%	0%	1%
	lymphocytes	83%	82%	73%	84%
	monocytes	0%	0%	0%	0%

Reference and study design	Results				
	myeloids	0%	0%	0%	0%
	blast forms	0%	0%	0%	0%
	Note: Statistical analysis not reported in study.				
Spleen weight					
University of Rochester (1954)	**Spleen weight** *(percent change compared to control[a])*				
Rat (Albino; no other strain designation); 5 males and 5 females/dose	Doses (M)	0	65	710	5,800
0, 0.1, 1, 5% (0, 65, 710, 5,800 mg/kg-day for males; 0, 82, 770, 4,700 mg/kg-day for females)[b]	*absolute weight*	2%	9%	7%	−13%
Diet	*relative weight*	0%	5%	17%	52%
Weaning to 4 months post-weaning	Doses (F)	0	82	770	4,700
	absolute weight	0%	8%	93%	−6%
	relative weight	0%	11%	80%	9%
	Note: Statistical analysis not reported in study.				

[a]Percent change compared to control = $\frac{\text{treated value} - \text{control value}}{\text{control value}} \times 100$

[b]Dose conversions were performed by EPA using this information: University of Rochester (1954) average BWs (measured at least once weekly) were 269, 277, 252, and 155 g for male rats, and 178, 170, 182, and 148 g for female rats at 0, 0.1, 1.0, and 5.0%, respectively; and the default food consumption of 0.018 kg/day for male rats and 0.014 kg/day for female rats (U.S. EPA, 1988) of an unspecified strain in a subchronic study were applied.

Hgb = hemoglobin; RBC = red blood cell; WBC = white blood cell

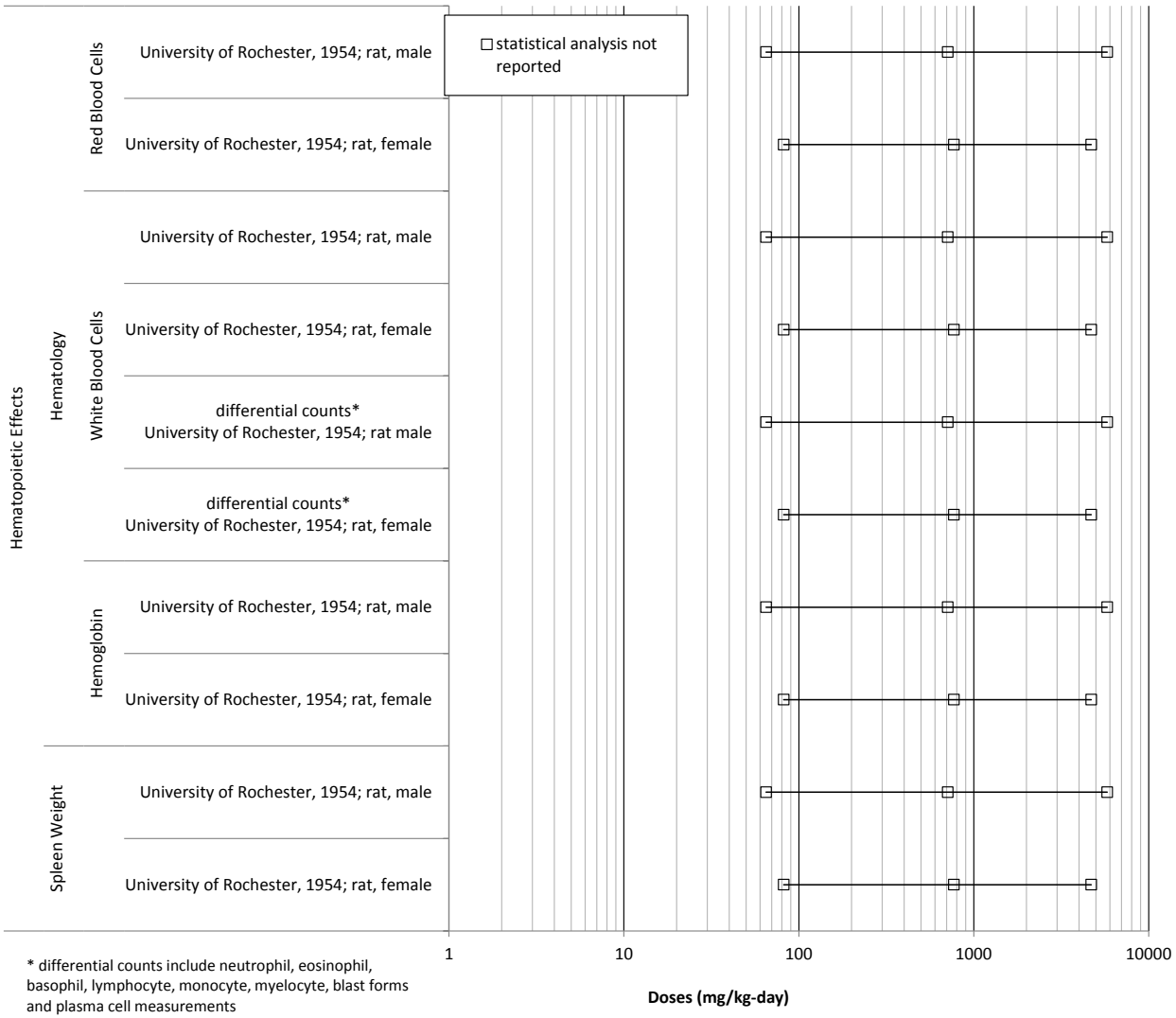


Figure 3-11. Exposure-response array of hematopoeitic effects following oral exposure to DIBP.

3.3.7. Other Effects

Table 3-23. Evidence pertaining to other toxicity effects in animals following oral exposure to DIBP

Reference and study design	Results				
Neurotoxicity effects					
University of Rochester (1954)	**Brain weight** *(percent change compared to control[a])*				
Rat (Albino; no other strain designation); 5 males and 5 females/dose	Doses (M)	0	65	710	5,800
0, 0.1, 1, 5% (0, 65, 710, 5,800 mg/kg-day for males; 0, 82, 770, 4,700 mg/kg-day for females)[b]	*absolute weight*	0%	1%	0%	−3%
Diet	*relative weight*	0%	−2%	11%	72%
Weaning to 4 months post-weaning	Doses (F)	0	82	770	4,700
	absolute weight	0%	3%	1%	2%
	relative weight	0%	4%	−6%	17%
	Note: Statistical analysis not reported in study.				
Cardiac effects					
University of Rochester (1954)	**Heart weight** *(percent change compared to control[d])*				
Rat (Albino; no other strain designation); 5 males and 5 females/dose	Doses (M)	0	65	710	5,800
0, 0.1, 1, 5% (0, 65, 710, 5,800 mg/kg-day for males; 0, 82, 770, 4,700 mg/kg-day for females)[b]	*absolute weight*	0%	2%	−6%	−28%
Diet	*relative weight*	0%	−3%	3%	24%
Weaning to 4 months post-weaning	Doses (F)	0	82	770	4,700
	absolute weight	0%	10%	−4%	11%
	relative weight	0%	10%	−11%	28%
	Note: Statistical analysis not reported in study.				
Lung effects					
University of Rochester (1954)	**Lung weight** *(percent change compared to control[a])*				
Rat (Albino; no other strain designation); 5 males and 5 females/dose	Doses (M)	0	65	710	5,800
0, 0.1, 1, 5% (0, 65, 710, 5,800 mg/kg-day for males; 0, 82, 770, 4,700 mg/kg-day for females)[b]	*absolute weight*	0%	10%	4%	−30%
Diet	*relative weight*	0%	5%	16%	23%

Reference and study design	Results					
Weaning to 4 months post-weaning	Doses (F)	0	82	770	4,700	
	absolute weight	0%	−20%	−6%	−27%	
	relative weight	0%	−19%	−12%	−16%	
	Note: Statistical analysis not reported in study.					
Stomach effects						
University of Rochester (1954) Rat (Albino; no other strain designation); 5 males and 5 females/dose 0, 0.1, 1, 5% (0, 65, 710, 5,800 mg/kg-day for males; 0, 82, 770, 4,700 mg/kg-day for females)[b] Diet Weaning to 4 months post-weaning	**Stomach weight** *(percent change compared to control[d])*					
	Doses (M)	0	65	710	5,800	
	absolute weight	0%	10%	6%	1%	
	relative weight	0%	7%	18%	80%	
	Doses (F)	0	82	770	4,700	
	absolute weight	0%	8%	7%	18%	
	relative weight	0%	9%	0%	35%	
	Note: Statistical analysis not reported in study.					
Clinical signs						
(Hazleton Laboratories (1992), 1987); NIOSH (1983)) Mouse (CD-1); 50 control females, 10 females/treated group 0, 1,000, 1,795, 3,225, 5,790, 10,400 mg/kg-day Gavage 8 days	**Clinical signs of toxicity** (incidence / total animals)						
	Doses	0	1,000	1,795	3,225	5,790	10,400
	languid	1/50	0/10	0/10	2/10	5/10	0/10
	prostrate	0/50	0/10	0/10	0/10	4/10	0/10
	ataxia	0/50	0/10	0/10	0/10	0/10	0/10
	hunched	0/50	0/10	0/10	0/10	0/10	0/10
	tremors	0/50	0/10	0/10	0/10	0/10	0/10
	head tilt	0/50	0/10	0/10	0/10	0/10	0/10
	thin	1/50	0/10	0/10	0/10	0/10	0/10
	wheezing	0/50	0/10	0/10	0/10	0/10	0/10
	dyspnea	0/50	0/10	0/10	0/10	0/10	0/10
	urine stains	0/50	0/10	0/10	0/10	0/10	10/10
	alopecia	0/50	0/10	0/10	0/10	0/10	0/10
	rough hair coat	0/50	0/10	0/10	0/10	0/10	10/10
	sores	0/50	0/10	0/10	0/10	0/10	0/10
	piloerection	0/50	0/10	0/10	0/10	0/10	0/10
	opaque eyes	N/A	0/10	0/10	0/10	1/10	0/10

Reference and study design	Results						
	discoloration (yellow hair)	N/A	0/10	0/10	0/10	1/10	0/10
	Note: Statistical analysis not reported in study for clinical signs data.						

[a]Percent change compared to control = $\frac{\text{treated value} - \text{control value}}{\text{control value}} \times 100$

[b]Dose conversions were performed using this information: University of Rochester (1954) average BWs (measured at least once weekly) were 269, 277, 252, and 155 g for male rats, and 178, 170, 182, and 148 g for female rats at 0, 0.1, 1.0, and 5.0%, respectively; and default food consumption of 0.018 kg/day for male rats and 0.014 kg/day for female rats (U.S. EPA, 1988) of an unspecified strain in a subchronic study were applied.

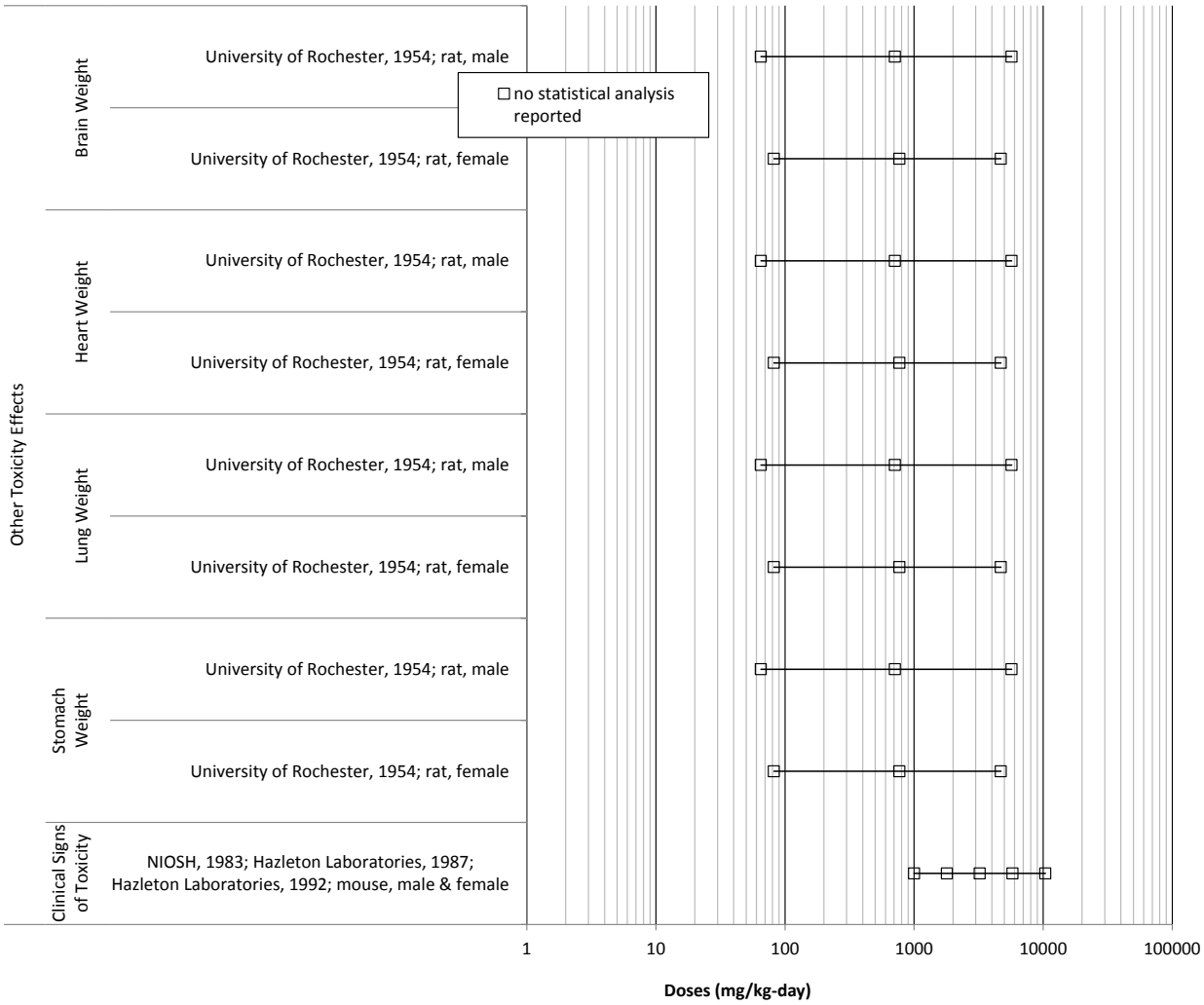


Figure 3-12. Exposure-response array of effects on other toxicities following oral exposure to DIBP.

3.4. PRELIMINARY MECHANISTIC INFORMATION FOR DIBP

The systematic literature search for DIBP also identified studies evaluating mechanisms of action considered potentially relevant to effects observed following exposure to DIBP. Studies were included if they evaluated mechanistic events following exposure to DIBP or the metabolite, MIBP, or contained information relevant to the mechanistic understanding of DIBP 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 the HERO record (contained within a URL that links to the study abstract in the HERO database), HERO ID, author(s), year, molecular formulation, in vitro/in vivo, species, cell type, endpoint(s) (i.e., mechanistic outcomes), assay, and mechanistic category. The database supports sorting capabilities, e.g., data can be organized by assay. The database is available through HERO at [http://hero.epa.gov/index.cfm?action=reference.details&reference_id=2508641]. 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 DIBP mechanistic studies consists of 32 mechanistic outcomes from 13 identified in vivo studies, as well as 28 mechanistic outcomes from 23 in vitro assays. Table 3-24 presents a summary of the mechanistic outcomes recording in the database from each study identified.

The mechanistic categories developed here are not mutually exclusive and are designed to facilitate the analysis of similar studies and experimental observations in a systematic manner. This process will allow the identification of mechanistic events that contribute to mode(s) of action (MOAs) and/or adverse outcome pathways (AOPs) following DIBP exposure. The mechanistic categories assigned to each mechanistic outcome reported by an individual study are as follows: (1) mutation, including investigations of gene and chromosomal mutation; (2) DNA damage, including indicator assays of genetic damage; (3) DNA repair; (4) oxidative stress; (5) cell death and division (this captures a broad range of assays, but it is useful to consider them together as observations resulting from cell cycle alterations; (6) pathology, which includes morphological evaluations pertaining to the dysfunction of organs, tissues, and cells; (7) epigenetic effects, which are observations of heritable changes in gene function that cannot be explained by changes in the DNA sequence; (8) receptor-mediated and cell signaling effects; (9) immune system effects; (10) cellular differentiation and transformation; (11) cellular energetics; and (12) "other," to

capture those mechanistic outcomes not easily assigned to a defined category. Mechanistic outcomes in the "other" category include sex steroid hormone (e.g., testosterone) production and gene expression.

Table 3-24. Summary of mechanistic outcomes evaluated following DIBP or MIBP administration

Mechanistic category	Total # outcomes/ # studies		In vivo (# outcomes/ # studies)			In vitro (# outcomes/# studies)				
		Total	Human	Rat	Mouse	Total	Human	Primate	Rat	Mouse
Mutation[a]	5/5	0	0	0	0	5/5	0	0	0	0
DNA damage	6/4	0	0	0	0	6/4	6/4	0	0	0
DNA repair										
Oxidative stress[b]	1/1	1/1	0	0	0	0	0	0	0	0
Cell death and division	7/5	3/2	0	2/2	1/1	4/3	3/2	0	0	1/1
Pathology	2/2	2/2	0	2/2	0	N/A	N/A			
Epigenetics										
Receptor-mediated and cell signaling[c]	14/9	8/4	1/1	7/3	0	6/5	0	1/1	0	0
Immune system	5/3	1/1	0	1/1	0	4/2	1/1	0	2/1	1/1
Cellular differentiation and transformation	1/1	1/1	1/1	0	0	0	0	0	0	0
Cellular energetics	1/1	0	0	0	0	1/1	0	0	1/1	0
Other[d]	18/11	16/10	0	14/8	2/2	2/2	0	0	2/2	0
Total	60/35		32/13			28/23				

[a]Database included five outcomes in five studies utilizing *Salmonella typhimurium.*
[b]Database included one outcome from one study utilizing *Caenorhabditis elegans.*
[c]Database included two outcomes from one study utilizing cultured hamster cells, two outcomes from two studies utilizing yeast, and one cell-free system.
[d]Database primarily composed of hormone (testosterone, estradiol) content or production in tissues from rats and mice.

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 DIBP-specific information available.

Information summarized in Table 3-24 and Figure 3-13 and detailed in the mechanistic database can be used to ascertain the breadth and scope of available mechanistic studies. At this preliminary stage, study results are not presented. Additionally, the inclusion of a study in the spreadsheet does not reflect conclusions reached as to mechanistic study quality or relevance. After the epidemiological and experimental studies on each health effect have been synthesized, mechanistic studies will be reviewed and findings synthesized to evaluate potential MOAs and/or AOPs, which can be used to inform hazard identification and dose-response assessment, specifically addressing questions of human relevance, susceptibility, and dose-response relationships.

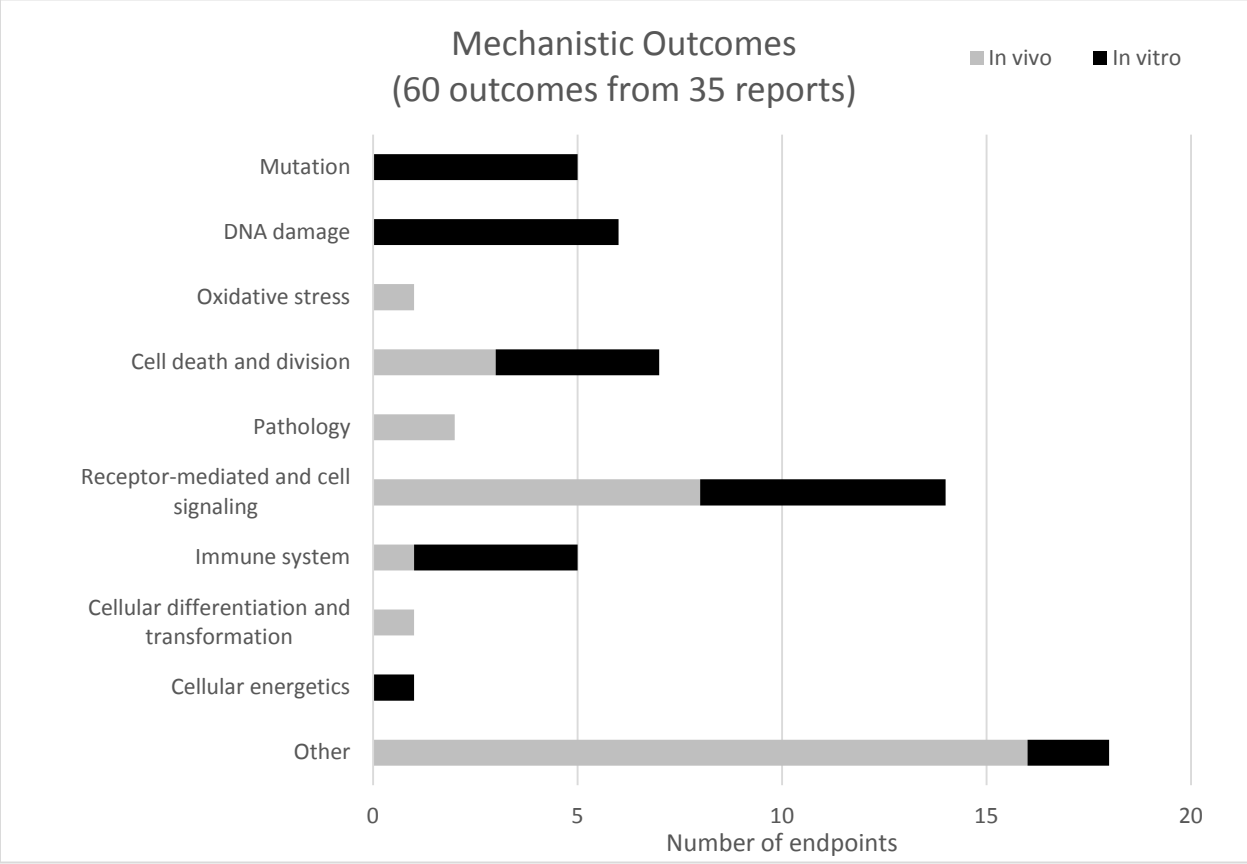


Figure 3-13. Summary of in vivo and in vitro mechanistic data for DIBP and MIBP by mechanistic category.

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