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Preliminary Materials
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Preliminary Materials for the Integrated Risk Information System (IRIS) Toxicological Review of Butyl Benzyl Phthalate (BBP)

(CASRN 85-68-7)

September 2014

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ABBREVIATIONS

ADME	absorption, distribution, metabolism, and excretion
AGD	anogenital distance
ALT	alanine aminotransferase
ANOVA	analysis of variance
BBP	butyl benzyl phthalate
BMI	body mass index
BP	blood pressure
BPA	bisphenol A
BW	body weight
CASRN	Chemical Abstracts Service Registry Number
CCCEH	Columbia Center for Children's Environmental Health
CERHR	Center for the Evaluation of Risks to Human Reproduction
CI	confidence interval
Con A	Concanavalin A
DBP	dibutyl phthalate
DEP	di-ethyl phthalate
DEHP	di(2-ethylhexyl)phthalate
DHEAS	dehydroepiandrosterone
DIBP	diisobutyl phthalate
DINP	diisononyl phthalate
DNA	deoxyribonucleic acid
DPP	dipentyl phthalate
EPA	Environmental Protection Agency
FEV_1	forced expiratory volume in 1 second
FSH	follicle stimulating hormone
FVC	forced vital capacity
GD	gestational day
E2	estradiol
feNO	fractional exhaled nitric oxide
GGT	gamma glutamyl transferase
HOMA	homeostatic model assessment
HOMA-IR	homeostatic model assessment of insulin resistance
HERO	Health and Environmental Research Online
HOME	Health Outcomes and Measures of the Environment
IgE	immunoglobulin E
ICC	intra-class correlation coefficient
IL	interleukin
IRIS	Integrated Risk Information System
IQR	interquartile range
ISAAC	International Study of Asthma and Allergies in Children
LABC	levator ani bulbocavernosus
LH	luteinizing hormone
LOD	level of detection
LOQ	level of quantification
m-RNA	messenger ribonucleic acid
MBP	monobutyl phthalate
MBzP	monobenzyl phthalate
MCPP	mono-(3-carboxypropyl) phthalate
MDI	mental delay index
MECPP	mono(2-ethyl-5-carboxypentyl) phthalate
MEHHP	mono-(2-ethyl-5-hydroxyhexyl)phthalate
MEHP	mono-(2-ethylhexyl) phthalate
MEOHP	mono-(2-ethyl-5-oxohexyl) phthalate
MEP	monoethyl phthalate
MGH	Massachusetts General Hospital
MIBP	monoisobuyl phthalate
MMEF	maximal midexpiratory flow
MMP	monomethyl phthalate
MOA	mode of action
MW	molecular weight
NCEA	National Center for Environmental Assessment
NHANES	National Health and Nutrition Examination Survey
NHS	Nurses Health Study
NIOSH	National Institute for Occupational Safety and Health
NRC	National Research Council
NTP	National Toxicology Program
OR	odds ratio
ORD	Office of Research and Development
PAH	polycyclic aromatic hydrocarbon
PCB	polychlorinated biphenyl
PCO	polycystic ovarian morphology
PCOS	polycystic ovarian syndrome
PDI	psychomotor delay index
PEF	peak expiratory flow
PND	postnatal day
PNW	postnatal week
PPS	preputial separation
PVC	polyvinyl chloride
RfD	reference dose
SD	standard deviation
SE	standard error
SFF	Study for Future Families
SHBG	sex-hormone binding globulin
T3	triiodothyronine
T4	thyroxine
TSCATS	Toxic Substances Control Act Test Submissions
TSH	thyroid stimulating hormone
VOC	volatile organic compound
WHO	World Health Organization

PREFACE

This draft document presents preliminary materials for an assessment of butyl benzyl phthalate (BBP) prepared by the United States Environmental Protection Agency's (EPA) 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 BBP. 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 BBP, occurrence of BBP 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 NRC 2011 report *Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde* (NRC, 2011). The IRIS Program's implementation of the NRC recommendations is following a phased approach that is consistent with the NRC's "Roadmap for Revision" as described in Chapter 7 of the formaldehyde review report. The NRC stated that "the committee recognizes that the changes suggested would involve a multi-year process and extensive effort by the staff at the National Center for Environmental Assessment and input and review by the EPA Science Advisory Board and others." Phase 1 of implementation has focused on a subset of the short-term recommendations, such as editing and streamlining documents, increasing transparency and clarity, and using more tables, figures, and appendices to present information and data in assessments. Phase 1 also focused on assessments near the end of the development process and close to final posting. Phase 2 of implementation is focused on assessments that are in the beginning stages of assessment development. The IRIS BBP 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 butyl benzyl phthalate (BBP). The planning and scoping summary includes information on the properties, sources, and uses of BBP, occurrence and fate of BBP in the environment, potential for human exposure, and the rationale for the development of this assessment.

1.1. BBP IN THE ENVIRONMENT

1.1.1. Production and Use

BBP (Chemical Abstract Service Registry Number [CASRN] 85-68-7) is a plasticizer used in a wide range of materials including polyvinyl chloride (PVC)-based flooring, other plastics, adhesives, coatings for automobiles, polyvinyl and cellulose resins, organic intermediates, sealants, foams, inks, car care products, and cosmetics (HSDB, 2009). Between 50 and 100 million pounds were imported or manufactured in United States in 2012 (http://www.epa.gov/oppt/cdr/index.html).

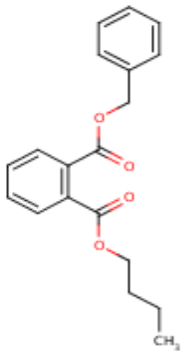


Figure 1-1. Chemical structure of BBP (HSDB, 2009).

1.1.2. Environmental Fate

If released to air, BBP will exist in both the vapor and particulate phases in the atmosphere. Vapor-phase BBP will be photolytically degraded with a half-life of about 1.5 days. Particulate-phase BBP will be removed from the atmosphere by wet or dry deposition. Once in soil, BBP is tightly absorbed given a high organic carbon partition coefficient (Koc). Binding to soil organic material limits volatilization as a route of dissipation. Biodegradation in aerobic soil and water is expected to occur over days or weeks. Anaerobic biodegradation rates are expected to be slower. If

released into water, BBP is expected to adsorb to suspended solids and sediment. Measured bioconcentration factors of 9.4–772 suggest that concentrations in aquatic organisms may vary, but metabolism of the chemical diminishes the likelihood of accumulation (HSDB, 2009). As noted by Wormuth et al. (2006), the majority of phthalates that are found in the environment come from slow release from plastics and other phthalate-containing articles. Certain waste streams, sludges, and contaminated sites, however, may contain higher levels of phthalates than other sites.

1.1.3. Human Exposure Pathways

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

The presence of phthalates or their metabolites in a body matrix, such as blood or urine, provides evidence of exposure to that chemical. The predominant metabolite of BBP in humans is monobenzyl phthalate (MBzP). Zota et al. (2014) evaluated the prevalence and temporal trends of MBzP in urine samples collected as part of the National Health and Nutrition Examination Survey (NHANES) conducted between 2001 and 2010. MBzP was found in more than 98% of the urine samples for each time period, and MBzP levels decreased recently, starting at about 10.4 ng/mL in the 2001–2002 cycle and dropping to about 7.0 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) determined a median intake of BBP of between 0.5 and 1.5 μg/kg-day for various lifestages as defined by the authors: adults (20–70 years of age), teens (12–19 years of age), children (5–11 years of age), toddlers (0.5–4 years of age), and infants (0–0.5 years of age). Toddlers had the highest intake noted. Pathways the authors assessed include ingestion of food, drinking water, dust/soil, and inhalation of air. Ingestion of food accounted for more than half of the total exposure for all age groups except infants, with the remainder primarily due to incidental ingestion of dust and a minor contribution due to inhalation of indoor air. For both the formula- and breast-fed infants, ingestion of dust accounted for approximately 94% of exposure, with ingestion of food comprising most of the remainder. Ingestion of food represented approximately 60% of total exposure for the adults and inhalation of spray paints comprised most of the remainder in the estimates by Wormuth et al. (2006), who determined total intakes of <0.5 μg/kg-day, except for infants and toddlers, who had intakes between 0.5 and 1.0 μg/kg-day.

Wittassek et al. (2011) reported median intakes of BBP in the range of 0.1−0.9 µg/kg-day based on a literature survey or urinary biomonitoring data and intake estimates provided therein. Their review included U.S. estimates generated using data from the NHANES 2001−2002 cycle to ascertain exposures in the range of 0.7−0.9 µg/kg-day. Qian et al. (2014) used NHANES 2007−2008 data and found a median intake of 0.3 µg/kg-day and a 95th percentile intake of 1.7 µg/kg-day. Christensen et al. (2014) combined the data from NHANES 2005−2008 and found similar results to Qian et al. (2014), with a median over that time span of 0.2 µg/kg-day and a 95th percentile intake of 1.0 µg/kg-day.

1.2. SCOPE OF THE ASSESSMENT

The National Research Council has recommended that, "cumulative risk assessment based on common adverse outcomes is a feasible and physiologically relevant approach to the evaluation of the multiplicity of human exposures and directly reflects EPA's mission to protect human health" (NRC, 2008, p11). They envisioned facilitating the process by "defining the groups of agents that should be included for a given outcome" (NRC, 2008, p12). In humans, the NRC cited results from the NHANES that demonstrate exposure to multiple phthalates in most people (NRC, 2008, p23-25). Recent reports on human exposure to phthalates suggest that the indoor environment is thought to contribute to over 60% of BBP exposure in children (CHAP, 2014, Appendix E1, p. 35) and 94% of exposure in infants (Clark et al., 2011). 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 BBP exposure and enable future cumulative risk assessments that assess effects on human health outcomes that might be associated with BBP and other phthalates. EPA's previous IRIS assessment of BBP (U.S. EPA, 1993) included an oral reference dose (RfD) and qualitative cancer assessment (classified as Group C, a possible human carcinogen). Since that time, a number of experimental animal and epidemiological studies have been published for BBP.

2. METHODS FOR IDENTIFYING AND SELECTING

The National Research Council (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 butyl benzyl phthalate (BBP). 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 BBP, and remaining references were sorted into categories for further evaluation. Section 2.1 describes the literature search and screening strategy in detail. The NRC (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 BBP 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 BBP was conducted in four online scientific databases, including PubMed, Toxline, Web of Science, and the Toxic Substances Control Act Test Submissions (TSCATS) database, in December 2012; the search was repeated in August 2013 and in April 2014. This document is complete through April 2014. Additional updates will be performed at regular (e.g., 6-month) intervals. The detailed search approach, including the search strings is presented in Table 2-1. The search strings and search terms described for BBP captured studies using the parent compound and metabolites. This search of online databases identified 1,105 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);

63 citations were obtained using these additional search strategies. In total, 1,166 citations were identified using online scientific databases and additional search strategies.

Table 2-1. Database search strategy for BBP

Database (search date)	Keywords[a]
PubMed 04/2014 08/2013 12/2012	"1-butyl 2-(phenylmethyl) ester 1,2-Benzenedicarboxylic acid"[tw] OR "benzyl butyl ester Phthalic acid"[tw] OR "Benzyl butyl phthalate"[tw] OR "Benzyl butylphthalate"[tw] OR "Benzyl n-butyl phthalate"[tw] OR "Butyl benzyl phthalate"[tw] OR "Butyl phenylmethyl 1,2-benzenedicarboxylate"[tw] OR "butyl phenylmethyl ester 1,2-Benzenedicarboxylic acid"[tw] OR "Butylbenzyl phthalate"[tw] OR "n-Butyl benzyl phthalate"[tw] OR "Palatinol BB"[tw] OR "Santicizer 160"[tw] OR "Sicol"[tw] OR "Unimoll BB"[tw] OR (("BBP"[tw] OR BzBP[tw]) AND (phthalic OR phthalate OR phthalates))
Web of Science 04/2014 08/2013 12/2012	TS="1-butyl 2-(phenylmethyl) ester 1,2-Benzenedicarboxylic acid" OR TS="benzyl butyl ester Phthalic acid" OR TS="Benzyl butyl phthalate" OR TS="Benzyl butylphthalate" OR TS="Benzyl n-butyl phthalate" OR TS="Butyl benzyl phthalate" OR TS="Butyl phenylmethyl 1,2-benzenedicarboxylate" OR TS="butyl phenylmethyl ester 1,2-Benzenedicarboxylic acid" OR TS="Butylbenzyl phthalate" OR TS="n-Butyl benzyl phthalate" OR TS="Palatinol BB" OR TS="Santicizer 160" OR TS="Sicol" OR TS="Unimoll BB" OR ((TS="BBP" OR TS="BzBP") AND (TS="phthalic" OR TS=phthalate*))
Toxline 04/2014 08/2013 12/2012	@OR+("1-butyl 2-(phenylmethyl) ester 1,2-Benzenedicarboxylic acid"+"benzyl butyl ester Phthalic acid"+"Benzyl butyl phthalate"+"Benzyl butylphthalate"+"Benzyl n-butyl phthalate"+"Butyl benzyl phthalate"+"Butyl phenylmethyl 1,2-benzenedicarboxylate"+"butyl phenylmethyl ester 1,2-Benzenedicarboxylic acid"+"Butylbenzyl phthalate"+"n-Butyl benzyl phthalate"+"Palatinol BB"+"Santicizer 160"+"Sicol"+"Unimoll BB"+@term+@rn+85-68-7) +@NOT+@org+pubmed+pubdart+crisp+tscats
TSCATS2 08/2013	85-68-7

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

Table 2-2. Summary of additional search strategies for BBP

Approach used	Source(s)	Date performed	Number of additional citations identified
Manual search from reviews conducted by other international and federal agencies	CPSC (2010). Toxicity review of butyl benzyl phthalate (BBP).	06/2013	1 citation
	ECJRC (2007). European Union risk assessment report butyl benzyl phthalate.	06/2013	33 citations

Electronic forward Search through Web of Science	Aso et al. (2005). A two generation reproductive toxicity study of butyl benzyl phthalatein rats. The Journal of Toxicological Sciences, 30, 39-58.	06/2013	0 citations
	Tyl et al. (2004). Reproductive toxicity evaluation of dietary butyl benzyl phthalate (BBP) in rats. Reproductive Toxicology, 18, 241-264.	06/2013	0 citations
	Nagao et al. (2000). Effect of butyl benzyl phthalate in Sprague-Dawley rats after gavage administration: a two-generation reproductive study. Reprod Toxicol 14(6): 513-532.	06/2013	1 citation
Electronic backward Search through Web of Science	Aso et al. (2005). A two generation reproductive toxicity study of butyl benzyl phthalatein rats. The Journal of Toxicological Sciences, 30, 39-58.	06/2013	0 citations
	Tyl et al. (2004). Reproductive toxicity evaluation of dietary butyl benzyl phthalate (BBP) in rats. Reproductive Toxicology, 18, 241-264.	06/2013	4 citations
	Nagao et al. (2000). Effect of butyl benzyl phthalate in Sprague-Dawley rats after gavage administration: a two-generation reproductive study. Reprod Toxicol 14(6): 513-532.	06/2013	3 citations
References obtained during the assessment process	BBP references obtained from submissions, full study reports from HERO, or in previous assessment	08/2014	63 citations

Background Check	Searched a combination of CASRNs and synonyms on the following databases: ACGIH (http://www.acgih.org/home.htm) ATSDR (http://www.atsdr.cdc.gov/substances/index.asp CalEPA Office of Environmental Health Hazard Assessment (http://www.oehha.ca.gov/risk.html) OEHHA Toxicity Criteria Database (http://www.oehha.ca.gov/tcdb/index.asp) Biomonitoring California-Priority Chemicals (http://www.oehha.ca.gov/multimedia/biomon/pdf/PriorityChemsCurrent.pdf) Biomonitoring California-Designated Chemicals (http://www.oehha.ca.gov/multimedia/biomon/pdf/DesignatedChemCurrent.pdf) Cal/Ecotox Database (http://www.oehha.ca.gov/scripts/cal_ecotox/CHEMLIST.ASP) OEHHA Fact Sheets (http://www.oehha.ca.gov/public_info/facts/index.html) Non-cancer health effects Table (RELs) and Cancer Potency Factors (Appendix A and Appendix B) (http://www.oehha.ca.gov/air/hot_spots/index.html) CPSC (http://www.cpsc.gov) eChemPortal (http://www.echemportal.org/echemportal/participant/page.action?pageID=9) Environment Canada − Search entire site (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) 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 (http://cfpub.epa.gov/ncea/iristrac/) to find dates (http://www.epa.gov/ncea/iris/index.html) to find data EPA NSCEP (http://www.epa.gov/ncepihom/) EPA RfD/RfC and CRAVE meeting notes EPA Science Inventory (http://cfpub.epa.gov/si/) (http://www.fda.gov/)	12/2012	7 citations added

	Federal Docket (www.regulations.gov) Health Canada First Priority List Assessments (http://www.hc-sc.gc.ca/ewh-semt/pubs/contaminants/psl1-lsp1/index-eng.php) Health Canada Second Priority List Assessments (http://www.hc-sc.gc.ca/ewh-semt/pubs/contaminants/psl2-lsp2/index-eng.php) IARC (http://monographs.iarc.fr/htdig/search.html) ITER (TERA database) (http://iter.ctcnet.net/publicurl/pub_search_list.cfm) NAP – Search Site (http://www.nap.edu/) NCI (http://www.cancer.gov) NCTR (http://www.fda.gov/AboutFDA/CentersOffices/OC/OfficeofScientificandMedicalPrograms/NCTR/default.htm) National Institute for Environmental Health Sciences (NIEHS) http://www.niehs.nih.gov/ NICNAS (PEC only covered by eChemPortal) (http://www.nicnas.gov.au/industry/aics/search.asp) NIOSH (http://www.cdc.gov/niosh/topics/) NIOSHTIC 2 (http://www2a.cdc.gov/nioshtic-2/) NTP - RoC, status, results, and management reports (http://ntpsearch.niehs.nih.gov/query.html) OSHA (http://www.osha.gov/dts/chemicalsampling/toc/toc_chemsamp.html) RTECS http://www.ccohs.ca/search.html (http://www.fda.gov/) Federal Docket (www.regulations.gov) Health Canada First Priority List Assessments (http://www.hc-sc.gc.ca/ewh-semt/pubs/contaminants/psl1-lsp1/index-eng.php) Health Canada Second Priority List Assessments (http://www.hc-sc.gc.ca/ewh-semt/pubs/contaminants/psl2-lsp2/index-eng.php) IARC (http://monographs.iarc.fr/htdig/search.html) ITER (TERA database) (http://iter.ctcnet.net/publicurl/pub_search_list.cfm)		

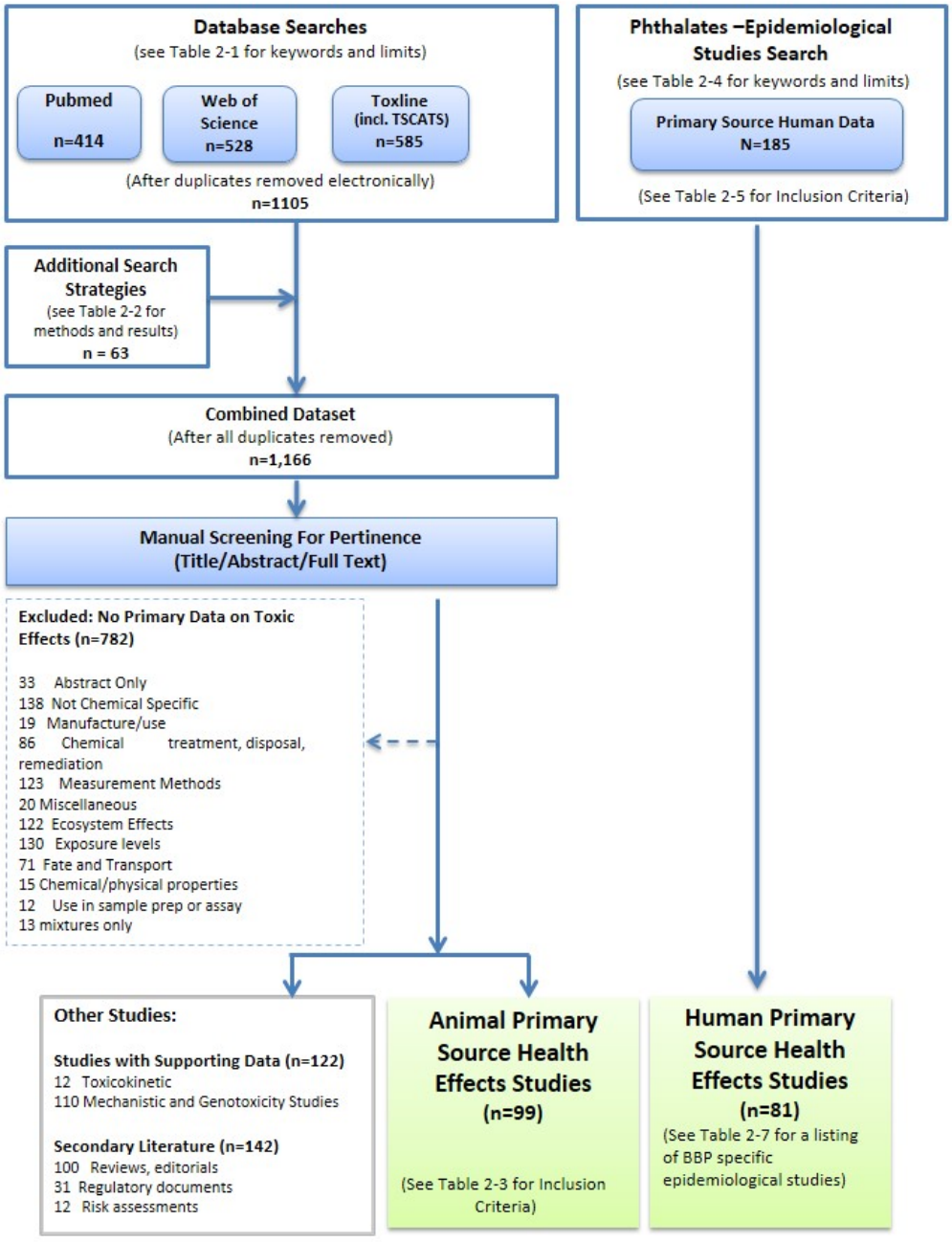
	NAP – Search Site (http://www.nap.edu/) NCI (http://www.cancer.gov) NCTR (http://www.fda.gov/AboutFDA/CentersOffices/OC/OfficeofScientificandMedicalPrograms/NCTR/default.htm) National Institute for Environmental Health Sciences (NIEHS) http://www.niehs.nih.gov/ NICNAS (PEC only covered by eChemPortal) (http://www.nicnas.gov.au/industry/aics/search.asp) NIOSH (http://www.cdc.gov/niosh/topics/) NIOSHTIC 2 (http://www2a.cdc.gov/nioshtic-2/) NTP - RoC, status, results, and management reports (http://ntpsearch.niehs.nih.gov/query.html) OSHA (http://www.osha.gov/dts/chemicalsampling/toc/toc_chemsamp.html) RTECS http://www.ccohs.ca/search.html FDA (http://www.fda.gov/) Federal Docket (www.regulations.gov) Health Canada First Priority List Assessments (http://www.hc-sc.gc.ca/ewh-semt/pubs/contaminants/psl1-lsp1/index-eng.php) Health Canada Second Priority List Assessments (http://www.hc-sc.gc.ca/ewh-semt/pubs/contaminants/psl2-lsp2/index-eng.php) IARC (http://monographs.iarc.fr/htdig/search.html) ITER (TERA database) (http://iter.ctcnet.net/publicurl/pub_search_list.cfm) NAP – Search Site (http://www.nap.edu/) NCI (http://www.cancer.gov) NCTR (http://www.fda.gov/AboutFDA/CentersOffices/OC/OfficeofScientificandMedicalPrograms/NCTR/default.htm) National Institute for Environmental Health Sciences (NIEHS) http://www.niehs.nih.gov/ NICNAS (PEC only covered by eChemPortal) (http://www.nicnas.gov.au/industry/aics/search.asp) NIOSH (http://www.cdc.gov/niosh/topics/)		

	NIOSHTIC 2 (http://www2a.cdc.gov/nioshtic-2/) NTP - RoC, status, results, and management reports (http://ntpsearch.niehs.nih.gov/query.html) OSHA (http://www.osha.gov/dts/chemicalsampling/toc/toc_chemsamp.html) RTECS http://www.ccohs.ca/search.html		

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

- 99 references were identified as animal studies with health effects data and were considered for data extraction to evidence tables and exposure-response arrays.
- 122 references were identified as supporting studies; of these, 12 were toxicokinetic studies and 110 were mechanistic and genotoxicity studies.
- 142 references were identified as secondary literature (e.g., reviews and editorials, risk assessments, and regulatory documents); these references were kept as additional resources for development of the Toxicological Review.
- 782 references were excluded because these studies did not include primary source data evaluating BBP in relation to any kind of toxicity or health endpoint, and did not provide either supporting information (e.g., toxicokinetic or mechanistic/genotoxic data) or secondary literature information (see Figure 2-1 for 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.



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 BBP.

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 BBP 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 BBP?

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

Six foreign language studies reporting pertinent evidence for hazard characterization and/or dose-response were identified. These studies by Agramunt et al. (2011); Li et al. (2004); Timofievskaya et al. (1988); Timofievskaya et al. (1980); Tyrkiel et al. (2007); and Zhuang et al. (2008) were tagged under "kept for possible further review" (not shown in figure). A translation was requested for the study by Zhuang et al. (2008) as it is one of the two available studies reporting endpoints considered relevant to neurological effects. The remaining foreign language studies report evidence for effects already described in English language publications and captured in the BBP draft evidence tables. They will be considered individually for translation and inclusion in evidence tables during development of the draft assessment of the available evidence of BBP-induced health effects.

Sixteen 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 BBP 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., BBP, dibutyl phthalate [DBP], diisobutyl phthalate [DIBP], 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 in an inefficient use of resources.

For these reasons, EPA developed a process for identifying epidemiological studies evaluating phthalates by performing a single broad search to create a listing of epidemiological studies of all phthalates mentioned above, from which the selection of studies examining potential health effects of an individual phthalate could be drawn. This list records each of the phthalates included in the study, based on information in the methods section of the paper, and the outcome(s) examined. This literature search for epidemiological studies examining phthalates in relation to health-related endpoints (from which the BBP 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	184
	Web of Science	409
	ToxNet (was not searched because no articles have been found solely through this source in all the previous searches)	0
	Merged Reference Set	494
	Additional epidemiology articles meeting inclusion criteria	**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)?

Inclusion criteria
- 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, 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 BBP, metabolite the primary metabolite of interest is MBzP (monobenzyl phthalate).

One hundred and seventy-three epidemiological studies examining one or more phthalate 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, 81 studies analyzed one or more health effects in relation to a measure of BBP (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 1–3 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. (2013b); James-Todd et al. (2012); Lind and Lind (2011); Boas et al. (2010); Cho et al. (2010); Engel et al. (2010); Lopez-Carrillo et al. (2010); Wolff et al. (2010); Adibi et al. (2009); Chou et al. (2009); Hatch et al. (2008); Wolff et al. (2008); Meeker et al. (2007); Stahlhut et al. (2007); Hauser et al. (2006); Reddy et al. (2006a); Jonsson et al. (2005); Swan et al. (2005); Bornehag et al. (2004); Hoppin et al. (2004); Aschengrau et al. (1998); Heineman et al. (1992); Nielsen et al. (1989); Nielsen et al. (1985))

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

Outcome category	Reference[a]	BBP measure
Sexual differentiation measures (Table 3-1)	Lin et al. (2011a) Main et al. (2006) Suzuki et al. (2012) Swan (2008) Swan et al. (2010)	MBzP (maternal urine) MBzP (breast milk) MBzP (maternal urine) MBzP (maternal urine) MBzP (maternal urine)
Male reproductive (semen parameters, infertility, and hormones) (Tables 3-2 and 3-3)	Buck Louis et al. (2014) Hauser et al. (2006) Hauser et al. (2007) Joensen et al. (2012) Jonsson et al. (2005) Jurewicz et al. (2013) Kranvogl et al. (2014) Liu et al. (2012) Meeker et al. (2009a) Mendiola et al. (2011) Mendiola et al. (2012) Toshima et al. (2012) Tranfo et al. (2012) Wirth et al. (2008)	MBzP (urine) MBzP (urine) MBzP (urine) MBzP (urine) MBzP (urine) MBzP (urine) MBzP (urine) MBzP (urine) MBzP (urine) MBzP (urine) MBzP (urine) MBzP (urine) MBzP (urine) MBzP (urine)
Male pubertal development (Table 3-4)	Ferguson et al. (2014b) Mieritz et al. (2012) Mouritsen et al. (2013b)	MBzP (maternal urine) MBzP (urine) MBzP (urine)

Outcome category	Reference [a]	BBP measure
Female pubertal development (Table 3-5)	Chen et al. (2013) Chou et al. (2009) Frederiksen et al. (2012) Hart et al. (2013) Lomenick et al. (2010) Mouritsen et al. (2013b)	MBzP (urine) MBzP (urine) MBzP (urine) MBzP (maternal serum) MBzP (urine) MBzP (urine)
Female reproductive (infertility, hormones, gynecological conditions) (Tables 3-6 and 3-7)	Buck Louis et al. (2013) Hart et al. (2013) Huang et al. (2010) Itoh et al. (2009) Reddy et al. (2006a) Reddy et al. (2006b) Sathyanarayana et al. (2014) Upson et al. (2013) Weuve et al. (2010)	MBzP (urine) MBzP (urine) MBzP (maternal serum) MBzP (urine) BBP (plasma) BBP (plasma) MBzP (maternal urine) MBzP (urine) MBzP (urine)
Pregnancy-related outcomes (fetal growth, preterm birth, pregnancy loss) (Table 3-8)	Ferguson et al. (2014c) Ferguson et al. (2014a) Huang et al. (2014b) Meeker et al. (2009b) Philippat et al. (2012) Suzuki et al. (2010) Toft et al. (2012) Wolff et al. (2008)	MBzP (maternal urine) MBzP (maternal urine) BBP (cord blood) MBzP (maternal urine) MBzP (maternal urine) MBzP (maternal urine) MBzP (maternal urine) MBzP (maternal urine)
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) Hsu et al. (2012) Just et al. (2012b) Kanazawa et al. (2010) Kolarik et al. (2008) Sun et al. (2009) Wang et al. (2014)	BBP (dust) BBP (dust) MBzP (urine) BBP (dust) MBzP (urine) BBP (dust), MBzP (urine) MBzP (maternal urine) BBP (dust) BBP (dust) BBP (dust) MBzP (maternal urine)
Asthma (Table 3-10)	Ait Bamai et al. (2014) Bertelsen et al. (2013) Bornehag et al. (2004) Callesen et al. (2014b) Callesen et al. (2014a) Hoppin et al. (2013) Hsu et al. (2012) Just et al. (2012a) Kolarik et al. (2008) Sun et al. (2009)	BBP (dust) MBzP (urine) BBP (dust) MBzP (urine) BBP (dust) MBzP (urine) BBP (dust), MBzP (urine) MBzP (urine) BBP (dust) BBP (dust)
Pulmonary Function (Table 3-11)	Cakmak et al. (2014) Hoppin (2004)	MBzP (urine) MBzP (urine)

Outcome category	Reference [a]	BBP measure
Neurodevelopment (Table 3-12)	Braun et al. (2014) Chopra et al. (2014) Kobrosly et al. (2014) Téllez-Rojo et al. (2013) Whyatt et al. (2012)	MBzP (maternal urine) MBzP (urine) MBzP (maternal urine) MBzP (maternal urine) MBzP (maternal urine)
Thyroid (Table 3-13)	Boas et al. (2010) Dirtu et al. (2013) Huang et al. (2007) Meeker et al. (2007)	MBzP (urine) MBzP (urine) MBzP (urine) MBzP (urine)
Obesity (Table 3-14)	Buser et al. (2014) Dirtu et al. (2013) Hart et al. (2013) Hatch et al. (2008) Song et al. (2014) Stahlhut et al. (2007) Svensson et al. (2011) Teitelbaum et al. (2012)	MBzP (urine) MBzP (urine) MBzP (maternal serum) MBzP (urine) MBzP (urine) MBzP (urine) MBzP (urine) MBzP (urine)
Diabetes and insulin resistance (Table 3-15)	Huang et al. (2014a) James-Todd et al. (2012) Svensson et al. (2011) Stahlhut et al. (2007) Sun et al. (2014) Trasande et al. (2013a)	MBzP (urine) MBzP (urine) MBzP (urine) MBzP (urine) MBzP (urine) MBzP (urine)
Other cardiovascular disease risk factors (Table 3-16)	Shiue (2014) Trasande et al. (2013b)	MBzP (urine) MBzP (urine)
Cancer (Table 3-17)	Aschengrau et al. (1998) Lopez-Carrillo et al. (2010)	Work history MBzP (urine)

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/BBP) and (http://hero.epa.gov/phthalates-humanstudies).

[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 BBP may not match the numbers of references identified in Figure 2-1 (current through September 2014).

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
- 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 (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 BBP experimental animal database consists of studies designed to examine repeat-dose oral toxicity (including chronic, subchronic, and short-term duration studies) and endpoint-specific toxicities (including reproductive and developmental toxicity). All studies involved administration of BBP via oral or inhalation routes. Acute or short-term studies are generally less pertinent for characterizing health hazards associated with chronic exposure; there are 25 acute and short-term studies that are not summarized in the preliminary evidence tables. In addition, studies using atypical exposure routes (e.g., intraperitoneal or subcutaneous exposure) (4 studies), and studies that used a single high dose (6 studies) when other multi-dose studies with similar endpoints were available, were also not included in the preliminary evidence tables. Nevertheless, these studies will still be evaluated as possible sources of supporting health effects information during assessment development. Two studies were identified that involved administration of very low doses (≤1 ppm) of BBP. Following the recommendations of a NTP-CERHR (2003) review, these studies were not included in the evidence tables due to: (1) lack of dose-response data; (2) lack of analytical data on levels of BBP in drinking water; (3) failure of the original laboratory to duplicate their findings; and (4) inability of other reputable laboratories to duplicate the findings. In addition, five studies were not summarized in the preliminary evidence tables because they presented data previously published in other studies that are included in the preliminary evidence tables; four studies were not summarized due to co-administration of other chemicals at the time of dosing; and one study was not included in the preliminary evidence tables due to the presence of a respiratory infection reported in the control colony. The remaining studies are all sources of health effects data that may be used in the assessment. The studies summarized in the evidence tables are considered the "critical" studies from which the study methods and results are presented in preliminary evidence tables and exposure-response arrays (Section 3).

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

Several considerations will be used in EPA's evaluation of epidemiological studies of human health effects of BBP. 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 Integrated Risk Information System (IRIS) Preamble, and are described below.

Study Population

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

The general considerations for evaluating issues relating to the study population include adequate documentation of participant recruitment, including eligibility criteria and participation rates, 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 BBP 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 BBP 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 BBP, in conjunction with knowledge of specific health outcomes, may motivate people to participate in a study or to continue participation throughout a follow-up period. In the absence of evidence that any of these scenarios is likely to occur in a study, EPA will not consider selection bias as a limitation of a study.

Exposure Considerations

General considerations for evaluating exposure include: (1) 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 BBP include polyvinyl chloride (PVC) flooring, food, and food packaging material (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 BBP is typically from multiple sources, and occurs episodically on a daily basis. Exposure to BBP may be decreasing; a recent study of the U.S. general population found that urinary concentrations of the BBP metabolite, MBzP, have decreased somewhat over time and were 32% lower in 2009–2010 compared to 2001–2002 (Zota et al., 2014).

Urine provides an integrated measure of phthalate exposure from all sources. Measurement of BBP 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, MBzP, is the most commonly measured BBP metabolite in epidemiologic studies. MBzP accounts for an estimated 73% of the urinary excretion of BBP (Anderson et al., 2001). This value is based on data from a 24-person (all adults) controlled dosing study (Koch et al., 2012). EPA considers the use of MBzP to be a good proxy for total BBP 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 BBP metabolites in breast milk or serum have generally reported low levels of detection. One study in Taiwan reported that MBzP above the limit of detection was found in 10% of breast milk samples

from 30 women and 10% of the corresponding 30 cord blood samples. The correlation between MBzP in maternal urine and breast milk was −0.27 and for maternal urine and cord blood was −0.09 (Pearson correlation of log-transformed levels) (Lin et al., 2011b). Hogberg et al. (2008) reported that few breast milk (3 out of 42) samples in a study in Sweden had detectable MBzP concentrations. Another study conducted among 60 men ages 18−26 years found that 10% of serum samples and 18.6% of seminal plasma samples had MBzP concentrations above the limit of detection (Frederiksen et al., 2010). Correlation coefficients between MBzP measured in urine and these other samples were not calculated because the detection rates were low (Frederiksen et al., 2010). The lower detection rate in tissues other than urine reduces EPA's confidence in BBP metabolite measures in these biological matrices.

Given their first-order kinetics with half-lives on the order of hours (~5−12 hours for MBzP) (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 found that sampling time was not a significant predictor of urinary MBzP concentrations; that is, there was little difference in MBzP levels for women whose samples were collected in early morning, morning, early afternoon, or evening time periods (geometric mean specific gravity adjusted MBzP 4.5, 3.9, 4.2, and 4.7, respectively, for these four periods, $p = 0.74$) (Cantonwine et al., 2014). Urinary measures of BBP metabolite concentrations in epidemiological studies are generally conducted using spot urine samples (i.e., collected at time of a clinic or study examination visit) rather than at a specified time (e.g., first morning void) or in 24-hour urine samples. Although the time of sample collection described above may affect the accuracy of an estimated intake for a single individual, studies of other phthalates (e.g., DEHP) have demonstrated that on a group level, spot urine samples provide a reasonable approximation of concentrations that would have been observed using full-day urine samples (Christensen et al., 2014) and that a single spot sample was reliable in ranking subjects according to tertile of MBzP (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 BBP 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 BBP metabolites as continuous measures.

Another potential limitation of measurement of BBP 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 0.64 for MBzP was reported in a study of 25 Hmong women ages 19–51 years with samples collected 2–4 weeks apart (Peck et al., 2010). For MBzP measures in 46 women ages 35–49 years, a moderate correlation was seen over a period of 2 days (ICC of 0.34 unadjusted, 0.53 creatinine-adjusted) (Hoppin et al., 2002). Similar values were seen in two studies in men with longer sampling periods (approximately 3 months): in 33 men ages 18–22 years, the ICCs for MBzP in spot urine samples were 0.38 (unadjusted) and 0.39 (osmolality-adjusted) in (Frederiksen et al., 2013), and in 11 men with up to 9 spot urine samples collected on 3 consecutive days in each of 3 monthly cycles, the ICC was 0.43 (Hauser et al., 2004). In studies of reproducibility of measures during pregnancy, Cantonwine et al. (2014) reported ICCs of 0.37 and 0.41 (unadjusted and specific-gravity adjusted) when comparing urine samples taken at approximately 18, 22, and 26 weeks of gestation. ICCs of 0.35 and 0.28, respectively, were seen before pregnancy and in early pregnancy (Braun et al., 2012), and an ICC of approximately 0.65 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 0.33 for all samples, and was 0.31 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 reported ICCs of 0.47 (unadjusted) and 0.62 (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 "high molecular weight" phthalate measure based on the summation of DEHP metabolites and MBzP. Because MBzP does not represent a major contributor to this summation, EPA has not included data from these studies in the BBP 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 result in a change in BBP exposure. This type of

scenario adds an additional challenge to the interpretation of the BBP 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.

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 the 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 AGD 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, have also been examined in relation to direct or indirect measures of fetal testosterone levels, including studies of BBP. 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 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 BBP 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 BBP 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 BBP 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.

Other female reproductive outcomes included in the BBP literature include 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 male are before the age of 9 years for precocious puberty and lack of pubertal development by the age of 14 years for delayed puberty (Marshall and Tanner, 1970). Clinical evaluation would involve hormone assays to distinguish between gonadotropin dependent

("central"), gonadotropin independent ("peripheral"), or a combination of both (Traggiai and Stanhope, 2003) forms of these conditions.

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).

Expectant mothers can encounter pregnancy loss either through a stillbirth (fetal death after 20 gestational weeks) or from a spontaneous abortion also known as a miscarriage (fetal death during the first 20 gestational weeks). Pregnancy loss can occur even before a clinically recognized pregnancy; early pregnancy (or "subclinical") loss, determined by measurement of human chorionic gonadotropin, is very common, accounting for approximately 20% of pregnancies (Wilcox et al., 1988). Thus, complete ascertainment of pregnancy loss requires this type of monitoring for subclinical loss.

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).

Pulmonary function

The American Thoracic Society has published guidelines for equipment performance requirements, validation, quality control, test procedures, and reference equations for each type of spirometric measurement (Miller et al., 2005), as well as the interpretation of testing results (Pellegrino et al., 2005). Lung function varies by race or ethnic origin, gender, age, and height, and is best compared when normalized to the expected lung function based on these variables (Pellegrino et al., 2005; Hankinson et al., 1999). Some measures (e.g., forced expiratory volume in 1 second [FEV_1] and peak expiratory flow [PEF]) exhibit diurnal variation (Chan-Yeung, 2000; Lebowitz et al., 1997); thus, time of day of the lung function measures should also be considered.

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 BBP 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 BBP (i.e., whether BBP 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 BBP. 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 BBP levels. With respect to variability relating to time of day, as noted previously, one study of 139 pregnant women in Puerto Rico reported little variation by sampling time (early morning, morning, early afternoon, or evening) of specific gravity-adjusted MBzP (Cantonwine et al., 2014)). Based on these data, EPA does not consider the lack of consideration of time of day or season in the analysis of thyroid outcomes to be a likely source of bias, but recognizes the limited nature of the available data.

Obesity

Most of the study of obesity measures in the BBP 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 BBP 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.

Confounding

The general considerations for evaluating issues relating to potential confounding include consideration of which factors may be potential confounders (i.e., those that 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., BBP) 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 MBzP 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 MBzP and monoethyl phthalate (MEP) (the primary metabolite of DEP) was low (0.28). A more moderate correlation was seen between MBzP and DEHP metabolites (correlations of approximately 0.5); higher correlations were seen with monoisubutyl phthalate (MIBP) (the primary metabolite of DIBP, Spearman r = 0.58) and with MBP (the primary metabolite of DBP, Spearman r = 0.70). Similar or somewhat lower correlations were seen between MBzP and other phthalate metabolites in 463 men seen in an infertility clinic (Hauser et al., 2006), 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 MBzP would not be considered a limitation in a study in which an association was seen with MBzP that was not seen with MBP; 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 MBzP levels decreased with age (geometric means of 15.1, 8.54, and 5.94 µg/g-creatinine, respectively, in ages 6–11, 12–19, and ≥20 years) (CDC, 2013). Smaller differences were seen when comparing distributions by sex (geometric means of 6.21 and 7.29 µg/g-creatinine, respectively, in males and females), and by ethnicity (geometric means of 7.53, 6.83, and 6.50 µg/g-creatinine, respectively, in Mexican Americans, non-Hispanic whites, and non-Hispanic blacks). EPA will consider these differences in assessing the potential influence of demographic factors on observed effect estimates for BBP.

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 BBP (or its metabolites).

Data Analysis

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

One other issue specific too much of the BBP literature concerns the optimal approach to addressing urinary volume or dilution in the analysis of spot urine or first morning void samples. Options include use of creatinine- or specific gravity-adjusted metabolite concentrations, or use of unadjusted concentrations. Although use of some kind of correction factor has been advocated for studies of obesity (Goodman et al., 2014), a simulation study reported that creatinine-adjusted exposure measures may produce biased effect estimates for outcomes that are strongly related to factors affecting creatinine levels, of which obesity is a prime example (Christensen et al., 2014). EPA recognizes the lack of consensus at this time, as well as the need for continued research into the potential bias introduced by different analytic approaches. Based on current understanding of this issue, EPA prefers results using unadjusted concentrations 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 BBP 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 BBP 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 mo 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 mo 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 or 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 mo 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, infections, pregnancy complications (e.g., pre-eclampsia), nutritional intake, smoking, alcohol/drug use, weight gain during pregnancy; maternal height/BMI, heavy metal exposures (consider if these are related to exposure)
Relevant exposure time window(s)	• In utero
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 mo): up to 12 mo preceding outcome assessment
Respiratory (noncancer) – pulmonary function **Measures**	• Standard protocol
Consideration of confounding	• Age, sex, height, smoking
Relevant exposure time window(s)	• Up to 6 months preceding pulmonary function measures
Neurobehavioral	• Standardized assessment tool, validation studies for specific study

Measures	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 BBP

Beyond the initial methodological screening described above in Section 2.2.2, methodological aspects of a study's design, conduct, or 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 and 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 of 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 butyl benzyl phthalate (BBP) 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 BBP 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 order by duration, followed by species and strain. Finally, animal metabolite studies are also presented as monobutyl phthalate (MBP) and monobenzyl phthalate (MBzP) are thought to contribute to developmental toxicity. Inclusion of these studies may help to inform the hazard identification for BBP. Most results are presented as the percent change from the control group; an asterisk (*) indicates a result that has been calculated and reported by study authors to be statistically significant compared to controls (p <0.05). Unless otherwise noted in a footnote, doses presented in the animal evidence tables were those reported by the study authors.

The information in the preliminary evidence tables for BBP 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 On-line (HERO) website at http://hero.epa.gov/BBP and http://hero.epa.gov/phthalates-humanstudies.

3.2. EPIDEMIOLOGICAL STUDIES

3.2.1. Sexual Differentiation Measures

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

Reference and study design	Results
Anogenital distance (AGD)	
Suzuki et al. (2012) (Japan) **Population:** 111 male infants from birth cohort study, time period not given **Outcome:** AGD measured 1–3 d after birth (AGD1 to anterior genitalia, mean 45.8 mm, 14.8 mm/kg; AGD2 to posterior genitalia, mean 20.3 mm, 6.6 mm/kg) **Exposure:** Maternal urine samples, mean 29 wks of gestation MBzP in urine (ng/mL): Median 75th percentile Unadjusted 3.57 8.73 SG-adjusted 4.73 10.8 **Analysis:** Linear regression considering gestational week, birth order, maternal age, maternal smoking during pregnancy, maternal environmental tobacco smoke exposure, maternal urinary daidzein (soy isoflavone) and equol (a urinary metabolite of daidzein) concentrations, and environmental tobacco smoke (smoking status of husbands of nonsmoking women) as potential confounders	Association between MBzP and AGD measures reported as not statistically significant (quantitative results not reported)
Swan (2008) (United States; Minnesota, Missouri, California) **Population:** 106 boys from birth cohort study (SFF), 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 MBzP in urine (ng/mL): Median 75th percentile Unadjusted 8.3 23.5 **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 MBzP concentration (*p*-value) MBzP −0.4 (0.826)

Reference and study design	Results
Cryptorchidism or testicular position	
Swan (2008) (United States; Minnesota, Missouri, California) **Population:** 106 boys from birth cohort study (SFF), 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 MBzP in urine (ng/mL): Median 75th percentile Unadjusted 8.3 23.5 **Analysis:** Logistic regression, adjusting for age and weight percentile **Related references:** Swan et al. (2005) (exposure data)	MBzP reported as not associated with testicular position (quantitative results not reported)
Main et al. (2006) (Denmark, Finland) **Population:** 62 cases, 68 controls from two pregnancy cohorts, born 1997–2001, age 3 mo **Outcome:** Cryptorchidism, at birth and/or 3 mo **Exposure:** Breast milk samples collected 1–3 mo of age MBzP in breast milk (µg/L), all samples: Median (range) Denmark 0.9 (0.2–14) Finland 1.3 (0.4–26) **Analysis:** Mann-Whitney U-test for comparison of MBzP concentrations in boys with and without cryptorchidism	Median MBzP in breast milk (µg/L) Controls Cases 1.20 1.25 (p >0.40)

Reference and study design	Results
Infant hormone levels	
Lin et al. (2011a) (Taiwan) **Population:** 155 infants (81 boys, 74 girls) from birth cohort, born 2000–2001 **Outcome:** Cord blood hormone levels **Exposure:** Maternal urine sample 3rd trimester MBzP in urine (percentile): Median 75th 95th Unadjusted (ng/mL) 8.85 15.1 40.3 Cr-adjusted (µg/g Cr) 15.6 25.9 43.9 **Analysis:** Pearson correlation analysis and linear regression adjusted for variables shown in the results column	Pearson correlation coefficient (r) and regression coefficient (β), log-MBzP (µg/g Cr) and cord blood hormone level (regression adjusted for maternal age, BMI, smoking habit, gestational age, parity, and use of contraceptive drugs) r β Boys Free testosterone (ng/dL) 0.05 NR Estradiol (pg/mL) 0.14 0.11 Free testostone:estradiol ratio −0.03 −0.01 Girls Free testosterone (ng/dL) −0.18 NR Estradiol (pg/mL) −0.20* 0.00 Free testostone:estradiol ratio −0.10 0.10 NR = not reported *p <0.10; all other p-values >0.10
Main et al. (2006) (Denmark, Finland) **Population:** 130 male infants from two pregnancy cohorts (cryptorchidism cases and controls combined for this analysis), born 1997–2001, age 3 mo **Outcome:** Serum steroidal and gonadotropin hormone levels in infants, samples collected when breast milk samples delivered to hospital **Exposure:** Breast milk samples collected 1–3 mo of age MBzP in breast milk (µg/L), all samples: Median (range) Denmark 0.9 (0.2–14) Finland 1.3 (0.4–26) **Analysis:** Cases and controls combined for analysis of association between metabolite concentration and hormone analysis using partial Spearman correlation coefficients adjusted for country of birth	Spearman correlation coefficient (p-value), MBzP (µg/L) and serum hormone level (n = 96 boys) SHBG (nmol/L) 0.188 (0.074) Free testosterone (nmol/L) −0.007 (0.951) Testosterone (nmol/L) 0.115 (0.271) LH (IU/L) 0.049 (0.643) FSH (IU/L) 0.045 (0.668)

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 (SFF), 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 MBzP in urine (ng/mL); distribution not reported for this analysis; EPA assumed similar distribution as seen in Swan et al. (2005) MBzP in urine (ng/mL): Median 75th percentile Unadjusted 8.3 23.5 **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)	log-MBzP reported as not associated with masculine or composite activity score (quantitative results not reported)

BMI = body mass index; FSH = follicle stimulating hormone; LH= luteinizing hormone; SFF = Study for Future Families; SHBG = sex-hormone binding globulin

3.2.2. Male Reproductive Effects in Humans

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

Reference and study design	Results
Jurewicz et al. (2013) (Poland) **Population:** 269 men from infertility clinic with normal sperm concentration (20–300 million/mL) or slight oligozoospermia (15–20 million/mL); mean age 32 yrs; time period not reported; MBzP measured in 268 samples **Outcome:** Plasma testosterone, E2, and FSH **Exposure:** Urine sample, collected at same time as plasma sample MBzP in urine: Geometric mean (SD) Unadjusted (µg/L) 8.3 (3.2) Cr-adjusted (µg/g Cr) 6.9 (3.5) **Analysis:** Linear regression, adjusting for variables shown in results column	Regression coefficient (*p*-value) for increase in hormone unit change in log = MBzP (adjusted for age, smoking, medical history [mumps, cryptorchidism, testes surgery, testes trauma], abstinence time, and urinary creatinine) Testosterone (ng/mL) −0.09 (0.52) E2 (pg/mL) 0.87 (0.11) FSH (IU/L) 0.26 (0.096)
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 MBzP in urine (ng/mL): Median 95^{th} percentile Unadjusted 34 164 **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 MBzP) 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. (2012) (United States; Minnesota, Missouri, California, Iowa, Boston) **Populations:** 425 fertile men with pregnant partners enrolled in birth cohort study (SFF), 1999–2005; mean age 32 yrs; 425 men who were male partners of infertile couples seeking evaluation (MGH); 2000–2004, mean age 36 yrs **Outcome:** Serum steroidal and gonadotropin hormones **Exposure:** Urine sample, collected at same time as serum sample for hormone analysis MBzP in urine (ng/mL): Median 90^{th} percentile SFF: Unadjusted 12.5 49.8	Authors report "no associations between any hormone levels [testosterone, estradiol, SHBG, LH, inhibin-B, or FSH] and any urinary metabolites of phthalates other than DEHP" [including MzBP] (quantitative results not reported)

Reference and study design	Results
MGH: Unadjusted 8.2 24.9 All: Unadjusted 9.8 41.2 **Analysis:** Pearson correlation coefficients of log(10)-transformed MzBP and hormone measures (bivariate analysis); linear regression considering age, age square, BMI, smoking status, ethnicity, urinary creatinine concentration (SFF models) or specific gravity (MGH models), time of sample collection, time of collection squared, and study center (SFF vs MGH) for each population separately and for the pooled population **Related references:** This is a pooled analysis of a study of fertile men (Mendiola et al., 2011) and men from infertile couples (Meeker et al., 2009a)	
Mendiola et al. (2011) (United States; Minnesota, Missouri, California, Iowa, New York) **Population**: 425 fertile men with pregnant partners enrolled in birth cohort study (SFF), 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; data reported in Mendiola et al. (2012) MBzP in urine (ng/mL): Median 90th percentile Unadjusted 12.5 49.8 **Analysis**: Pearson correlation coefficients of log(10)-transformed MzBP and hormone measures (univariate analysis); linear regression considering age, age square, BMI, smoking status, ethnicity, urinary creatinine concentration, time of sample collection, and time of collection squared	Authors report "little or no association with metabolites of phthalate other than DEHP" [including MzBP] with testosterone, estradiol, SHBG, LH, inhibin-B, or FSH (quantitative results not reported)
Meeker et al. (2009a) (United States; Boston) **Population:** 425 men from subfertility clinic, 2000–2004; mean age 36 yrs **Outcome:** Serum steroidal and gonadotropin hormones **Exposure:** Urine sample, collected at same time as serum sample MBzP in urine (ng/mL) (percentile): Median 75th percentile 95th percentile SG-adjusted 8.20 15.9 40.6 **Analysis:** Linear regression using untransformed (testosterone, estradiol) or natural logarithm transformed (free androgen index, FSH, LH) hormone levels; considering age, BMI, smoking status, race, previous infertility example, prior ability to impregnate partner, and season and time of sample collection as potential covariates **Related references:** Duty et al. (2005)	Regression coefficient (95% CI) for change in hormone with IQR increase in adjusted MBzP concentration (adjusted for age, BMI, smoking, season and time of day sample was collected, and [for testosterone and estradiol only] SHBG) Untransformed hormone level (0.0 = no effect) Testosterone (ng/dL) 4.58 (−7.91, 17.0) Estradiol (pg/mL) −0.21 (−1.53, 1.09) Inhibin B (pg/mL) 1.81 (−6.54, 10.2) Ln-transformed hormone level (1.0 = no effect) Free androgen index 1.03 (0.99, 1.07) FSH (IU/L) 0.98 (0.92, 1.04) LH (IU/L) 1.00 (0.95, 1.05) SHBG (nmol/mL) 1.00 (0.95, 1.04)

Reference and study design	Results
	Prolactin (ng/mL) 1.01 (0.96, 1.06)
Jonsson et al. (2005) (Sweden) **Population:** 234 men from general population, assessed at military conscription exam in 2000; ages 18–21 yrs **Outcome:** Serum steroidal and gonadotropin hormones **Exposure:** Urine sample, collected at same time as serum sample for hormone analysis MBzP in urine (percentile): Median 75th 95th Unadjusted (ng/mL) 16 37 74 Adjusted (nmol/mmol Cr) 4.4 7.6 19 **Analysis:** Mean difference between high and low quartiles	Mean difference (95% CI), highest (≥7.71 nmol/mmol Cr) compared with lowest quartile of MBzP (≤1.10 nmol/mmol Cr) Testosterone (nM) −0.03 (−2.1, 2.0) Free testosterone (T/SHBG) 0.06 (−0.05, 0.2) Estradiol (pM) 0.7 (−5.3, 6.7) FSH (IU/L) 0.1 (−0.5, 0.7) LH (IU/L) 0.4 (−0.2, 1.0)

CI = confidence interval; DEHP = di(2-ethylhexyl)phthalate; E2 = estradiol; IQR = interquartile range; MGH = Massachusetts General Hospital; SD = standard deviation

3.2.3. Male Pubertal Development in Humans

Table 3-3. Evidence pertaining to BBP 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 MBzP in urine (ng/mL): Median 95th percentile Maternal sample 5.20 15.4 Child's sample 5.60 19.9 **Analysis:** Logistic regression for analysis of puberty onset, adjusting for variables shown in results column; linear regression for analysis of hormone levels, considering age, BMI z-score, socioeconomic status, and maternal smoking potential covariates	OR (95% CI) for adrenarche or puberty per interquartile increase in ln-transformed MBzP (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): 0.27 (0.08, 0.94) / 0.73 (0.21, 2.58) Genitalia (stage ≥2): 0.76 (0.47, 1.23) / 1.71 (0.78, 3.76) Testicular volume (>3 mL): 0.76 (0.41, 1.41) / 2.17 (0.80, 5.87) Percent change (95% CI) in serum hormone level per interquartile increase in ln-transformed MzBP (adjusted for urine specific gravity, child age, and BMI z-score) Exposure basis Serum hormone / Maternal urine (prenatal) / Child urine Testosterone: 3.82 (−18.4, 32.1) / −23.5 (−47.3, 11.1) Free testosterone: −3.21 (−24.6, 24.3) / −28.3 (−51.5, 6.04) SHBG: 11.0 (2.33, 20.3) / 7.77 (−5.56, 23.0) DHEAS: −3.35 (−14.0, 8.58) / 8.49 (−9.56, 30.2) Estradiol: −1.18 (−8.36, 6.57) / −10.2(−20.1, 0.96) Inhibin B: −4.81 (−12.8, 3.95) / 9.50 (−4.40, 25.4)

Reference and study design	Results
Mouritsen et al. (2013b) (Denmark) Population: 53 boys from population-based cohort (COPENHAGEN Puberty Study), 2006–2010; age 11 yrs 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 MBzP in urine (ng/mL): Geometric mean: 49; Maximum: 1,660 (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)	Median age (yrs) at development by MBzP level Pubarche (pubic hair stage ≥2): Low 12.1; High 11.4 Testicular volume >3 mL: Low 11.6; High 11 Median hormone concentration by MBzP level Testosterone (nmol/L): Low <0.23; High <0.23 DHEAS (µmol/L): Low 2.14; High 1.33 (p <0.05) Adione (nmol/L): Low 1.46; High 1.13 Estradiol (pmol/L): Low <18; High <18 FSH (IU/L): Low 1.38; High 1.5 LH (IU/L): Low 0.25; High 0.28
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 MBzP in urine (ng/mL): Group 3 (boys without gynecomastia, all ages): Median 47.70; 95th percentile 219.2 **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	MBzP concentration (ng/mL) by group Median: Group 1 (n = 38) 56.79; Group 2 (n = 189) 47.20; Group 3 (n = 517) 47.70 95th percentile: Group 1 211.0; Group 2 185.3; Group 3 219.2 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 MBzP concentration and timing of puberty or serum testosterone level (quantitative results not reported)

OR = odds ratio

3.2.4. Semen Parameters and Infertility

Table 3-4. Evidence pertaining to BBP 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 MBzP in urine Unadjusted (µg/L) 3.5 20.7 Cr-adjusted (µg/g Cr) 2.9 15.5 **Analysis:** Spearman correlation	Spearman correlation coefficient, MBzP and sperm parameters: Sperm concentration −0.014 Sperm motility 0.058 (p >0.05 for both parameters)
(Jurewicz et al. (2013)) (Poland) **Population:** 269 men from infertility clinic with normal sperm concentration (20–300 million/mL) or slight oligozoospermia (15–20 million/mL); mean age 32 yrs; time period not reported; MBzP measured in 268 samples **Outcome:** Semen analysis **Exposure:** Urine sample, collected at same time as semen sample MBzP in urine: Geometric mean (SD) Unadjusted (µg/L) 8.3 (3.2) Cr-adjusted (µg/g Cr) 6.9 (3.5) **Analysis:** Linear regression, adjusting for variables shown in results column	Regression coefficient (p-value) for change in sperm parameter with unit change in log-MBzP (adjusted for age, smoking, medical history [mumps, cryptorchidism, testes surgery, testes trauma], abstinence time, and urinary creatinine) Log-transformed sperm concentration (million/mL) −0.07 (0.25) Sperm motility (%) 1.86 (0.10) Abnormal sperm morphology (%) 1.17 (0.28) DNA fragmentation index −0.05 (0.20)
Joensen et al. (2012) (Denmark) **Population:** 881 men from general population, assessed at military conscript exam*, 2007–2009, median age 19.1 yrs (5^{th}–95^{th} percentile: 18.4–22.0 yrs) **Outcome:** Semen analysis **Exposure:** Urine sample, collected at same time as semen sample MBzP in urine (ng/mL): Median 95^{th} percentile Unadjusted 34 164 **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	Results for individual phthalate metabolites (including MBzP) reported as "few significant associations" with sperm volume, count, or percentage progressively motile sperm (quantitative results not reported; analyses adjusted for abstinence time [volume, concentration, and count] or time from ejaculation to analysis [progressively motile]; percent of morphologically normal sperm was left unadjusted)

Reference[a] and Study Design	Results
*As reported by Ravnborg et al. (2011)	
Liu et al. (2012) (China) **Population:** 97 men from subfertility clinic, 2009–2010; mean age 32 yrs **Outcome:** Semen analysis; results dichotomized above and below WHO reference values; n = 43 with normal semen parameters **Exposure:** Urine sample, collected at same time as semen sample MBzP in urine: Unadjusted (ng/mL): Median <LOD*, 66th percentile 0.06 Cr-adjusted (µg/g Cr): Median <LOD, 66th percentile 0.07 **Analysis:** Logistic regression, considering age, BMI, abstinence time, smoking, alcohol use, and education as potential covariates *LOD = 0.15 ng/mL	OR (95% CI) by tertile of MBzP (adjusted for age, BMI, abstinence time, smoking, and alcohol use) MBzP Tertile: Sperm concentration <20 × 10^6/mL (n = 11); Sperm motility <50% motile (n = 34); Semen volume <2 mL (n = 15) 1 (low): 1.0 (referent); 1.0 (referent); 1.0 (referent) 2: 3.1 (0.4, 26.4); 0.7 (0.2, 3.4); 0.5 (0.1, 4.8) 3 (high): 1.2 (0.2, 6.9); 1.4 (0.5, 4.0); 0.3 (0.1, 1.6) (trend *p*): (0.87); (0.47); (0.33)
Toshima et al. (2012) (Japan) **Population:** 42 men visiting gynecology clinic for infertility consultation in 2010; mean age 37 yrs **Outcome:** Semen analysis; results also dichotomized above and below WHO reference values (semen volume of 1.5 mL, sperm concentration of 15 × 10^6/mL, and motility of 40%) **Exposure:** Urine sample, collected on same day as semen sample MBzP in urine (ng/mL): Geometric mean (SD) SG-adjusted: 9.73 (3.12) **Analysis:** Urine concentrations compared between dichotomized groups using t-test; linear regression between SG-adjusted MBzP and continuous outcome variables, considering age, abstinence time, BMI, smoking status, frequency of consumption of vegetables, fruits, and coffee, and presence of detectable levels of equol potential covariates	No statistically significant differences in urinary MBzP concentrations were observed in groups dichotomized on sperm concentration or motility (quantitative results not reported) Authors reported no statistically significant association between urinary MBzP and semen volume, sperm concentration, or sperm motility analyzed by linear regression (quantitative results not reported)
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) MBzP in urine (ng/mL) (percentile): Median 75th 95th 17.4 31.3 166.6 **Analysis:** Dichotomized outcomes (above and	OR (95% CI) for MBzP above versus below median Low sperm concentration <20 × 10^6/mL: 1.4 (0.3, 6.3)[a] Low sperm motility <50% motile: 1.3 (0.3, 5.5)[b] Abnormal sperm morphology: 0.9 (0.2, 3.0)[c] [a]Adjusted for race (whites, nonwhites) and specific gravity [b]Adjusted for age, alcohol use (≤3 and >3 servings/wk), and specific gravity [c]Adjusted for specific gravity

<table>
<tr><th>Reference[a] and Study Design</th><th>Results</th></tr>
<tr><td>below WHO reference values), MBzP dichotomized at median or divided into tertiles; age, education (3 levels), income (3 levels), race, BMI (3 levels), current smoking status, and alcohol use (2 levels) considered as potential confounders; specific gravity also included in all models</td><td>Results of tertile analysis not reported</td></tr>
<tr><td>Hauser et al. (2007) (United States; Boston)
Population: 379 male partners from subfertility clinic, 2000–2004; mean age 36 yrs
Outcome: Sperm DNA damage assessed by neutral comet assay
Exposure: Urine sample, collected at same time as semen sample
MBzP in urine (ng/mL) (percentile):
Median 75th 95th
SG-adjusted 7.9 15.0 46.2
Analysis: Linear regression, considering age, abstinence time, smoking status, and race as potential covariates
Related reference: Duty et al. (2003b)</td><td>Regression coefficient (95% CI) for DNA damage associated with interquartile range increase in ln-MBzP (adjusted for age and smoking status)
Comet extent (µm): 5.12 (0.98, 9.25)
Tail distribution (µm): 2.49 (0.82, 4.13)
%DNA tail: 0.11 (−1.56, 1.77)</td></tr>
<tr><td>Hauser et al. (2006) (United States; Boston)
Population: 443 male partners from subfertility clinic 2000–2004; mean age 36 yrs
Outcome: Semen analysis; results dichotomized above and below WHO reference values
Exposure: Urine sample, collected at same time as serum sample for hormone analysis
MBzP in urine (ng/mL) (percentile):
Median 75th 95th
SG-adjusted 8.0 15.5 40.6
Analysis: Logistic regression, considering age, race, BMI, abstinence time, and smoking as potential covariates
Related references: (Hauser et al. (2005); Duty et al. (2004); Duty et al. (2003a))</td><td>OR (95% CI) by quartile of MBzP (ng/mL) (adjusted for age, abstinence time, and smoking; comparison group = 210 men without deficiencies on any of these three parameters)
<table>
<tr><th>MBzP quartile</th><th>Sperm concentration <20 × 10^6/mL</th><th>Sperm motility <50% motile</th><th>Sperm morphology <4% normal</th></tr>
<tr><td>1 (low)</td><td>1.0 (referent)</td><td>1.0 (referent)</td><td>1.0 (referent)</td></tr>
<tr><td>2</td><td>1.1 (0.4, 2.6)</td><td>1.3 (0.7, 2.3)</td><td>0.7 (0.3, 1.4)</td></tr>
<tr><td>3</td><td>1.1 (0.4, 2.5)</td><td>1.3 (0.8, 2.3)</td><td>0.9 (0.4, 1.7)</td></tr>
<tr><td>4 (high)</td><td>1.9 (0.8, 4.3)</td><td>1.3 (0.7, 2.3)</td><td>1.1 (0.6, 2.1)</td></tr>
<tr><td>(trend p)</td><td>(0.13)</td><td>(0.36)</td><td>(0.76)</td></tr>
</table>
Regression coefficient (95% CI) for sperm motion parameters by quartile of MBzP (ng/mL) (adjusted for age, smoking, and abstinence time)
<table>
<tr><th>MBzP (ng/mL) quartile</th><th>Straight line velocity (µm/s)</th><th>Curvilinear velocity (µm/s)</th><th>Linearity (%)</th></tr>
<tr><td>1 (low)</td><td>1.0 (referent)</td><td>1.0 (referent)</td><td>1.0 (referent)</td></tr>
<tr><td>2</td><td>0.66 (−2.01, 3.34)</td><td>1.44 (−3.10, 5.99)</td><td>−0.23 (−2.12, 1.66)</td></tr>
<tr><td>3</td><td>0.11 (−2.59, 2.81)</td><td>1.29 (−3.29, 5.88)</td><td>−1.13 (−3.04, 0.77)</td></tr>
<tr><td>4 (high)</td><td>−1.31</td><td>−1.20</td><td>−0.69</td></tr>
</table>
</td></tr>
</table>

Reference[a] and Study Design	Results
	(−3.98, 1.36) (−5.73, 3.34) (−2.58, 1.20) (trend *p*) (0.29) (0.60) (0.33) MBzP quartile cut points: 0.04−4.2, 4.2−8.0, 8.0−15.3, 15.5−540.2 ng/mL No interaction with PCBs
Jonsson et al. (2005) (Sweden) **Population:** 234 men from general population, assessed at military conscription exam in 2000; ages 18−21 yrs **Outcome:** Semen analysis **Exposure:** Urine sample, collected at same time as semen sample MBzP in urine (percentile): Median 75th 95th Unadjusted (ng/mL) 16 37 74 Adjusted (nmol/mmol Cr) 4.4 7.6 19 **Analysis:** Mean difference between high and low quartiles	Mean difference (95% CI), highest (≥7.71 nmol/mmol Cr) compared with lowest (≤1.10 nmol/mmol Cr) quartile MBzP (positive difference indicates lower value in highest exposure quartile) Sperm concentration (× 10^6/mL) 7.2 (−16, 31) Sperm motility (%) −4.3 (−10, 1.6) Sperm damage (chromatin integrity) −0.3 (−3.7, 3.1)
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 MBzP in urine (ng/mL) among couples achieving pregnancy: Geometric mean (95% CI) Women 4.61 (4.06−5.23) Men 2.79 (2.44−3.19) **Analysis:** Fecundability ORs calculated using Cox models, adjusting for variables shown in results column	Fecundability OR (95% CI) per unit increase in log-transformed MBzP scaled by SD (adjusted for female age, difference in couples' ages, research site, and both partners' urinary creatinine, BMI, and serum cotinine; in addition, results for exposure in each partner adjusted for exposure in the other partner, and models accounted for left truncation or time off contraception) Women 0.98 (0.81, 1.20) Men 0.80 (0.67, 0.97)

Reference[a] and Study Design	Results
Tranfo et al. (2012) (Italy) **Population:** 56 infertile couples from assisted reproduction center, 56 fertile couples (parents of one or more children, living in same area), time period not reported; mean age 39–40 yrs in both groups **Outcome:** Primary or secondary infertility as assessed by WHO criteria (cause attributed to males in 8/56 couples) **Exposure:** Urine sample MBzP in urine, fertile couples: Median 95th percentile Cr-adjusted (µg/g Cr) 8.8 85.32 **Analysis:** Mann-Whitney U-test for comparison of MBzP concentrations by group	MBzP concentration in urine (µg/g Cr) in fertile and infertile couples Fertile Infertile *p*-value Median 8.80 12.37 0.009 95th percentile 85.32 88.10 Sex-stratified comparison was similar for men and for women, though the *p*-value was slightly higher than 0.05 (quantitative results not reported)

DNA = deoxyribonucleic acid; LOD = level of detection; PCB = polychlorinated biphenyl; WHO = World Health Organization

3.2.5. Female Reproductive Effects in Humans

Table 3-5. Evidence pertaining to BBP 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 (SFF), 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 MBzP in urine (ng/mL): Median 75th percentile Unadjusted 11.0 38.6 **Analysis:** Linear regression, log-transformed MBzP, and log-transformed hormone level	Regression coefficient (95% CI) for change in maternal log-transformed serum hormone level with unit increase in log-transformed MBzP, stratified by sex of fetus Mothers with male fetus (n = 94) / Mothers with female fetus (n = 86) Testosterone (total): 0.06 (−0.07, 0.19) / −0.13 (−0.26, 0.01) Testosterone (free): 0.07 (−0.07, 0.21) / −0.10 (−0.25, 0.04) Estradiol: −0.03 (−0.12, 0.07) / −0.10 (−0.23, 0.03)
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) MBzP in serum (ng/mL): Median 90th percentile MBzP 1.26 3.87 **Analysis:** Correlation between quartiles of serum MBzP and log-transformed hormone levels	Correlation coefficient between log-transformed maternal serum hormone level and quartiles of MBzP in maternal serum At 18 wks of gestation (n = 119) / At 34–36 wks of gestation (n = 114) Androstene-dione (nmol/L): −0.006 / −0.045 DHEAS (µmol/L): −0.057 / −0.132 Testosterone (pmol/L): −0.009 / −0.063 SHBG (nmol/L): −0.123 / −0.149 Free testosterone (pmol/L): 0.037 / 0.027 Free testosterone index: 0.053 / 0.033 *p* >0.10 for all correlations

3.2.6. Female Pubertal Development in Humans

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

Reference and study design	Results
Precocious puberty or thelarche	
Chen et al. (2013) (Taiwan) Population: 71 girls with central precocious puberty from pediatric endocrinology clinic and 29 controls from schools recruited 2006–2009; mean ages 8.1 and 6.8 yrs, respectively Outcome: Premature puberty based on appearance of thelarche, pubic hair or menarche before 8 yrs of age; Tanner staging and serum levels of LH releasing hormone used for additional classification Exposure: Urine sample (child's), collected at same time as clinical assessment MBzP in urine of controls: Mean (95% CI) Unadjusted (ng/mL) 2.45 (0.70, 18.4) Cr-adjusted (µg/g Cr) 3.74 (0.95, 50.4) Analysis: MBzP concentrations in cases and controls compared with Mann-Whitney U-test	Mean (95% CI) MBzP in cases and controls Controls / Cases / (*p*-value) Unadjusted (ng/mL): 2.45 (0.70, 18.4) / 6.22 (0.70, 167) / (0.002) Cr-adjusted (µg/g Cr): 3.74 (0.95, 50.4) / 9.0 (1.14, 172) / (0.005)
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 years **Outcome:** Precocious puberty, early normal puberty, or premature thelarche, based on Tanner staging by physician **Exposure:** Urine sample (child's), collected at clinical evaluation MBzP in urine (ng/mL), controls: Median 95th percentile Unadjusted 48 212 (based on larger sample of 725 controls) **Analysis:** MBzP 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) MBzP (ng/mL) in cases and controls Controls / Precocious puberty / (*p*-value) 54 (4.6–779) / 38 (7.5–177) / (<0.05)

Reference and study design	Results
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 MBzP in urine of controls: Mean ± SE Unadjusted (ng/mL) 42.8 ± 8.8 Cr-adjusted (µg/g Cr) 40.5 ± 7.1 **Analysis:** MBzP concentrations in cases and controls compared with Wilcoxon rank-sum test	Mean ± SE MBzP in cases and controls Unadjusted (ng/mL): Controls 42.8 ± 8.8; Central precocious puberty 40.2 ± 8.4; (*p*-value) (0.81) Cr-adjusted (µg/g Cr): Controls 40.5 ± 7.1; Central precocious puberty 50.6 ± 11.4; (*p*-value) (0.92)
Chou et al. (2009) (Taiwan) **Population:** 30 girls with premature thelarche and 26 girls with central precocious puberty from pediatric endocrinology clinic; 33 controls from school exams; mean ages 6.7, 8.0, and 8.2 yrs, respectively, in the groups, time period not reported **Outcome:** Premature puberty based on appearance of any physical characteristics of puberty before 8 yrs of age **Exposure:** Urine sample (child's) collected at same time as clinical assessment MBzP in urine (ng/mL), controls: Mean ± SD Unadjusted 3.3 ± 6.1 **Analysis:** One-way ANOVA comparing MBzP concentrations between groups	Unadjusted MBzP in urine; mean ± SD (ng/mL) Controls: 3.3 ± 6.1 Central precocious puberty cases: 12.7 ± 33.0 Premature thelarche cases: 7.4 ± 9.4 *p* >0.3 for comparison with controls
Pubertal development (general population)	
Hart et al. (2013) (Australia) **Population:** 121 girls from birth cohort study (Western Australian Pregnancy Cohort), whose mothers were recruited at 18 wks of gestation 1989–1991; follow-up at ages 14–16 yrs **Outcome:** Age at menarche **Exposure:** Maternal serum samples (n = 123) collected at 18 and 34–36 wks of gestation (combined aliquot from both time periods) MBzP in serum (ng/mL): Median 90th percentile Unadjusted 1.26 3.87	Authors reported no association between MBzP and age at menarche (quantitative results not reported) Authors reported no correlation between MBzP and serum SHBG, FSH, total testosterone, free androgen index, anti-Müllerian hormone, or inhibin B in adolescents (quantitative results not reported by study authors)

Reference and study design	Results
Analysis: Correlation between log-transformed MBzP and age at menarche	
Mouritsen et al. (2013b) (Denmark) Population: 47 girls from population-based cohort (COPENHAGEN Puberty Study), 2006–2010; age 10 yrs 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 Geometric mean Maximum MBzP in urine (ng/mL): 37 433 (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 MBzP level Low / High Pubarche (pubic hair stage ≥2): 10.8 / 10.8 Pubarche (breast stage ≥2): 10.5 / 10.2 Median hormone concentration by MBzP level Low / High Testosterone (nmol/L): <0.23 / <0.23 DHEAS (µmol/L): 1.03 / 0.83 Adione (nmol/L): 1.63 / 1.3 Estradiol (pmol/L): 19 / 20 FSH (IU/L): 2.12 / 1.82 LH (IU/L): 0.08 / 0.11
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; Serum steroid and gonadotropin hormones **Exposure:** Urine sample (child's), collected at time of pubertal stage assessment MBzP in urine (ng/mL), all 725 participants: Median 95th percentile Unadjusted 48 212 **Analysis:** Probit analysis, results verified using Pool-Adjacent-Violators algorithm	Mean age (95% CI) (yrs) at entry into breast stage 2 or pubic hair stage 2, by quartile of MBzP MBzP quartile / Breast stage 2 (n = 394) / Pubic hair stage 2 (n not reported) 1 (low): 9.66 (9.16, 10.14) / 10.96 (10.67, 11.27) 2: 9.92 (9.44, 10.40) / 11.25 (10.93, 11.58) 3: 10.10 (9.63, 10.55) / 10.95 (10.68, 11.24) 4 (high): 10.06 (9.59, 10.54) / 11.39 (11.08, 11.72) Levels of FSH, LH, and estradiol were similar across MBzP exposure groups (quantitative results not reported). A lower prevalence of detectable testosterone was seen with increasing MBzP quartile; however, the association did not remain significant after a correction was applied for skewed age distribution between quartiles (quantitative results not reported)

ANOVA = analysis of variance; DHEAS = dehydroepiandrosterone; SE = standard error

3.2.7. Gynecological Conditions in Humans

Table 3-7. Evidence pertaining to BBP 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 MBzP in urine (ng/mL), unadjusted: Geometric mean Operative cohort-controls 7.82 Population cohort-controls 6.46 **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-MBzP, by cohort (adjusted for age, BMI, and creatinine) Operative cohort 0.84 (0.65, 1.07) Population cohort 1.47 (0.76, 2.85) Adjusted OR (95% CI) for endometriosis per unit increase in ln-MBzP in operative cohort (sensitivity analysis) Endometriosis stage 3 and 4 (n = 339) 0.77 (0.52, 1.14) Visual/histological confirmed endometriosis (n = 473) 1.02 (0.72, 1.42) Comparison with women with postoperative diagnosis normal pelvis (n = 320) 0.79 (0.59, 1.07) 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) MBzP in urine, controls: Median (interquartile range) Unadjusted (ng/mL) 5.0 (2.0–11.5) **Analysis:** Logistic regression (quartiles of exposure), covariates considered based on directed acyclic graph; final model adjusted for variables shown in results column	OR (95% CI) for endometriosis by quartile MzBP (adjusted for ln-transformed urinary creatinine, age, and reference year) MBzP quartile (ng/mL) OR (95% CI) 1 (≤2.0) 1.0 (referent) 2 (2.0–4.0) 1.7 (0.8, 3.8) 3 (5.0–11.5) 1.5 (0.6, 4.0) 4 (>11.5) 1.3 (0.4, 4.0) (trend *p*-value) (0.80) Adjustment for education, smoking status, and alcohol consumption did not alter the results

Reference and study design	**Results**
Huang et al. (2010) (Taiwan) **Population:** 28 endometriosis cases, 36 leiomyoma cases, n = 16 adenomyosis cases, n = 29 controls recruited from the laparotomy patients in medical center, 2005–2007; mean ages ~38, 41, and 36 yrs, respectively **Outcome:** Clinical diagnosis of endometriosis, leiomyoma, or adenomyosis confirmed by pathology **Exposure:** Urine sample MBzP in urine, controls: Median (range) Unadjusted (ng/mL) 5.9 (2.1–26.2) Cr-adjusted (µg/g Cr) 8.9 (2.1–38.7) **Analysis:** Logistic regression, considering age, BMI, and GSTM1 polymorphism as covariates	OR (95% CI) for case status by MBzP above compared with below the median (for endometriosis, adjusted for GSTM1 polymorphism and BMI; for leiomyomas and adenomyosis, adjusted for GSTM1 polymorphism and age) Endometriosis: 1.07 (0.35, 3.28) Leiomyomata: 1.40 (0.48, 4.05) Adenomyosis: 1.33 (0.29, 6.13)
Weuve et al. (2010) (United States, NHANES) **Population:** 87 endometriosis cases, 151 leiomyomata cases, 1,020 controls from population-based survey (NHANES), 1999–2004; ages 20–54 yrs, mean age ~36 yrs **Outcome:** Self-reported diagnosis of endometriosis or leiomyomata; median time since diagnosis, 9 yrs **Exposure:** Urine sample, collected at time of survey MBzP in urine, controls: Geometric mean (SE) Cr-adjusted (ng/mg Cr) 14.1 (0.6) **Analysis:** Logistic regression, adjusting for variables shown in results column	OR (95% CI) for gynecological condition by quartile of MBzP (ng/mg Cr) (adjusted for age, race/ ethnicity, age at menarche, current pregnancy status and current breast-feeding status) MBzP quartile / Endometriosis / Leiomyomata 1 (low) / 1.0 (referent) / 1.0 (referent) 2 / 0.84 (0.37, 1.89) / 1.11 (0.59, 2.07) 3 / 1.17 (0.47, 2.94) / 1.16 (0.64, 2.13) 4 (high) / 1.17 (0.42, 3.27) / 1.14 (0.54, 2.39) (trend *p*) / (0.6) / (0.8)
Itoh et al. (2009) (Japan) **Population:** 57 endometriosis cases, 80 controls; all seeking evaluation for infertility **Outcome:** Clinical diagnosis of endometriosis (American Fertility Society stages II–IV) by laparoscopy; controls were stages 0–1 **Exposure:** Urine sample MBzP in urine, controls: Median 75th percentile Unadjusted (µg/L) 3.2 6.5 Cr-adjusted (µg/g Cr) 1.8 3.3 **Analysis:** Logistic regression, adjusting for variables shown in the results column	OR for endometriosis by MBzP (µg/g Cr), above compared with below the median (adjusted for menstrual regularity and average menstrual cycle length) OR (95% CI) = 1.38 (0.65, 2.91) Median MBzP in urine by stage of endometriosis Endometriosis stage / Unadjusted (µg/L) / Cr-adjusted (µg/g Cr) 0 / 3.0 / 1.8 I / 3.7 / 1.9 II / 4.6 / 2.9 III / 3.3 / 2.0 IV / 4.4 / 2.0 (trend *p*) / (0.06) / (0.37)

Reference and study design	**Results**
Reddy et al. (2006a) (India) **Population:** 49 endometriosis cases, 38 gynecology patient controls (group 1), 21 tubal sterilization controls (group 2), time period not reported; mean age ~27 yrs **Outcome:** Endometriosis based on laparoscopy (American Fertility Society severity staging) **Exposure:** Plasma sample BBP in plasma (µg/mL): Mean ± SD Control group 1 0.12 ± 0.20 Control group 2 0.11 ± 0.22 **Analysis:** Two-sample t-test for comparisons between groups; correlation analysis for association with severity (details not reported)	Plasma BBP, mean ± SD, µg/mL Control 1: 0.12 ± 0.20 Control 2: 0.11 ± 0.22 Endometriosis: 0.66 ± 0.61 $p \leq 0.0002$ compared with either control group BBP concentration positively correlated with severity (r = 0.73, $p < 0.0001$)
Reddy et al. (2006b) (India) **Population:** 85 endometriosis cases, 135 tubal sterilization controls, from subfertility clinic, 1999–2005; mean age ~31 yrs **Outcome:** Endometriosis based on laparoscopy (American Fertility Society severity staging) **Exposure:** Plasma sample BBP in plasma (µg/mL): Mean ± SD Controls 0.14 ± 0.26 **Analysis:** ANOVA for concentration comparisons across stages	Plasma BBP, mean ± SD (µg/mL), by stage of endometriosis Controls: 0.14 ± 0.26 Stage I: 0.28 ± 0.38 Stage II: 0.67 ± 0.50 Stage III: 0.98 ± 0.59 Stage IV: 1.27 ± 0.61 $p < 0.05$ for difference between means
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 MBzP and parameter Uterine volume (mL): r ≤ 0.20 ($p \geq 0.17$) Ovarian volume (cm^3): r ≤ 0.10 ($p \geq 0.29$) Antral follicle count: r ≤ −0.01 ($p \geq 0.25$)

Reference and study design	**Results**
follicle count measured by ultrasound; PCO defined as ≥1 ovary more than 10 cm^3 or ≥12 follicles between 2 and 9 mm in diameter; PCOS defined either as (1) presence of at least two of: polycystic ovarian morphology, clinical or biochemical hyperandrogenism, or oligo-anovulation; or (2) oligo-anovulatory menstrual cycles with either clinical or biochemical hyperandrogenism; all clinical assessments conducted on d 2−5 of menstrual cycle **Exposure:** Maternal serum samples (n = 123) collected at 18 and 34−36 wks of gestation (combined aliquot from both time periods) MBzP in serum (ng/mL): Median 90th percentile MBzP 1.26 3.87 **Analysis:** Correlation between log-transformed MBzP and uterine volume, ovarian volume, and antral follicle counts; MBzP concentrations in PCO or PCOS cases and controls compared calculated using t-tests or Mann-Whitney U-tests	Authors reported no association between MBzP and polycystic ovarian syndrome using either definition (quantitative results not reported)

NHANES = National Health and Nutrition Examination Survey; PCO = polycystic ovarian morphology; PCOS = polycystic ovarian syndrome

3.2.8. Pregnancy Related Outcomes

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

<table>
<tr><th>Reference and study design</th><th>Results</th></tr>
<tr><td colspan="2">Fetal growth (birth weight, birth length, head circumference)</td></tr>
<tr><td>Huang et al. (2014b) (China)
Population: 207 women delivering at one hospital in Chongqing between 2011 and 2012, aged 18–35 yrs, with no history of tobacco or alcohol use; mean age 28 yrs
Outcome: Standard clinical measures at birth
Exposure: Cord blood sample
BBP in cord blood (µg/L):
Median 75th percentile 95th percentile
All samples (<LOD) 0.99 89.87
Analysis: Linear regression, adjusting for variables shown in results column</td><td>Regression coefficients (95% CI) for change in clinical measurement at birth with increase in BBP (as categorical variable, detectable or not detectable) (adjusted for gestational age)
Girls Boys
Birth weight (g) −76 (−208, 56) 128 (−30, 287)
Birth length (cm) −0.18 (−0.99, 0.64) 0.48 (−0.42, 1.39)
Head circumference (mm) −4.07 (−14.57, 6.43) 4.82 (−2.31, 11.94)</td></tr>
<tr><td>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
MBzP in urine (ng/mL):
Median 95th percentile
Measured 17.7 116.6
Standardized* 21.7 209.2
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</td><td>Regression coefficient (95% CI) for change in birth outcome by MBzP tertile and per unit change in ln-MBzP (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)
MBzP tertile (µg/L) | Birth weight (g) | Birth length (cm) | Head circumference (cm)
1 (<17.6) | 0 (referent) | 0 (referent) | 0 (referent)
2 (17.6–57.2) | 14 (−141, 170) | 0.0 (−0.7, 0.7) | −0.2 (−0.8, 0.4)
3 (≥57.2) | −50 (−223, 123) | 0.1 (−0.9, 0.7) | −0.3 (−0.9, 0.3)
(trend p-value) | (0.43) | (0.88) | (0.32)
ln (MBzP) | −23 (−71, 24) | 0.1 (−0.3, 0.2) | 0.0 (−0.2, 0.2)</td></tr>
</table>

Reference and study design	Results
Suzuki et al. (2010) (Japan) **Population:** 149 infants from birth cohort, 2005–2008 **Outcome:** Standard clinical measurements at birth **Exposure:** Maternal urine sample, gestation wks 9–40 (mean ± SD = 29 ± 8 wks) MBzP in urine: Median; 75th percentile Unadjusted (ng/mL) 3.46; 11.2 Cr-adjusted (mg/g Cr) 4.70; 9.83 **Analysis:** Pearson's correlation analysis for individual metabolites and high MW phthalates (∑MBzP, MEHP, MEHHP, and MEOHP molar concentration)	Pearson's correlation coefficient between MBzP (mg/g Cr) or high MW phthalate (molar concentration) and birth outcome Birth outcome; MBzP (mg/g Cr); High MW phthalate (molar concentration) Birth weight (g); 0.005; −0.096 Birth length (cm); −0.030; −0.064 Head circumference (cm); −0.113; −0.072 Gestational age (wks); 0.069; 0.043 *p* >0.5 for all correlations
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 MBzP in urine (ng/mL): Median; 75th percentile Unadjusted 22; 50 **Analysis:** Linear regression, adjusting for variables shown in results column	Regression coefficient (95% CI) for change in birth outcome with unit increase in ln-MBzP (ng/mL) (adjusted for race/ethnicity, infant sex, gestational age at delivery, ln-creatinine, prenatal smoking, prepregnancy BMI, maternal education, and marital status) Birth weight (g): 1.4 (−34, 37) Birth length (cm): 0.20 (0.00, 0.40) Head circumference (cm): 0.11 (−0.02, 0.25) Restricted to observations with creatinine ≥20 mg/dL
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 first trimester), 2006–2008; controls randomly selected from those delivering ≥37 wks of gestation; mean age 33 yrs **Outcome:** Preterm birth (<37 wks of gestation; gestational age estimated from first trimester ultrasound) **Exposure:** Maternal urine samples (one to four samples at median 9.7, 17.9, 26.0, and 35.1 wks of gestation; last sampling period not included for mothers who had already delivered) SG-adjusted MBzP in urine (µg/L), geometric mean of visits 1–3: Geometric mean; 75th percentile Controls 6.34; 10.9 Cases 6.85; 13.4 **Analysis:** Logistic regression, considering maternal age, race/ethnicity, education level, health insurance	OR (95% CI) for preterm birth per unit increase in ln-transformed MBzP (geometric mean of visits 1–3) (adjusted for urine specific gravity, maternal age, race/ethnicity, education level, and insurance provider (Ferguson et al., 2014a) All preterm: 1.09 (0.86, 1.38) Spontaneous preterm: 1.41 (1.02, 1.95) [Results weaker than those seen with DEHP metabolites] OR (95% CI) for preterm birth per unit increase in ln-transformed MBzP at each study visit (adjusted for urine specific gravity, maternal age, race/ethnicity, education level, and insurance provider) (Ferguson et al., 2014c) Visit 1: 1.02 (0.73, 1.43) Visit 2: 1.07 (0.73, 1.55) Visit 3: 1.00 (0.68, 1.48) Visit 4: 1.02 (0.57, 1.84)

Reference and study design	Results
provider, BMI at first study visit, smoking status, alcohol use, parity, use of assisted-reproductive technology, and sex of infant as potential covariates; additional analyses conducted for subgroup with preterm labor or premature rupture of membranes ("spontaneous preterm," n = 57) Ferguson et al. (2014c) provides the analysis based on individual sample results for each of the four visits	
Huang et al. (2014b) (China) **Population:** 207 women delivering at 1 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 BBP in cord blood (μg/L): Median 75th percentile 95th percentile All samples (<LOD) 0.99 89.87 **Analysis:** Logistic and linear regression, adjusting for variables shown in results column	OR (95% CI) for preterm delivery per increase in MBzP (as categorical variable, detectable or not detectable)(adjusted for maternal age, BMI, frequency of prenatal exam, and pregnancy history); with additional stratification by history of intravenous infusions (26% of total, 55% of preterm birth group) Total sample (n = 207) 9.97 (3.25, 30.53) No intravenous infusions (n = 154) 0.06 (0.01, 0.58) Intravenous infusions (n = 53) 0.16 (0.04, 0.63) [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) with change in BBP (as categorical variable, detectable or not detectable) (adjusted for maternal age, BMI, frequency of prenatal examination, history of intravenous infusions therapy, and pregnancy history): −1.05** (−1.59, −0.51)
Meeker et al. (2009b) (Mexico) **Population:** 30 cases, 30 controls (term births) from pregnancy cohort, 2001−2003. **Outcome:** Preterm birth (<37 wks of gestation), determined using maternal recall of last menstrual period **Exposure:** Maternal urine sample, third trimester MBzP in urine, among term births Median 75th percentile Unadjusted 2.9 5.2 SG-adjusted (μg/L) 3.2 7.8 Cr-adjusted (μg/g Cr) 4.6 9.1 **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 MBzP above compared with below the median (adjusted for marital status, maternal education, and infant sex and gestational age at time of urine sample)

Reference and study design	Results
	Cr-unadjusted (µg/L) 2.5 (0.8, 8.5) SG-adjusted (µg/L) 2.2 (0.7, 6.7) Cr-adjusted (µg/g Cr) 2.2 (0.7, 6.7)
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 MBzP in urine (ng/mL): Median 75th percentile Unadjusted 22 50 **Analysis:** Linear regression, adjusting for variables shown in results column	Regression coefficient (95% CI) for change in gestational age with unit increase in ln-MBzP (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) 0.07 (−0.07, 0.22) Restricted to observations with creatinine ≥20 mg/dL
Early pregnancy loss	
Toft et al. (2012) (Denmark) **Population:** 48 women with pregnancy loss, 80 with pregnancies ending in a live birth from cohort of couples planning first pregnancy, 1992−1994 **Outcome:** Any pregnancy loss (n = 48), early (subclinical) embryonal loss (pregnancy identified by elevation in human chorionic gonadotropin; n = 32) or clinically-identified pregnancy loss (n = 16) **Exposure:** Urine samples (one conception cycle, one preconception cycle) MBzP in urine (ng/mL), among live births: Mean Maximum Live birth 20.3 117 **Analysis:** Logistic regression, adjusting for variables shown in results column	OR (95% CI) for any pregnancy loss by tertile MBzP (ng/mL) in the preconception cycle or conception cycle (adjusted for age, BMI, smoking, alcohol and caffeine intake, and MBzP in the other cycle) MBzP Tertile: Preconception cycle / Conception cycle 1 (low): 1.0 (referent) / 1.0 (referent) 2: 1.38 (0.53, 3.62) / 1.72 (0.63, 4.69) 3 (high): 0.59 (0.21, 1.65) / 2.10 (0.74, 5.88) OR (95% CI) for types of pregnancy loss by tertile MBzP (ng/mL) in the conception cycle (adjusted for age, BMI, smoking, alcohol and caffeine intake, and MBzP in the preconception cycle) MBzP tertile: Subclinical pregnancy loss / Clinical pregnancy loss 1 (low): 1.0 (referent) / 1.0 (referent) 2: 2.39 (0.70, 8.22) / 1.08 (0.25, 4.66) 3 (high): 3.11 (0.87, 11.09) / 0.96 (0.20, 4.59)

MEHHP = mono-(2-ethyl-5-hydroxyhexyl)phthalate; MEHP = mono-(2-ethylhexyl) phthalate; MEOHP = mono-(2-ethyl-5-oxohexyl) phthalate; MW = molecular weight

3.2.9. Immune Effects in Humans

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

Reference and study design	Results
Ait Bamai et al. (2014) (Japan)[a] Population: Children (n = 122, ages <15 yrs) and adults (n = 374, ages ≥15 yrs) living in 148 detached dwellings in which at least 25 mg of dust was collected; 2006 follow-up of 2003 baseline survey Outcome: Allergic condition assessed by self-administered questionnaire (positive response to: in the past 2 yrs have you been seen at a hospital for allergic rhinitis, allergic conjunctivitis, or atopic dermatitis?); parents completed questionnaires for children <6 yrs old) Exposure: Dust samples BBP in dust (µg/g dust) (percentile): Median 75th Floor dust (n = 148) 1.9 3.9 Multi-surface dust (n = 120) 1.7 3.9 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 BBP in floor dust (µg/g dust) (adjusted for gender, age strata, smoking status, dampness index, furry pets inside the home, Der 1, and sum of other phthalates) BBP tertile — Full sample — Children — Adults Allergic rhinitis 1 (low) — 1.0 (referent) — 1.0 (referent) — 1.0 (referent) 2 — 1.27 (0.64, 2.52) — 1.90 (0.63, 5.75) — 0.85 (0.39, 1.86) 3 (high) — 1.98 (0.98, 4.03) — 3.04 (0.92, 10.0) — 1.29 (0.60, 2.80) (trend *p*-value) — (0.058) — (0.068) — (0.51) Allergic conjunctivitis 1 (low) — 1.0 (referent) — 1.0 (referent) — 1.0 (referent) 2 — 0.65 (0.23, 1.83) — 0.66 (0.14, 3.12) — 0.64 (0.19, 2.17) 3 (high) — 1.40 (0.56, 3.49) — 1.48 (0.33, 3.56) — 1.34 (0.47, 3.79) (trend *p*-value) — (0.46) — (0.61) — (0.59) Atopic dermatitis 1 (low) — 1.0 (referent) — 1.0 (referent) — 1.0 (referent) 2 — 3.69 (1.41, 9.68) — 4.02 (1.01, 14.5) — 3.40 (0.78, 14.8) 3 (high) — 5.46 (2.06, 14.48) — 6.55 (1.71, 25.3) — 4.54 (1.06, 19.4) (trend *p*-value) — (0.001) — (0.007) — (0.041) *p*-value for age interaction >0.2 for all endpoints Results for multisurface dust stratified by age indicated increased adjusted ORs for allergic conjuctivitis in children; ORs (95% CI) were 9.81 (1.06, 91.23) in BBP tertile 2 and 7.71 (0.85, 69.97) in tertile 3. No other significantly increased adjusted ORs (either in the full sample or stratified by age) were observed in analyses using BBP measurements in multisurface dust.

Reference and study design	Results
Wang et al. (2014) (Taiwan) **Population:** 218 children from birth cohort, born 2004–2005; follow-up at age 2 (n = 218) and age 5 (n = 191) **Outcome:** Atopic dermatitis based on ISAAC questionnaire (three questions—itchy rash coming and going for at least 6 mo; if yes, itchy rash in last 12 mo; ever diagnosed with atopic dermatitis by a doctor?); total serum IgE **Exposure:** Maternal urine sample, third trimester; urine samples in children (ages 2 and 5 yrs) Cr-adjusted MBzP in urine (µg/g Cr): Geometric mean (SE) At 3rd trimester 1.84 (1.11) Age 2 3.76 (1.10) Age 5 3.46 (1.08) **Analysis:** Linear regression and logistic regression of log transformed data, considering sex, gestational age, parity, maternal age, education and occupation, diets and supplements during pregnancy, family income, parental atopy, duration of breast feeding, tobacco smoke exposure, incense and carpets in home, and fungi on house walls as potential covariates	OR (95% CI) for atopic dermatitis by quartile of MBzP (µg/g Cr) (adjusted for gender, gestational age, maternal education, maternal history of atopy, and prenatal environmental tobacco smoke exposure) MBzP quartile (µg/g Cr) — Age 2 yrs — Age 5 yrs 1 (<1.9048) — 1.0 (referent) — 1.0 (referent) 2 (1.9048–4.4776) — 1.10 (0.44–2.69) — 1.12 (0.43–2.88) 3 (4.4776–8.2000) — 0.93 (0.37–2.31) — 0.59 (0.22–1.61) 4 (>8.2000) — 2.50 (1.08–5.79) — 1.98 (0.81–4.87) Regression coefficient (*p*-value) for log-serum total IgE at 2 yrs of age according to log-urine phthalate metabolite concentrations at age 2 yrs (adjusted for gestational age, maternal education, maternal history of atopy, and prenatal environmental tobacco smoke exposure) All children (n = 218) — 0.008 (0.84) Boys (n = 114) — 0.016 (0.74) Girls (n = 104) — −0.006 (0.96)
(Callesen et al. (2014a); Callesen et al. (2014b)) (Denmark)[a] **Population:** 81 rhinoconjunctivitis cases, 88 atopic dermatitis cases, and 242 healthy controls from population-based survey (Danish Indoor Environment and Children's Health); ages 3–5 yrs; 2008 **Outcome:** Allergic rhinoconjunctivitis or atopic dermatitis based on clinical exam and parent interview; allergic rhinoconjunctivitis diagnosed by: 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 diagnosed by: presence of at least 3 of 4 major features and 3 of 23 minor	Median BBP in dust (µg/g), by case-control status based on clinical examination, from Callesen et al. (2014a) Controls (n = 242) — Rhinoconjunctivitis (n = 81) — Atopic dermatitis (n = 88) Home — 3.9 — 3.5 — 3.9 Daycare — 15.4 — 16.6 — 15.4 Weighted average — 7.8 — 8.9 — 7.7 Similar results when based on case status defined by parent questionnaire data (n = 56 rhinoconjunctivitis, n = 83 atopic dermatitis) OR (95% CI) for rhinoconjunctivitis or atopic dermatitis (number of cases and controls revised after reclassification of some cases and controls during clinical examination and elimination of participants with missing data on covariates) by quartile of MBzP in urine (ng/mL) (adjusted for sex, breastfeeding <3 mo, smoking in the home, single allergic predisposition, and social class), from Callesen et al. (2014b)

Reference and study design	Results		
features; 70% of rhinoconjunctivitis and 50% of atopic dermatitis cases were IgE positive based on 20 allergen tests **Exposure**: BBP concentration in dust samples from bedroom and daycare centers (Callesen et al., 2014a); MBzP in urine samples from subset of population (76 with rhinoconjunctivitis, 81 with atopic dermatitis, and 222 controls) (Callesen et al., 2014b) BBP in dust (μg/g dust) among controls: Median Home 3.9 Daycare 15.4 Weighted* average 7.8 (*weighted by assumed time spent in each environment) MBzP in urine (ng/mL) of controls: Median 95th percentile Unadjusted 13.7 71.4 **Analysis:** Mann-Whitney U-test for concentration comparisons between groups; logistic regression for ORs, considering sex, breastfeeding <3 mo, antibiotic use, single allergic predisposition, visible mold, visible moisture, window condensation, cat or dog in the home, pet avoidance, changed cleaning habits, smoking in the home, and social class as potential covariates	MBzP quartile	Rhinoconjunctivitis (71 cases, 216 controls)	Atopic dermatitis (76 cases, 216 controls)
	1 (low)	1.0 (referent)	1.0 (referent)
	2	1.48 (0.68, 3.23)	1.23 (0.58, 2.63)
	3	0.89 (0.39, 2.01)	0.69 (0.31, 1.55)
	4 (high)	1.18 (0.56, 2.48)	1.43 (0.72, 2.88)

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 year; allergic sensitization as measured by serum IgE (19 allergen specific IgEs, ≥0.35kU/L) **Exposure:** Urine sample collected same day as serum sample; data reported in Unadjusted MBzP in urine (µg/L) (percentile): Median 75th 95th Children 17.98 37.79 106.75 Adults 7.57 17.37 57.37 **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 MBzP level (adjusted for age, race/ethnicity, gender, BMI, creatinine, and cotinine) Children (n = 779) Hay fever (n = 23) 3.6% 0.42 (0.22, 0.79) Rhinitis (n = 188) 27.6% 1.02 (0.62, 1.67) IgE sensitization (any) 46.1% 1.18 (0.74, 1.86) Adults (n = 1,546) Hay fever (n = 88) 7.4% 1.68 (1.09, 2.59) Rhinitis (n = 498) 35.4% 1.24 (1.01, 1.52) IgE sensitization (any) 44.0% 1.41 (0.96, 2.06) Authors reported that adjustment for poverty income ratio did not alter ORs
Just et al. (2012b) (United States, New York City) **Population:** 376 children from birth cohort (CCCEH), born 1999–2006; 376 completed at least 1 of 4 follow-ups in yr 1 and 1 of 4 follow-ups in yr 2; 339 continued through 60 mo (4 follow-ups between 24 and 60 mo) **Outcome:** Mother's report of doctor-diagnosis of eczema (telephone and in-person interviews; early onset: reported at or before age 24 mo; late onset: first reported between 24 and 60 mo; total serum IgE **Exposure:** Maternal urine sample, third trimester MBzP in urine (ng/mL): Geometric mean Percentile 25th 75th Unadjusted 13.6 5.7 31.1 **Analysis:** Poisson and logistic regression, considering sex, race/ethnicity, prenatal exposure to tobacco smoke, maternal age and education, marital status, maternal self-report of asthma, and maternal log total IgE as potential covariates	RR (95% CI) for IQR increase in log-transformed MBzP among all reporters (adjusted for specific gravity, sex, and race/ethnicity) Eczema (by 24 mo) 1.52 (1.21, 1.91) OR (95% CI) for interquartile increase in log-transformed MBzP among consistent reporters of eczema Eczema (by 24 mo) 1.91 (1.23, 2.97) Eczema (late onset) 0.90 (0.51, 1.58) Regression coefficient (95% CI) for IQR increase in log MBzP concentration and log total IgE in early onset eczema cases (adjusted for specific gravity, sex, and race/ethnicity) IgE (at 60 mo) −0.14 (−0.41, 0.13)

<table>
<tr><th>Reference and study design</th><th>Results</th></tr>
<tr><td>Hsu et al. (2012)[a] (Taiwan)
Population: 59 cases (48 with allergic rhinitis, 36 with eczema), 42 controls, ages 3–9 yrs, recruited through kindergartens and day care centers, 2005–2006.
Outcome: Allergic rhinitis or eczema; initial case/control status determined through parent report of history; final status determined by clinical examination
Exposure: Settled dust samples from child's major and minor activity rooms; urine samples collected at clinical examination
BBP in dust, all subjects:
Median 75th percentile
Dust (µg/g) 1.0 3.9
MBzP in urine, all subjects:
Median 75th percentile
Unadjusted (µg/L) 4.8 11.8
Cr-adjusted (µg/g Cr) 5.1 12.9
Analysis: Logistic regression adjusting for variables shown in the results column</td><td>OR (95% CI) for allergic rhinitis or eczema by quartile of exposure (adjusted for age, sex, presence of fever, medication use, parents' smoking status, parents' allergy history, parents' education, and mo of sampling)

BBP quartile, dust (µg/g dust) | Rhinitis | Eczema
1 (0.08–1.00) | 1.0 (referent) | 1.0 (referent)
2 (1.00–1.00) | 1.0 | 1.0
3 (1.01–3.88) | 2.04 (0.50, 8.33) | 2.00 (0.42, 9.58)
4 (3.89–40.16) | 7.01 (1.75, 28.17) | 7.71 (1.67, 35.61)
(trend p) | 0.006 | 0.011

MBzP quartile, urine (µg/g Cr) | Rhinitis | Eczema
1 (0.97–2.56) | 1.0 (referent) | 1.0 (referent)
2 (2.57–5.11) | 1.27 (0.33, 4.84) | 2.48 (0.59, 10.50)
3 (5.12–12.87) | 1.18 (0.30, 4.69) | 1.42 (0.30, 6.74)
4 (12.88–217.16) | 2.31 (0.55, 9.70) | 2.27 (0.46, 11.26)
(trend p) | >0.05 | >0.05

OR for all cases (at least one among asthma, rhinitis, or eczema) significantly elevated in highest quartile BBP in dust (OR = 5.82, 95% CI = 1.52, 22.32; trend p = 0.01)</td></tr>
<tr><td>Kanazawa et al. (2010) (Japan)
Population: 134 residents (41 dwellings), including 33 reporting at least one symptom and 101 with no reported symptoms
Outcome: Self-reported "sick house syndrome" symptoms (fatigue; feeling heavy-headed; headache; nausea/ dizziness; difficulty concentrating; itching, burning or irritation of the eyes; irritated, stuffy, or runny nose; hoarse, dry throat; cough; dry or flushed facial skin; scaling/itching of the scalp or ears; and dry, itching or red-skinned hands)
Exposure: Air and dust sample in dwellings
BBP in room air (ng/m3):
Median Range
Total concentration <2.9 <2.9–26.6
BBP in dust (mg/kg):
Median Range
Multi-surface 2.4 <0.2–35.8
Floor 4.2 <0.2–52.1</td><td>OR (95% CI) for mucosal symptoms per 10-fold increase in BBP concentration (adjusted for age, gender, history of allergy, and time spent at home; similar results with additional adjustment for moldy odor and for condensation)

Multi-surface dust (mg/kg) 1.9 (0.8–4.7)
Floor dust (mg/kg) 1.7 (0.5–6.0)</td></tr>
</table>

Reference and study design	Results
Analysis: Logistic regression, adjusting for variables shown in the results column	
Sun et al. (2009) (China) **Population:** Cases of rhinitis (n = 89) or eczema (n = 56) and controls (n = 331 and 118 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 BBP in dust (µg/g): Median 75th percentile 26.22 42.03 **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 BBP concentrations of cases and controls; t-test for comparisons between log transformed concentrations	OR for rhinitis and eczema comparing BBP 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 BBP in dust (µg/g dust) Cases / Control Rhinitis: 20.11 / 26.05 Eczema: 19.40 / 22.51 *p* >0.35 for Mann-Whitney and t-tests
Kolarik et al. (2008) (Bulgaria) **Population:** 100 cases, 77 controls from population-based survey (ALLHOME study), 2004–2005; ages 2–7 yrs **Outcome:** Cases: positive response to wheezing during the last 12 mo, rhinitis during the last 12 mo, when not having a cold, or itching rash eczema in the last 12 mo; controls: negative response to all three questions and other questions on history of wheezing, asthma, allergy symptoms or diagnosis in past **Exposure:** Surface dust samples from children's bedrooms	Concentration BBP in dust (mg/g dust) Median / Mean / *p*-value for Dunnett test Controls: 0.32 / 0.45 / (0.37) All cases: 0.38 / 0.53 / (0.34) Rhinitis: 0.32 / 0.49 / (0.58) Eczema: 0.40 / 0.60 / (0.21)

Reference and study design	Results
BBP in dust (mg/g): Geometric mean All homes 0.32 **Analysis:** Dust concentrations compared between case and control homes overall, and between cases with specific symptoms in the preceding 12 mo and controls, using Mann-Whitney U-test (untransformed data) and Dunnett test (log-transformed data)	
Bornehag et al. (2004)[a] (Sweden) **Population:** 198 cases, 202 controls from population-based cohort (Dampness in Buildings and Health cohort) (n = 10,852), 2001–2002; ages 2–7 yrs **Outcome:** Rhinitis or eczema (cases report at least two incidents of rhinitis or eczema in the preceding year, and at follow-up 1.5 yrs later) **Exposure:** Surface dust samples from children's bedrooms BBzP in dust (mg/g): Median All homes 0.135 **Analysis:** Logistic regression adjusting for variables shown in results column	OR (95% CI) for case status by quartile of BBP in dust (mg/g dust) (adjusted for sex, age, smoking in home, type of building, construction period, flooding during preceding 3 yrs, and DEHP in dust) BBP quartile (mg/g dust) — Rhinitis (n = 79) — Eczema (n = 115) 1 (≤0.05) — 1.0 (referent) — 1.0 (referent) 2 (0.05–0.13) — 1.03 (0.44, 2.39) — 0.84 (0.40, 1.76) 3 (0.13–0.25) — 1.23 (0.53, 2.88) — 1.45 (0.71, 2.97) 4 (0.25–45.55) — 3.04 (1.34, 6.89) — 2.56 (1.24, 5.32)

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

CCCEH = Columbia Center for Children's Environmental Health; ISAAC = International Study of Asthma and Allergies in Children; IgE = immunoglobulin E; VOC = volatile organic compound

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

Reference and study design	Results
Ait Bamai et al. (2014) (Japan)[a] **Population:** Children (n = 122, ages <15 yrs) and adults (n = 374, ages ≥15 yrs) living in 148 detached dwellings in which at least 25 mg of dust was collected; 2006 follow-up of 2003 baseline survey **Outcome:** Bronchial asthma assessed by self-administered questionnaire (positive response to: in the past 2 yrs have you been seen at a hospital for bronchial asthma?); parents completed questionnaires for inhabitants <6 yrs old **Exposure:** Dust samples BBP in dust (µg/g dust) (percentile): Floor dust (n = 148) Median 1.9, 75th 3.9 Multi-surface dust (n = 120) Median 1.7, 75th 3.9 **Analysis:** Generalized linear mixed effects model, considering gender, age strata (<15, ≥15 yrs), smoking status (personal and environmental tobacco smoke), furry pets in home, signs of dampness, Der 1 (not defined by authors), other phthalates dust, airborne fungi, formaldehyde, total VOC, and building characteristic as potential covariates	OR (95% CI) for bronchial asthma by tertile of BBP in floor dust (µg/g dust) (adjusted for gender, age strata, smoking status, dampness index, furry pets inside the home, Der 1, and sum of other phthalate dusts) BBP tertile / Full sample / Children / Adults 1 (low) 1.0 (referent) 1.0 (referent) 1.0 (referent) 2 3.46 (0.82, 14.55) 3.30 (0.57, 19.2) 3.63 (0.39, 34.2) 3 (high) 2.97 (0.78, 11.35) 2.98 (0.51, 17.4) 2.96 (0.29, 30.2) (trend *p*-value) (0.11) (0.23) (0.36) *p*-value for age interaction = 0.95 No significantly increased adjusted ORs (either in the full sample or stratified by age) were observed in analyses of bronchial asthma using BBP 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 (Danish Indoor Environment and Children's Health); ages 3–5 yrs; 2008 **Outcome:** Asthma based on clinical exam and parent interview. Asthma diagnosed by recurrence of at least two of three symptoms: cough, wheeze, and shortness of breath within the previous 12 mo (symptoms not 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**: BBP concentration in dust samples from bedroom and daycare centers (Callesen et al., 2014a); MBzP in urine samples from subset of population (68 with asthma and 222 controls) (Callesen et al., 2014b) BBP in dust (µg/g), controls: Median Home 3.9 Daycare 15.4 Time-weighted 7.8 (weighted by assumed time spent in each environment) MBzP in urine (ng/mL) of controls: Median 95th percentile Unadjusted 13.7 71.4 **Analysis:** Mann-Whitney U-test for concentration comparisons between groups; logistic regression for ORs, considering sex, breastfeeding <3 mo, antibiotic use, single allergic predisposition, visible mold, visible moisture, window condensation, cat or dog in the home, pet avoidance, changed cleaning habits, smoking in the home, and social class as potential covariates	Median BBP in dust (µg/g), by case-control status based on clinical examination, from Callesen et al. (2014a) Controls (n = 242) Asthma (n = 72) Home 3.9 2.9 Daycare 15.4 18.3 Time-weighted 7.8 8.2 (p >0.05 for all tests) Similar results when based on case status defined by parent questionnaire data (n = 110 cases) OR (95% CI) for bronchial asthma (60 cases, 216 controls after reclassification of some cases and controls during clinical examination and elimination of participants with missing data on covariates) by quartile of MBzP (urine sample), adjusting for sex, breastfeeding <3 mo, smoking in the home, and single allergic predisposition (Callesen et al., 2014b) 1 (low) 1.0 (referent) 2 1.18 (0.55, 2.55) 3 0.63 (0.26, 1.53) 4 (high) 1.11 (0.51, 2.44)

Reference and study design	Results
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 MBzP in urine (µg/L) (percentiles): Median 75th 95th Unadjusted 29.3 52.9 128.7 SG-adjusted 30.8 53.2 135.3 **Analysis:** Logistic regression, adjusting for variables shown in the results column	OR (95% CI) for current asthma by quartile of MBzP (µg/L) (adjusted for urine specific gravity, sex, parental asthma, and household income) 1: ≤16.9 (referent) 1 (referent) 2: >16.9–29.2 0.70 (0.39, 1.3) 3: >29.2–52.9 0.83 (0.45, 1.5) 4: >52.9 1.3 (0.75, 2.4) Increase in odds of current asthma per $\log_{10}$ IQR MBzP (95% CI) = 1.2 (0.88, 1.5)
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 year) **Exposure:** Urine sample collected same day as serum sample Unadjusted MBzP in urine (µg/L) (percentile): Median 75th 95th Children 17.98 37.79 106.75 Adults 7.57 17.37 57.37 **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 MBzP level (adjusted for age, race/ethnicity, gender, BMI, creatinine, and cotinine) Children (n = 779) Asthma (n = 65) 8.4% 1.06 (0.33, 3.45) Wheeze (n = 80) 10.7% 0.92 (0.35, 2.37) Adults (n = 1,546) Asthma (n = 116) 7.4% 1.46 (1.01, 2.11) Wheeze (n = 219) 16.6% 1.78 (1.22, 2.60) Authors reported that adjustment for poverty income ratio did not alter ORs

Reference and study design	Results
Just et al. (2012a) (United States, New York) **Population:** 244 children from birth cohort (CCCEH), born 1999–2006; follow-up in 2006–2010, ages 4.9–9.1 yrs **Outcome:** Measured feNO (1–3 measures per child), measured seroatopy (specific IgE to dust mite, cockroach, or mouse allergens, ≥0.35 IU/mL), wheeze within past year or in subsequent year (based on parent report at feNO study visit and at the next study visit), with additional information to model wheezing phenotype **Exposure:** Urine sample (child's), collected at time of feNO measurement MBzP in urine (ng/mL): Geometric mean (95% CI) Unadjusted 24 (20–28) **Analysis:** Generalized estimating equation regression models adjusted for variables shown in results column	Percent difference in feNO per unit increase in ln-MBzP (ng/mL) (adjusted for specific gravity, age, sex, race/ethnicity, time of day of feNO collection, and ambient NO; similar results with additional adjustment for seroatopy and MBP, MEP, and MEHHP) % Difference (95% CI) — *p*-value 6.8 (1.1, 12.9) — 0.019 OR (95% CI) for incident seroatopy (over 2-yr follow-up) by log unit change in MBzP (adjusted for specific gravity, age at atopy measure, time since phthalate measure, sex, and race/ethnicity) 1.08 (0.89, 1.32) OR (95% CI) for wheeze in past year (at age 5 or 7 yrs) by log unit change in MBzP (adjusted for specific gravity, sex, and race/ethnicity) Age 5: Subjects in feNO study only: 0.94 (0.72, 1.22) n = 202; Entire CCCEH cohort: 1.00 (0.83, 1.22) n = 350 Age 7: Subjects in feNO study only: 1.12 (0.81, 1.54) n = 161; Entire CCCEH cohort: 1.07 (0.85, 1.34) n = 289
Hsu et al. (2012)[a] (Taiwan) **Population:** 9 cases, 42 controls, ages 3–9 yrs, recruited through kindergartens and day care centers, 2005–2006. **Outcome:** Initial case/control status determined through parent report of history; final status determined by clinical examination. **Exposure:** Settled dust samples from child's major and minor activity rooms; urine samples collected at clinical examination BBP in dust, all subjects: Median; 75th percentile Dust (µg/g) 1.0; 3.9 MBzP in urine, all subjects: Median; 75th percentile Unadjusted (µg/L) 4.8; 11.8 Cr-adjusted (µg/g Cr) 5.1; 12.9 **Analysis:** Logistic regression adjusting for variables shown in the results column	OR (95% CI) for asthma by quartile of exposure (adjusted for age, sex, presence of fever, medication use, parents' smoking status, parents' allergy history, parents' education, mo of sampling) BBP quartile, dust (µg/g dust) — Asthma 1 (0.08–1.00) — 1.0 (referent) 2 (1.00–1.00) — 1.0 3 (1.01–3.88) — 4.21 (0.35, 50.98) 4 (3.89–40.16) — 3.54 (0.32, 39.06) (trend *p*) — (>0.05) MBzP quartile, urine (µg/g Cr) — Asthma 1 (0.97–2.56) — 1.0 (referent) 2 (2.57–5.11) — Not reported 3 (5.12–12.87) — 4.63 (0.15, 144.06) 4 (12.88–217.16) — 68.52 (1.08, >999) (trend *p*) — (0.03)

Reference and study design	Results
Sun et al. (2009) (China) **Population:** 233 cases of asthma/wheezing, rhinitis, or eczema, and 194 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 months, 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 BBP in dust (µg/g): Median 75th percentile 26.22 42.03 **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 BBP concentrations of cases and controls; t-test for comparisons between log transformed concentrations	OR for asthma comparing BBP 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 BBP in dust (µg/g dust) Cases Control Wheezing 20.11 23.81 (p >0.5 by Mann Whitney or t-test)
Bornehag et al. (2004)[a] (Sweden) **Population:** 106 cases, 177 controls from population-based cohort (Dampness in Buildings and Health cohort); n = 10,852; 2001–2002; ages 2–7 yrs **Outcome:** asthma/wheezing without a cold, in the preceding year, and at follow-up 1.5 yrs later **Exposure:** Surface dust samples from children's bedrooms BBP in dust (mg/g): Median All homes 0.135 **Analysis:** Logistic regression adjusting for variables shown in results column	OR (95% CI) for case status by quartile of BBP in dust (mg/g dust) (adjusted for sex, age, smoking in home, type of building, construction period, flooding during preceding 3 yrs, and DEHP in dust) BBP quartile (mg/g dust) Asthma (n = 106) 1 (≤0.05) 1.0 (referent) 2 (0.05–0.13) 0.67 (0.33, 1.38) 3 (0.13–0.25) 0.88 (0.43, 1.80) 4 (0.25–45.55) 1.87 (0.92, 3.81)

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

feNO = fractional exhaled nitric oxide; MEP = monoethyl phthalate

3.2.10. Thyroid Effects in Humans

Table 3-11. Evidence pertaining to BBP 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) MBzP in urine (ng/mL): Median / 75th percentile / 90th percentile Controls: 6 / 11 / 20 Obese (at baseline): 8 / 16 / 25 **Analysis:** Linear regression, adjusting for variables shown in results column	Regression coefficient (*p*-value) for change in hormone level with unit change in ln-MBzP (adjusted for age, weight loss, and sex, or stratified by sex) (0.0 = no effect) Full sample / Men / Women Overweight/obese group Free T4: −0.10 (0.23) / −0.14 (0.37) / −0.10 (0.34) TSH: 0.11 (0.19) / 0.03 (0.83) / 0.16 (0.13) Referent group Free T4: 0.30 (0.06) / 0.45 (0.15) / 0.21 (0.29) TSH: 0.30 (0.06) / −0.11 (0.75) / 0.44 (0.02)
Boas et al. (2010) (Denmark) **Population:** 758 children from birth cohort study, born 1997–2001; examined 2006–2007, ages 4–9 yrs **Outcome:** Serum thyroid hormone levels (nonfasting sample) **Exposure:** Urine sample (child's), collected same day as serum samples Unadjusted MBzP in urine (µg/L): Median / 75th percentile Boys: 17 / 37 Girls: 12 / 31 Cr-adjusted MBzP in urine (µg/g Cr): Median / 75th percentile Boys: 26 / 49 Girls: 20 / 42 **Analysis:** Linear regression, adjusting for variables shown in the results column	Regression coefficient (*p*-value) for change in hormone level with unit change in ln-MBzP (adjusted for sex and age) (0.0 = no effect) Unadjusted MBzP / Cr-adjusted MBzP T3: −0.05 (0.016) / −0.03 (0.27) Free T3: −0.08 (0.032) / −0.02 (0.71) T4: −2.34 (0.026) / −2.90 (0.027) Free T4: −0.19 (0.059) / −0.32 (0.012) TSH: −0.01 (0.47) / 0.00 (0.96) IGF-1: −0.01 (0.38) / 0.00 (0.74) IGFBP-3: −0.01 (0.27) / 0.00 (0.91) Similar patterns seen in analyses stratified by gender. Units for hormone analyses were not reported in the publication

Reference and study design	Results
Meeker et al. (2007) (United States, Boston) **Population:** 408 male partners from subfertility clinic, 2000–2004; mean (± SD) age 36 (± 5.3) yrs **Outcome:** Serum thyroid hormone levels **Exposure:** Urine sample, collected same day as serum samples MBzP in urine (ng/mL): Median 75th percentile 95th percentile SG-adjusted 8.16 15.7 42.4 **Analysis:** Linear regression, considering age, BMI, smoking status, race, previous examination for infertility, prior impregnation of partner, timing of blood and urine samples, and time of day as potential covariates	Regression coefficient (95% CI) for change in hormone level per IQR change in SG-adjusted MBzP (ng/mL, after back-transformation from ln-MBzP) (adjusted for age, BMI, current smoking, and time of blood sample) Untransformed hormone levels (0.0 = no effect) Total T3 (ng/mL) 0.001 (−0.018, 0.021) Free T4 (ng/dL) −0.017 (−0.046, 0.011) Ln-transformed hormone levels (1.0 = no effect) TSH (µIU/mL) 1.01 (0.94, 1.08)
Huang et al. (2007) (Taiwan) **Population:** 76 pregnant women undergoing amniocentesis due to age >35 yrs or abnormal α-fetoprotein or β-hCG test, 2005–2006 **Outcome:** Serum thyroid hormone levels collected during 2nd trimester **Exposure:** Urine sample, collected same day as serum samples MBzP in urine: Median 75th percentile 95th percentile Unadjusted (ng/mL) 0.9 0.9 33.4 Cr-adjusted (µg/g Cr) 3.7 6.0 24.0 **Analysis:** Spearman correlation analysis; linear regression, adjusting for variables shown in results column	Spearman correlation coefficient between hormone level and MBzP Unadjusted MBzP (ng/mL) / Cr-adjusted MBzP (µg/g Cr) T3 (ng/dL) −0.084 / −0.075 T4 (µg/dL) 0.034 / 0.040 Free T4 (ng/dL) −0.007 / 0.083 TSH (µIU/mL) −0.080 / −0.113 All coefficients *p* >0.05 Adjusted regression coefficient (*p*-value) for change in ln-T4 with change in ln-MBzP (adjusted for age, BMI, gestational age, and other phthalate metabolites [MEP, MBP, MEHP, MMP]) T4 (nmole/L) 0.032 (0.224) Free T4 (pmole/L) 0.022 (0.232)

MMP = monomethyl phthalate; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone

3.2.11. Pulmonary Function in Humans

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

Reference and study design	Results
Cakmak et al. (2014) (Canada) Population: 3,147 participants* in population-based survey (Canadian Health Measures Survey), ages 6–49 yrs Outcome: Pulmonary function based on FVC and FEV_1 (expressed as percent of values predicted based on age, height, and sex) Exposure: Urine sample collected at same time as pulmonary function testing MBzP in urine (µg/g Cr), all participants: Geometric mean (95%CI) Cr-adjusted 16.4 (15.84–16.98) **Analysis:** Linear regression, generalized linear mixed models (weighted based on sampling weights), considering BMI, ethnicity, education, income, passive smoking, current smoking, and ambient conditions on day of lung function measures (temperature, relative humidity, barometric temperature, nitrogen dioxide, ozone, and fine particulates ($PM_{2.5}$) as potential covariates; stratified by age (6–16, 17–49 yrs) and sex *Study reports number of participants inconsistently; Table 3 reports 3,071 participants, while the Methods section and all other data tables report 3,147 participants.	Change in pulmonary function (95% CI) per interquartile range increase in Cr-adjusted urinary MBzP (adjusted for age, sex, smoking, fasting, income education, and $PM_{2.5}$) FEV_1 / FVC: −0.9 (−1.6, −0.2); FVC: −0.6 (−1.2, 0.1); $FEV_{1/}$ FVC: −0.5 (−0.9, −0.1) All participants (n = 3,071) By age Age 6–16 (n = 1,642): −0.6 (−1.5, 0.3); −0.7 (−1.6, 0.2); 0.0 (−0.5, 0.5) Age 17–49 (n = 1,505): −0.5 (−1.5, 0.6); 0.4 (−0.6, 1.4); −0.8 (−1.4, −0.2) By sex Male (n = 1,555): 0.8 (−1.5, 3.1); 0.6 (−2.6, 3.6); −0.1 (−1.3, 1.1) Female (n = 1,592): −0.3 (−2.1, 1.5); −0.6 (−2.4, 1.2); 0.1 (−0.8, 1.0)
Hoppin et al. (2004) (United States, NHANES) **Population:** 240 participants in population-based survey (NHANES III), 1988–1994; ages 20–60 yrs **Outcome:** FVC, FEV1, PEF, MMEF **Exposure:** Urine sample, collected at time of pulmonary function testing Mean (SD) MBzP in urine: Men Women Unadjusted (ng/mL) 22 (3.0) 22 (2.9) Cr-adjusted (ng/g Cr) 17 (2.5) 23 (2.4) **Analysis:** Linear regression, stratified by sex and adjusted for variables shown in results column	Regression coefficient (SE) for change in pulmonary function measure per interquartile range increase in MBzP (19.77 ng/g creatinine) (adjusted for age, age squared, height, BMI, smoking, and race) β (SE) Men Women FVC −74 (68) 64 (63) FEV1 −52 (56) 34 (54) PEF −226 (196) −153 (155) MMEF −76 (136) −61 (120) *p* >0.05 for all; results among nonsmokers only showed no significant associations for either men or women

3.2.12. Neurodevelopmental Effects in Humans

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

Reference and study design	Results
Neurobehavioral measures in school-aged children	
Chopra et al. (2014) (United States, NHANES) **Population:** 1,493 participants in population-based survey (NHANES), 2001–2004, ages 6–15 yrs **Exposure:** Urine sample collected same day as NHANES exam MBzP in urine (µg/g Cr) (percentile): Median 75th 95th Cr-adjusted 24.7 48.7 96.3 **Outcome:** Attention deficit disorder or learning disorder as reported by parent **Analysis:** Logistic regression, considering age, sex, race, household income, low birth weight, health insurance coverage, routine source of healthcare, mental health professional use in past yr, child blood lead level, maternal age at birth, and maternal smoking during pregnancy as potential covariates	Geometric mean (95% CI) Cr-adjusted MBzP in urine (µg/g Cr) by diagnosis Neither condition (n = 1,262): 28.7 (26.6, 31.0) Attention deficit disorder only (n = 56): 25.8 (17.6, 38.0) Learning disorder only (n = 116): 28.8 (22.3, 37.3) Both conditions (n = 56): 46.6 (29.0, 75.1) (trend *p*-value = 0.14) OR (95% CI) per 10-fold increase in Cr-adjusted log-transformed MBzP (adjusted for sex, age, race, household income, log-transformed blood lead, and maternal smoking during pregnancy) Attention deficit disorder only (n = 112): 1.5 (0.7, 3.4) Learning disorder only (n = 173): 1.2 (0.6, 2.5) Both conditions (n = 56): 2.0 (0.6, 6.3) Authors reported no interaction between child's blood lead and phthalate concentration (quantitative results not reported)
Kobrosly et al. (2014) (United States; Minnesota, Missouri, California, Iowa) **Population:** 153 children (n = 76 girls, n = 77 boys) from birth cohort study (SFF), 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) MBzP in urine (ng/mL): Geometric mean (95% CI) Unadjusted 6.6 (5.3, 8.2) **Analysis:** Linear regression, considering sex, age, mother's education, urinary creatinine, family stress measure, and race/ethnicity as potential covariates	Regression coefficient (95% CI) for change in raw score on child behavior checklist per unit increase in ln-transformed MBzP (adjusted for sex, age, mother's education and urinary creatinine, and family stress score) Boys / Girls Anxiety/depression: −0.06 (−0.25, 0.13) / −0.20 (−0.39, −0.01) Withdrawn: 0.02 (−0.14, 0.17) / −0.13 (−0.29, 0.02) Somatic complaints: 0.0 (−0.15, 0.16) / −0.08 (−0.24, 0.07) Social problems*: 0.06 (−0.10, 0.22) / −0.14 (−0.30, 0.02) Thought problems: −0.06 (−0.22, 0.11) / −0.04 (−0.20, 0.12) Attention problems: 0.0 (−0.18, 0.19) / −0.10 (−0.29, 0.08) Rule-breaking behavior: 0.08 (−0.07, 0.23) / −0.10 (−0.25, 0.05) Aggressive behavior: 0.19 (−0.01, 0.40) / 0.0 (−0.21, 0.20)

Reference and study design	Results
	Internalizing behavior: −0.04 (−0.25, 0.18); −0.22 (−0.44, 0.0) Externalizing behavior: 0.18 (−0.03, 0.40); −0.04 (−0.25, 0.17) Total problems: 0.10 (−0.20, 0.40); −0.21 (−0.51, 0.10) *Sex interaction *p*-value = 0.05; all other interaction *p*-values >0.05
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 MBzP in urine (µg/g Cr) (percentile): Median 75th 95th Cr-adjusted 11 17 48 **Analysis:** Semi-Bayesian hierarchical regression model	Regression coefficient (95% CI) for change in total score per unit increase in log-transformed Cr-adjusted MBzP (adjusted for maternal demographic and perinatal factors, depressive symptoms, caregiving environment, and serum cotinine) −0.8 (−2.9, 1.3)
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 MBzP in urine (ng/mL): Geometric mean (95% CI) SG-adjusted 3.54 (2.94, 4.26) **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-MBzP (adjusted for birthweight, breastfeeding practices, weight-for-age, child's age, mother's age, mother's education, and laboratory) Total sample (n = 135); Boys (n = 64); Girls (n = 71) MDI: 0.30 (−1.11, 1.73); 1.30 (−0.37, 2.97); −0.72 (−2.45, 1.01) PDI: 0.10 (−1.16, 1.37); 1.79 (0.14, 3.45); −1.21 (−3.31, 0.88)

Reference and study design	Results
Whyatt et al. (2012) (United States, New York City) **Population:** 297 children from birth cohort (CCCEH), 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 MBzP in urine (ng/mL): Geometric mean Unadjusted 19.0 **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-MBzP (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: −0.45 (−2.23, 1.32) / −1.07 (−2.48, 0.33) PDI: −0.57 (−2.74, 1.60) / −1.05 (−2.77, 0.67) Adjusted OR (95% CI) for risk of mental or psychomotor delay (score ≤85) per ln-unit increase in maternal ln-MBzP (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: 0.89 (0.64, 1.25) / 0.94 (0.66, 1.35) PDI: 0.96 (0.66, 1.39) / 1.25 (0.80, 1.95) Regression coefficient (95% CI) for change in neurobehavior per unit increase in maternal ln-MBzP (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: 0.34 (−0.008, 0.69) / 0.26 (−0.05, 0.57) Anxious/depressed: −0.05 (−0.46, 0.35) / 0.51 (0.17, 0.85) Somatic complaints: −0.23 (−0.63, 0.17) / 0.42 (0.10, 0.73) Withdrawn behavior: 0.24 (−0.09, 0.58) / 0.61 (0.29, 0.93) Internalizing behavior: 0.29 (−0.83, 1.42) / 1.79 (0.88, 2.69) Effect modification by gender observed for anxious/depressed, somatic complaints, and internalizing behavior (*p*-values of 0.035, 0.01, and 0.04, respectively). OR (95% CI) for child's score in the borderline or clinical range

Reference and study design	Results		
	(compared to normal) per unit increase in maternal ln-MBP (adjusted for specific gravity, maternal demoralization and satisfaction during pregnancy, and child's sex and age at testing)		
		Borderline	Clinical
	Somatic complaints	0.83 (0.59, 1.15)	1.20 (0.78, 1.86)
	Withdrawn behavior	0.79 (0.48, 1.28)	1.57 (1.07, 2.31)
	Internalizing behavior	1.38 (1.01, 1.90)	1.43 (1.01, 1.90)

BPA = bisphenol A; FEV1= forced expiratory volume in 1 second; FVC = forced vital capacity; HOME = Health Outcomes and Measures of the Environment; MDI = mental delay index; MMEF = maximal midexpiratory flow; PAH = polycyclic aromatic hydrocarbon; PDI = psychomotor delay index; PEF = peak expiratory flow

3.2.13. Obesity Effects in Humans

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

Reference and study design	Results
Buser et al. (2014) (United States, NHANES) **Population:** Participants in population-based survey (NHANES), 2007–2010, ages ≥6 yrs [sample size not reported] **Outcome:** BMI measured at exam; divided into obese (BMI z-score ≥95th percentile in children, BMI ≥30 in adults) and overweight (BMI z-score 85th–95th percentiles in children, BMI 25–29.9 in adults) **Exposure:** Urine sample, collected at same time as exam Unadjusted MBzP in urine (ng/mL) Geometric mean (SE): Ages 6–19 yrs 11.94 (0.63) Ages ≥20 yrs 5.88 (0.25) **Analysis:** Logistic regression, considering age, race/ethnicity, sex, urinary creatinine, poverty income ratio, calorie intake, and serum cotinine as potential covariates in analyses of ages 6–19 yrs; or age, race/ethnicity, sex, education, diabetes, alcohol consumption, cigarette smoking, calorie intake, vigorous recreational activities, urinary creatinine, and serum cotinine as potential covariates in analyses of ages ≥20 yrs)	OR (95% CI) in children (6–19 yrs of age) for obesity or overweight comparing highest quartile urinary MBzP (>27.58 ng/mL) with lowest quartile (≤5.66 ng/mL) (adjusted for age, race/ethnicity, calorie intake, serum cotinine, urinary creatinine, and income level) Obese / Overweight All: 2.15 (0.80, 5.57) / 1.50 (0.75, 3.02) Boys: 3.99 (1.20, 13.23) / 3.23 (1.12, 9.34) Girls: 0.84 (0.23, 3.06) / 1.01 (0.45, 2.24) OR (95% CI) in adults (≥20 yrs of age) for obesity or overweight comparing highest quartile urinary MBzP (>143.04 ng/mL) with lowest quartile (<2.66 ng/mL) (adjusted for age, gender, race/ethnicity, calorie intake, recreational activity, serum cotinine, education level, smoking status, alcohol intake, and diabetes) Obese / Overweight All: 1.09 (0.80, 1.47) / 0.88 (0.64, 1.21) Men: 0.97 (0.59, 1.58) / 0.89 (0.55, 1.43) Women: 1.06 (0.61, 1.83) / 0.78 (0.44, 1.37)
Song et al. (2014) (United States) **Population: 977** Controls from nested case-control study of incident diabetes in the NHS (n = 393, mean age 65.6 yrs, followed until 2010) and NHS II (n = 577, mean age 45.6 yrs, followed until 2009) **Outcome:** Change in body weight based on self-reported data from biennial questionnaires; self-reported body weights in these cohorts of registered nurses was highly accurate: a correlation coefficient of 0.96 was observed between self-reported weight and measured weights among 184 NHS participants **Exposure:** Urine sample collected at beginning of follow-up period (collected 2000–2001 for NHS; 1995–2000 for NHS II) MBzP in urine (nmol/L): Median by quartile Unadjusted 20, 47, 90, 252	Annual rate of weight change (95% CI) by quartile urinary MBzP (adjusted for cohort origin, age at sample collection, menopausal status, smoking status, physical activity, alcohol use, alternative healthy eating index score, caloric intake, baseline body weight, and urinary creatinine levels) MBzP quartile (median concentration, nmol/L) / Annual rate of weight change in kg/yr (95% CI) 1 (20): 0.0 (referent) 2 (47): 0.29 (0.13, 0.44) 3 (90): 0.33 (0.17, 0.48) 4 (252): 0.42 (0.26, 0.57) (trend p <0.001)

Reference and study design	Results
Analysis: Logistic regression, mixed-effect models for prospective annual weight change rate by quartile MBzP using product terms between concentrations and year after baseline; adjusting for variables shown in results column	
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) MBzP in serum (ng/mL): Median 90th percentile Unadjusted 1.26 3.87 **Analysis:** Correlation between log-transformed MBzP 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)
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) MBzP, in urine (ng/mL) (percentile): Median 75th 90th Controls 6 11 20 Obese 8 16 25 (at baseline) **Analysis:** Linear regression, adjusting for variables shown in results column; treatment of repeated urinary phthalate measures was not specified	Regression coefficient (*p*-value) for change in waist circumference with unit change in ln-MBzP (adjusted for age, weight loss, and sex, or stratified by sex) (0.0 = no effect) Full sample / Men / Women Overweight/ obese group: 0.12 (0.16) / 0.09 (0.56) / 0.08 (0.45) Referent group: −0.11 (0.48) / 0.08 (0.77) / −0.08 (0.67)

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: MBzP ∑high MW phthalates Boys 49.6 356.0 Girls 34.0 326.6 High molecular weight phthalate metabolites included MECPP, MEHHP, MEOHP, MEHP, and MBzP. **Analysis:** Linear regression, considering sex, age at baseline, sedentary hours, metabolic equivalent hours, caloric intake, race, ethnicity, season of urine collection, family income, and parent education as potential covariates; restricted to children with creatinine ≥10 mg/dL	Full sample results, regression coefficient (95% CI) for change in body metric per unit change in ln-MBzP (µg/g Cr) (adjusted for creatinine, age, sex, sedentary hours, metabolic equivalent hours, Hispanic ethnicity, caloric intake, season, and parental education level) BMI (kg/m^2) −0.50 (−1.51, −0.51) Waist circumference (cm) 0.12 (−0.91, −1.14)
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 MBzP in urine (µg/g Cr): Geometric mean (SD) No diabetes 7.0 (2.9) **Analysis:** Spearman correlation coefficient **Related references:** Lopez-Carrillo et al. (2010)	Spearman correlation coefficient between anthropometric measure and ln-MBzP in urine (µg/g Cr) BMI (kg/m^2) 0.0059 Waist circumference (cm) −0.0063 Waist/height ratio 0.0883 (p >0.05 for all parameters)

Reference and study design	Results				
Hatch et al. (2008) (United States, NHANES) **Population:** 4,369 (2,251 males, 2,118 females) participants in population-based survey (NHANES), 1999–2002; ages 6–80 yrs **Outcome:** BMI, waist circumference (measured) **Exposure:** Urine sample, collected at time of obesity measurement MBzP in urine (µg/g Cr): Range of geometric means in different age-sex groups = 10–35 **Analysis:** Linear regression, adjusting for variables shown in results column; separate analyses by sex-age group (ages 6–11, 12–19, 20–59, 60–80 yrs)	Regression coefficient (95% CI) for change in body metric per quartile increase in unadjusted MBzP (µg/L), by age (age, creatinine, height, race/ethnicity, socioeconomic status, fat intake, dairy intake, fruit and vegetable intake, physical activity, TV/video and computer use, and smoking status, and for women, menopausal status, parity)				
	MBzP quartile	6–11 yrs β	12–19 yrs β	20–59 yrs β	60–80 yrs β
	Waist circumference, males				
	1 (low)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
	2	2.52 (−1.71, 6.74)	2.14 (−0.99, 5.28)	1.27 (−1.34, 3.87)	−0.11 (−3.65, 3.43)
	3	2.42 (−1.43, 6.27)	1.36 (−1.47, 4.19)	4.87 (2.18, 7.56)	−1.84 (−5.61, 1.93)
	4 (high)	0.55 (−3.31, 4.40)	3.10 (−0.67, 6.88)	6.63 (3.42, 9.84)	−3.18 (−7.64, 1.29
	(trend *p*)	(0.85)	(0.15)	(<0.0001)	(0.09)
	Waist circumference, females				
	1 (low)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
	2	1.69 (−1.63, 5.02)	2.48 (−0.68, 5.64)	3.55 (0.51, 6.59)	−1.33 (−5.24, 2.59)
	3	1.33 (−1.75, 4.41)	0.59 (−2.86, 4.05)	2.08 (−1.62, 5.79)	−2.18 (−6.26, 1.91)
	4 (high)	−0.50 (−3.66, 2.66)	1.46 (−3.06, 5.98)	3.18 (−0.90, 7.26)	−2.41 (−6.65, 1.84)
	(trend *p*)	(0.65)	(0.74)	(0.29)	(0.24)
	BMI, males				
	1 (low)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
	2	1.05 (−0.60, 2.71)	0.60 (−0.65, 1.86)	0.47 (−0.53, 1.48)	−0.35 (−1.60, 0.89)
	3	1.09 (−0.36, 2.54)	0.21 (−0.85, 1.27)	1.70 (0.65, 2.76)	−1.27 (−2.97, 0.42)
	4 (high)	−0.13 (−1.53, 1.28)	0.84 (−0.47, 2.15)	2.35 (1.04, 3.65)	−1.59 (−3.43, 0.24)
	(trend *p*)	(0.80)	(0.3)	(0.0002)	(0.06)
	BMI, females				
	1 (low)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
	2	0.52	1.42	1.26	−0.67

Reference and study design	Results			
		(−0.89, 1.92)	(−0.07, 2.91)	(−0.11, 2.62)	(−2.13, 0.80)
	3	0.68 (−0.50, 1.85)	0.53 (−0.96, 2.01)	0.78 (−1.01, 2.56)	−0.72 (−2.85, 1.40)
	4 (high)	−0.18 (−1.43, 1.08)	0.84 (−0.97, 2.65)	0.82 (−1.26, 2.90)	−0.73 (−2.67, 1.22)
	(trend *p*)	(0.80)	(0.59)	(0.62)	(0.49)
Stahlhut et al. (2007) (United States, NHANES) **Population:** 1,451 men in population-based survey (NHANES), 1999−2002; ages >18 yrs; excluded if taking insulin, oral hypoglycemic agents, or sex hormone agonists/antagonists **Outcome:** Waist circumference (measured) **Exposure:** Urine sample, collected at time of obesity measurement MBzP in urine (µg/g Cr): Median Cr-adjusted 14.2 **Analysis:** Linear regression, adjusting for variables shown in results column	Regression coefficient per unit increase in ln-MBzP (adjusted for age, age-squared, race/ethnicity, fat intake, calorie intake, physical activity level, smoking exposure based on cotinine, urinary creatinine, glomerular filtration rate, serum ALT, and GGT) B ± SE (*p*-value) Waist circumference (n = 1,292): 1.09 ± 0.36 (0.005) Increase in waist circumference began in 3rd quartile of exposure (data shown graphically)			

ALT = alanine aminotransferase; GGT = gamma glutamyl transferase; NHS = Nurses' Health Study

3.2.14. Diabetes Effects in Humans

Table 3-15. Evidence pertaining to BBP and diabetes/insulin resistance in humans

Reference and study design	Results		
Diabetes diagnosis			
Sun et al. (2014) (United States) **Population:** 971 incident diabetes cases and 970 controls from among participants in the NHS (394 cases and 393 controls, mean age 65.6 yrs, 2000–2008) and NHS II (577 cases and 577 controls, mean age 45.6 yrs, 1996–2007) **Outcome:** Incident type 2 diabetes assessed in biennial follow-up questionnaires. Confirmed based on: (a) self-report of elevated fasting glucose ≥7.0 mmol/L, random plasma glucose ≥11.1 mmol/L, or plasma glucose ≥11.1 mmol/L and at least one symptom (excessive thirst, polyuria, weight loss, or hunger); (b) no symptoms but elevated glucose on two separate occasions; or (c) treatment with insulin or oral hypoglycemic medication **Exposure:** Urine sample, collected at beginning of follow-up period (2000–2002 for NHS; 1996–2001 for NHS II) Unadjusted MBzP in urine (µg//L): Median by quartile NHS I 3.5, 7.2, 13.4, 31.8 NHS II 8.8, 17.2, 33.3, 87.1 **Analysis:** Conditional logistic regression, adjusting for variables shown in results column	OR (95% CI), highest compared with lowest quartile MBzP, adjusting for matching factors including age at sample collection, race, fasting status, time of sample collection, menopausal status, use of hormone replacement therapy (NHS II only), urinary creatinine levels, BMI, smoking status, postmenopausal hormone use (NHS only), oral contraceptive (NHS II only), physical activity, alcohol use, family history of diabetes, history of hypercholesterolemia or hypertension, and alternative healthy eating index score		
	MBzP quartile	NHS	NHS II
	1 (low)	1 (referent)	1 (referent)
	2	0.91 (0.55, 1.51)	0.85 (0.50, 1.44)
	3	0.85 (0.51, 1.40)	1.08 (0.62, 1.86)
	4 (high)	0.82 (0.48, 1.43)	1.14 (0.65, 2.01)
	(*p*-value for trend)	(0.54)	(0.44)

Reference and study design	Results
James-Todd et al. (2012) (United States, NHANES) **Population:** 215 cases, 1,235 controls from population-based survey (NHANES), 2001–2008; women ages 20–79 yrs **Outcome:** Positive response to, "Other than during pregnancy, have you ever been told by a doctor or health professional that you have diabetes or sugar diabetes?" **Exposure:** Urine sample, collected at time of survey MBzP in urine (units not reported): Geometric mean Unadjusted 9.7 (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 MBzP (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) MBzP quartile 1 (low) 1.0 (referent) 2 0.78 (0.41–1.49) 3 1.80 (1.16–2.81) 4 (high) 1.96 (1.11–3.47)
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 MBzP in urine (µg/g creatinine): Geometric mean (SD) No diabetes 7.0 (2.9) Diabetes 3.8 (3.9) **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-MBzP (adjusted for creatinine and education) 0.74 (0.55, 1.00)
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 MBzP in urine (µg/g Cr): Median 75th percentile Men 10.4 19.5 Women 13.4 23.8 **Analysis:** Logistic regression, adjusting for	Median change (95% CI) in biomarker for diabetes by quartile of MBzP (adjusted for age, gender, race/ethnicity, fasting time, urinary creatinine, total caloric intake, triglycerides, education, poverty, and smoking status) MBzP quartile / Fasting glucose / Fasting insulin / HOMA-IR 1 (low) / referent / referent / referent 2 / −0.30 (−1.48, 0.87) / 0.77 (0.16, 1.39) / 0.21 (0.06, 0.37) 3 / −0.06 (−1.25, 1.13) / 1.09 (0.39, 1.79) / 0.26 (0.09, 0.44) 4 (high) / −0.24 (−1.49, 1.02) / 1.44 (0.50, 2.38) / 0.37 (0.15, 0.59)

Reference and study design	Results
variables shown in the results column	(*p*-value for trend) (0.7058) (0.0070) (0.0028)
[Trasande et al. (2013a)] (United States, NHANES) **Population:** 760 participants in the 2003−2008 NHANES, 12−19 yrs old **Outcome:** HOMA-IR, calculated as fasting glucose (mmol/L) multiplied by fasting insulin (μU/mL divided by 22.5 **Exposure:** Urine sample, collected at same time as insulin resistance measurements. ΣHigh MW phthalates in urine (μM): Median 75th percentile Unadjusted 0.50 0.98 ΣHigh MW phthalates = sum of MBzP, MCPP, MEHP, MECPP, MEHHP, MEOHP; urinary concentration of MBzP alone not reported **Analysis:** HOMA-IR assessed as continuous or categorical variable; categorical analysis used cut point of 4.39, reflecting >2 SD above the mean HOMA-IR for normal weight adolescents with normal fasting glucose in NHANES 1999−2002. Linear and logistic regression analyses, adjusting for variables shown in results column. HOMA-IR and urinary phthalate measures natural-log transformed for analysis.	OR (95% CI) for insulin resistance and ln-urinary metabolite concentration (μM), adjusted for urinary creatinine, BMI category, continuous age, race/ethnicity, caregiver education, poverty-income ratio, gender, serum cotinine, and caloric intake Ln-MBzP 1.26 (0.97, 1.63) Ln-Σhigh MW phthalates 1.45 (1.13, 1.87) 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-MBzP 0.02 (−0.08, 0.13) Ln-Σhigh MW phthalates 0.26 (0.13, 0.40)
[James-Todd et al. (2012)] (United States, NHANES) **Population:** 2,092 women without history of diabetes with various measures of insulin resistance from population-based survey (NHANES), 2001−2008; women age 20−79 yrs **Outcome:** (Among women without history of diabetes, fasting blood glucose (FBG) (n = 985), HOMA-IR (n = 971), glycosolated hemoglobin A1c (n = 2,092) **Exposure:** Urine sample, collected at time of survey MBzP in urine (units not reported): Geometric mean Unadjusted 9.7 **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 MBzP (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) MBzP Quartile Model 1 Model 2 Fasting glucose (mg/dL) 1 (low) (referent) (referent) 2 0.00 (−1.70, 1.70) 0.77 (−1.11, 2.64) 3 −1.13 (−3.24, 0.98) −1.08 (−3.34, 1.18) 4 (high) −2.27 (−4.76, 0.21) −2.80 (−5.32, −0.28) Ln (HOMA) 1 (low) (referent) (referent) 2 0.09 (−0.07, 0.25) −0.01 (−0.12, 0.11) 3 0.13 (−0.02, 0.28) 0.06 (−0.07, 0.19)

Reference and study design	Results		
	4 (high)		
	A1c (%)		
	1 (low)	(referent)	(referent)
	2	0.01 (−0.04, 0.06)	−0.01 (−0.05, 0.04)
	3	0.00 (−0.05, 0.05)	−0.03 (−0.08, 0.01)
	4 (high)	−0.03 (−0.09, 0.03)	−0.03 (−0.09, 0.02)
Stahlhut et al. (2007) (United States, NHANES) **Population:** 1,451 men in population-based survey (NHANES), 1999−2002; ages >18 yrs; excluded if taking insulin, oral hypoglycemic agents, or sex hormone agonists/antagonists **Outcome:** HOMA-IR **Exposure:** Urine sample, collected at time of obesity measurement MBzP in urine: Median Cr-adjusted (µg/g Cr) 14.2 **Analysis:** Linear regression, adjusting for variables shown in results column	Regression coefficient per unit increase in ln-MBzP (adjusted for age, age-squared, race/ethnicity, fat intake, calorie intake, physical activity level, smoking exposure based on cotinine, urinary creatinine, glomerular filtration rate, serum ALT, and GGT) B ± SE (*p*-value) 0.061 ± 0.022 (0.005)		

HOMA-IR = homeostasis model assessment of insulin resistance; MCPP = mono-(3-carboxypropyl) phthalate; MECPP = mono(2-ethyl-5-carboxypentyl) phthalate

3.2.15. Cardiovascular Effects in Humans

Table 3-16. Evidence pertaining to BBP 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 (BP) (systolic blood pressure ≥140 mmHg and diastolic blood pressure ≥90 mmHg) **Exposure:** Urine sample collected at time of clinical exam MBzP in urine (units not given): Mean ± SD Normal BP 11.21 ± 19.74 High BP 16.91 ± 29.84 **Analysis:** Survey-weighted logistic regression, adjusting for variables shown in results column; t-test for comparison between concentrations	OR (95% CI) for high blood pressure per unit increase in log-transformed MBzP (adjusted for urinary creatinine, age, sex, ethnicity, BMI, and sampling weights) 1.40 (1.15, 1.69) Mean ± SD MBzP in urine (units not given) in participants with normal and high blood pressure Normal BP (n = 2,180) 11.21 ± 19.74 High BP (n = 309) 16.91 ± 29.84* *p <0.001
Trasande et al. (2013b) (United States, NHANES) **Population:** 2,447 children in population-based survey (NHANES), 2003–2008; ages 8–19 yrs old **Outcome:** Systolic BP and diastolic BP z-score (based on CSC norms, sex, and age); prehypertension (BP ≥90th percentile for age/height/sex); fasting serum triglycerides (n = 906; high = ≥100 mg/dL); nonfasting high density cholesterol (HDL; n = 2,555; low = <40 mg/dL) **Exposure:** Urine sample, collected at time of BMI measurement ∑High MW phthalates in urine (µM): Geometric mean BP <90th percentile 0.541 BP ≥90th percentile 0.509 ∑High MW phthalates = sum of MECPP, MCPP, MEHHP, MEOHP, MEHP, and MBzP	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) ∑High MW phthalates: Systolic BP 0.04 (−0.002, 0.08); Diastolic BP 0.004 (−0.04, 0.04); Triglycerides −0.28 (−2.55, 2.06); HDL 0.42 (−0.31, 1.15) MBzP: Systolic BP 0.03 (−0.02, 0.08); Diastolic BP 0.03 (−0.02, 0.09); Triglycerides not reported; HDL not reported OR (95% CI) for BP ≥90th percentile per unit increase in ln-phthalates ∑High MW phthalates: BP ≥90th percentile 0.94 (0.82, 1.09); High triglycerides 1.06 (0.90, 1.24) MBzP: BP ≥90th percentile 1.12 (0.87, 1.44); High triglycerides not reported

Reference and study design	Results		
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	Low HDL	0.93 (0.80, 1.07)	not reported
	Interactions with covariates examined in supplemental analyses; stratified analyses showed a statistically significant association between ∑high MW phthalates and systolic BP for gender (males), age (children), race/ethnicity (Hispanics), cotinine level (low and high), and BMI (≤85th percentile)		

BP = blood pressure; HDL = high density lipoprotein

3.2.16. Cancer Effects in Humans

Table 3-17. Evidence pertaining to BBP 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) MBzP in urine, controls: Geometric mean Cr-adjusted (µg/g Cr) 6.27 **Analysis:** Logistic regression, adjusting for variables shown in results column	Geometric mean (95% CI) MBzP in urine (µg/g Cr), all subjects and by menopausal status Controls / Cases All: 6.27 (5.38, 7.31) / 5.43 (4.81, 6.13) Pre-menopause: 7.22 (5.67, 9.20) / 5.29* (4.42, 6.34) Post-menopause: 5.84 (4.80, 7.10) / 5.51 (4.68, 6.49) *p <0.05 OR (95% CI) for breast cancer, by tertile of MBzP (adjusted for current age, age at menarche, parity, menopausal status, and other phthalate metabolites) MBzP tertile (µg/g Cr) / Full sample / Pre-menopause / Post-menopause 1 (0–5.18): 1.0 (referent) / 1.0 (referent) / 1.0 (referent) 2 (5.19–10.79): 0.60 (0.37, 0.98) / 0.36 (0.15, 0.89) / 0.71 (0.38, 1.30) 3 (10.8–259): 0.46 (0.27, 0.79) / 0.22 (0.08, 0.61) / 0.61 (0.31, 1.19) (trend p): (0.008) / (0.006) / (0.169) Urinary MBzP was inversely associated with breast cancer risk
Aschengrau et al. (1998) (United States, Massachusetts) Population: 261 incident cases, 753 population controls of similar age and race; both cases and controls were permanent residents of five Cape Cod towns Outcomes: Breast Cancer diagnosis (1983–1986) Exposure: Occupational exposure to xenoestrogens (including phthalates) based on self-reported full-time jobs held since age 18; exposure determined for each job using the NIOSH Occupational Exposure Survey Database, chemical production and usage information, and the expert judgment of a certified industrial hygienist Analysis: Logistic regression, adjusting for variables shown in results column	Incidence (%) of females with probable exposure to BBP Cases: 26/261 (10.0%) / Controls: 100/753 (13.3%) OR (95% CI) for breast cancer and probable occupational exposure to BBP (adjusted for age at diagnosis or index year, vital status at the interview, family history of breast cancer, age at first birth, and personal history of prior breast cancer and benign breast disease) Any BBP exposure: 0.7 (0.4, 1,2) BBP-only exposure: 0.9 (0.3, 2.9) BBP+other xenoestrogens: 0.7 (0.4, 1.2)

NIOSH = National Institute for Occupational Safety and Health

3.3. EXPERIMENTAL STUDIES

3.3.1. Male Reproductive Effects

Table 3-18. Evidence pertaining to male reproductive puberty effects and indicators of reproductive development following oral exposure to BBP

Reference and study design	Results[a]				
Tyl et al. (2004)	**PPS or AGD** *(percent change compared to control)*				
Rat (CD); 30 F0 and 30 F1 parental rats/sex/dose	mg/kg-day	0	50	250	750
	F1 age at PPS	0	1	−1	11*
0, 750, 3,750, 11,250 ppm 0, 50, 250, 750 mg/kg-day[b]	*F1 age at PPS adjusted for body weight*	0	0.2	−1	11*
Diet	*F1 neonatal AGD*	0	−2	−8*	−17*
Multigenerational study	*F2 neonatal AGD*	0	0	−3	−14*
	Nipple retention *(number per male or percentage of males)*				
	F1 nipples (number per male)	0	0	0	0.72*
	percent of F1 males with at least one nipple on PNDs 11−13	0	0	0	19*
	percent of F1 males with at least one areolae PNDs 11−13	3	0	1	32*
	areolae (number per F1)	0	0	0	1.29*
	percent of F2 males with at least one nipple on PNDs 11−13	0	0	0	16*
	F2 number of nipples/male	0	0	0	0.51*
	percent of F2 males with at least one areola on PNDs 11−13	2	5	5	72*
	F2 number of areolae	0.05	0.12	0.19	3.14*

Reference and study design	Results[a]				
Hotchkiss et al. (2004)	**Nipple retention** *(number per male rat)*				
Rat (Sprague-Dawley); 6 pregnant females/dose	mg/kg-day	0			500
0, 500 mg/kg-day Gavage GDs 14–18	*areolae (number per F1 neonatal male)*	0			1.1
	nipples (number per F1 adult male)	0			1
	AGD *(percent change compared to control)*				
	neonatal AGD[c]	0%			−13*
	adult AGD[c]	0%			−2
Gray et al. (2000)	**PPS or AGD** *(percent change compared to control)*				
Rat (Sprague-Dawley);	mg/kg-day	0			750
13–19 pregnant females/dose 0, 750 mg/kg-day	*litter mean age at PPS*	0			3
Gavage	*AGD*	0			−26*
GDs 14–PND 3	**Nipple retention** *(number or percentage per neonatal male)*				
	nipples (number per neonatal male)	0			5.1*
	percent of neonatal males with areolae	0			70*
	PPS *(% incidence)*				
	incomplete PPS due to genital malformation	0/19			9/46* (20%)
Nagao et al. (2000)	**PPS or AGD** *(percent change compared to control)*				
Rat (Sprague-Dawley); 25/sex /dose	mg/kg-day	0	20	100	500
0, 20, 100, 500 mg/kg-day	*AGD at birth*	0	0	−4	−8*
Gavage	*age at PPS*	0	0.5	0.2	3*
Multigenerational study					

Reference and study design	Results[a]				
Aso et al. (2005)	**PPS** *(% incidence)*				
Rat (Crj:CD(SD)IGS); 24/sex/dose	mg/kg-day	0	100	200	400
0, 100, 200, 400 mg/kg-day	*F1 complete PPS*	23/24 (96%)	17/24 (71%)	22/24 (92%)	14/24* (58%)
Gavage	**AGD** *(percent change compared to control)*				
Multigenerational study	Absolute change				
	F1, AGD, males	0	1	−2	−3
	F2, AGD, males	0	−12*	−8	−14*
	Relative change				
	F1, AGD, males	0	0	−1	−2
	F2, AGD, males	0	−8*	−8*	−12*
Ema and Miyawaki (2002)	**AGD** *(percent change compared to control)*				
Rat (Wistar); 16 pregnant females/dose	mg/kg-day	0	250	500	1,000
0, 250, 500, 1,000 mg/kg-day	*AGD*[c]	0	−1	−20*	−35*
Gavage	*AGD adjusted for BW*[c]	0	−4	−21*	−32*
GDs 15−17					
Ahmad et al. (2014)	**AGD or developmental milestones** *(percent change compared to control)*				
Rat (Albino); P0, female (6/group)	mg/kg-day	0	4	20	100
0, 4, 20, 100 mg/kg	AGD				
Gavage	*F1 male AGD PND 25*	0	−1	−1	−2
GD 14 to parturition	*F1 male AGD PND 5*	0	−6	−6	−8
	Developmental milestones				
	F1 male eye opening	NR	NR	NR	NR
	F1 male fur formation	NR	NR	NR	NR
	F1 male pinna detachment	NR	NR	NR	NR
	F1 male testis descend	–	0	1	0

Reference and study design	Results[a]				
TNO (1998a)	***PPS*** *(percent change compared to control)*				
Rat (Wistar); P0, female (28/group)	mg/kg-day	0	0.015	0.147	0.442
0, 100, 1,000, 3,000 µg/L (equivalent to 0.016, 0.171, 0.489 mg/kg-day, average of reported intake over premating, gestation, and lactation) Drinking water F0 females: 2 weeks prior to mating, through mating, gestation, and lactation; F0 males: during mating; F1 animals were not treated after weaning	*F1 male PPS*	NR	NR	NR	NR

*Statistically different from controls (p <0.05) as reported by study authors.
[a]Percent change compared to control calculated as 100 × ((treated value − control value) ÷ control value).
[b] Calculated as follows: [% in diet × intake food/water (mg)] ÷ body weight (kg) = mg/kg-day.
[c]Values reported by the study authors were estimated from published graphs using "Grab It!", a Microsoft Excel based free software application used to digitizes data from image files. Publisher: www.datatrendsoftware.com.

BW = body weight; GD = gestation day; PND = postnatal day; PPS = preputial separation; NR = not reported

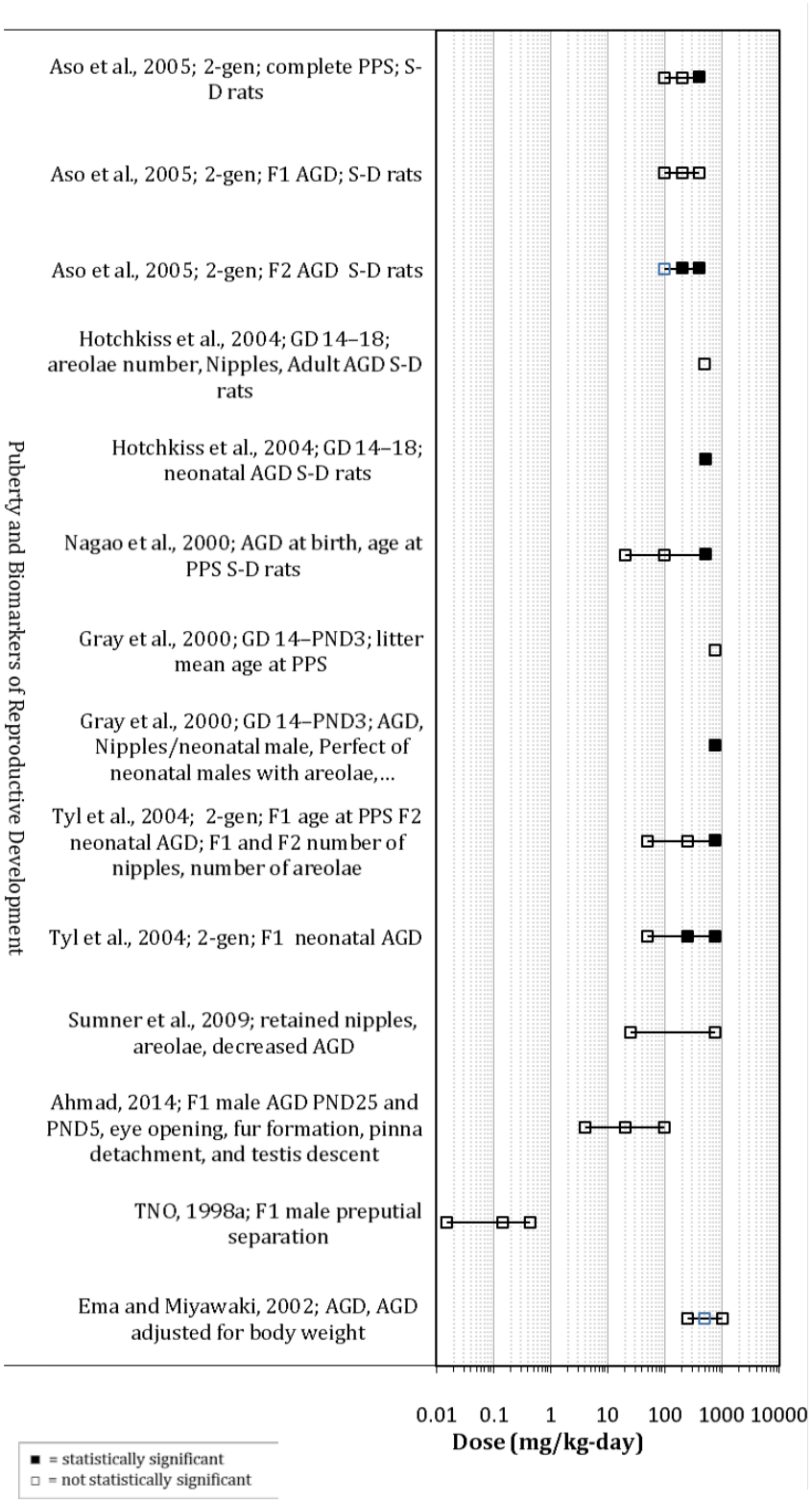


Figure 3-1. Exposure-response array of male reproductive puberty effects and indicators of reproductive development following oral exposure to BBP.

Table 3-19. Evidence pertaining to male reproductive toxicity following oral exposure to BBP: Alterations in hormone concentrations, mating, and sperm decrements

Reference and study design	Results[a]					
Götz et al. (2001)	**Mating behavior** *(percent change compared to control)*					
Rat (Wistar (Crl:WI)); 10–15 pregnant females/group 0, 10 mg/L BBP to pregnant females during the whole pregnancy and during lactation Drinking water	mg/L	0			10	
	% male-typical mounting behavior	0			−39*	
NTP (1997b)	**Sperm parameters** *(percent change compared to control)*					
Rat (F344); 15 males/dose 0, 300, 2,800, 25,000 ppm 0, 20, 200, 2,200 mg/kg-day Diet 10-week modified mating study	mg/kg-day	0	20	200	2,200	
	sperm motility	0	−8	−3	Not measured	
	epididymal sperm concentration	0	−13	−30	−100*	
	abnormal epididymal sperm	0	−13	−3	Not measured	
	Note: Percentages of motile and abnormal sperm were not measured at the high dose due to an absence of sperm.					
NTP (1997b)	**Sperm parameters** *(percent incidence)*					
Rat (F344); 15 males/dose 0, 300, 900, 2,800, 8,300, 25,000 ppm 0, 30, 60, 180, 550, "high" mg/kg-day[b] Diet 26 weeks	mg/kg-day	0	30	60	180	550	'High'
	seminiferous tubule hypospermia	0	0	0	0	0	100*
	epididymal hypospermia	0	0	0	0	0	100*
Tyl et al. (2004)	**Sperm count** *(percent change compared to control)*					
Rat (CD); 30 F0 and 30 F1 parental rats/sex/dose 0, 750, 3,750, 11,250 ppm 0, 50, 250, 750 mg/kg-day Diet Multigenerational study	mg/kg-day	0		50	250	750
	F1 epididymal sperm count	0		4	2	−21*
	Mating, fertility, and sperm parameters *(raw percentages)*					
	F1 mating index (%)	96.7		96.7	93.3	70.0*
	F1 fertility index (%)	100		96.6	92.9	81.0*
	F1 motile sperm (%)	68.6		74.0	71.7	52.1*

Reference and study design	Results[a]				
	F1 progressively motile sperm (%)	57.3	61.2	60.1	42.1*
Hotchkiss et al. (2004) Rat (Sprague-Dawley); 6 pregnant females/dose 0, 500 mg/kg-day Gavage GDs 14–18	**Fetal hormones** *(percent change compared to control)*				
	mg/kg-day	0		500	
	testicular testosterone production	0		−45*	
	testicular testosterone concentration	0		−35*	
	fetal whole-body testosterone concentration	0		−71*	
	testicular progesterone production	0		−33*	
	Note: Data shown graphically, but magnitude of change (percent change from control) reported by study authors in text.				
Gray et al. (2000) Rat (Sprague-Dawley); 13–19 pregnant females/dose 0, 750 mg/kg-day Gavage GD 14–PND 3	**Adult hormones** *(percent change compared to control)*				
	mg/kg-day	0		750	
	adult serum testosterone	0		26	
	Note: Study authors indicate that sperm production and caudal sperm numbers were significantly affected by BBP exposure although data are not shown.				
Nagao et al. (2000) Rat (Sprague-Dawley); 25/sex/dose 0, 20, 100, 500 mg/kg-day Gavage Multigenerational study	**Mating, fertility, and sperm parameters** *(raw percentages)*				
	mg/kg-day	0	20	100	500
	F0 mating index (%)	96	96	96	100
	F0 fertility index (%)	91.7	83.3	95.8	96
	F0 sperm motility (%)	96	94	94	95
	F0 progressively motile sperm (%)	93	80	78	81
	F1 mating index (%)	100	94.7	90.9	91.7
	F1 fertility index (%)	77.3	77.8	95	77.3
	F1 adult males sperm motility (%)	95	96	97	88
	F1 adult males progressively motile sperm (%)	83	83	85	77

Reference and study design	Results[a]				
	Testosterone and sperm concentration *(percent change compared to control)*				
	F0 serum testosterone	0	3	−23	−46*
	F0 sperm concentration	0	0	−5	−2
	F1 weanling males serum testosterone	0	33	−11	0
	F1 adult males serum testosterone	0	23	8	−44*
	F1 adult males sperm concentration	0	−9	−4	−9
Aso et al. (2005) Rat (Crj:CD(SD)IGS); 24 mated pairs of F0 parents/dose 0, 100, 200, or 400 mg/kg-day Gavage Multigenerational study	**Testosterone and sperm count** *(percent change compared to control)*				
	mg/kg-day	0	100	200	400
	F0 serum testosterone	0	Not evaluated		−42
	F0 sperm in testes	0	6	−8	−2
	Mating, fertility, and sperm parameters *(raw percentages)*				
	F0 mating index (%)	100	91.7	95.7	95.8
	F0 fertility index (%)	83.3	86.4	90.9	91.3
	F0 epididymal sperm motility (%)	71	65	74	58
	F1 mating index (%)	91.3	91.7	83.3	83.3
	F1 fertility index (%)	76.2	95.5	85	65
	Epididymal sperm *(percent incidence)*				
	F1 spermatozoa decreased in epididymal lumina	0	4	8	13
	Note: Spermatozoa decreased in the epididymal lumina of F0 males at 400 mg/kg-day also (quantitative data not reported).				
	F1 sperm in testes, caudal epididymis	Not affected			
	epididymal sperm motility and abnormalities	No treatment-related effect observed by study authors			

Reference and study design	Results[a]					
Howdeshell et al. (2008)	**Fetal testicular testosterone** *(percent change compared to control)*					
Rat (Sprague-Dawley); 4–9 pregnant females/dose 0, 100, 300, 600, 900 mg/kg-day Gavage GDs 8–18	mg/kg-day	0	100	300	600	900
		0	6	−22*	−66*	−90*

*Statistically different from controls (p <0.05) as reported by study authors.
[a]Percent change compared to control calculated as 100 × ((treated value − control value) ÷ control value).
[b]The high-dose group corresponds to 25,000 ppm BBP; a reliable estimate of dose could not be calculated. The study authors estimated doses for all but the high-dose group based on measured body weights and food consumption. Food consumption was not measured in the 25,000 ppm BBP group due to excessive scattering of feed and because the mean body weight of this group was 30% lower than controls.

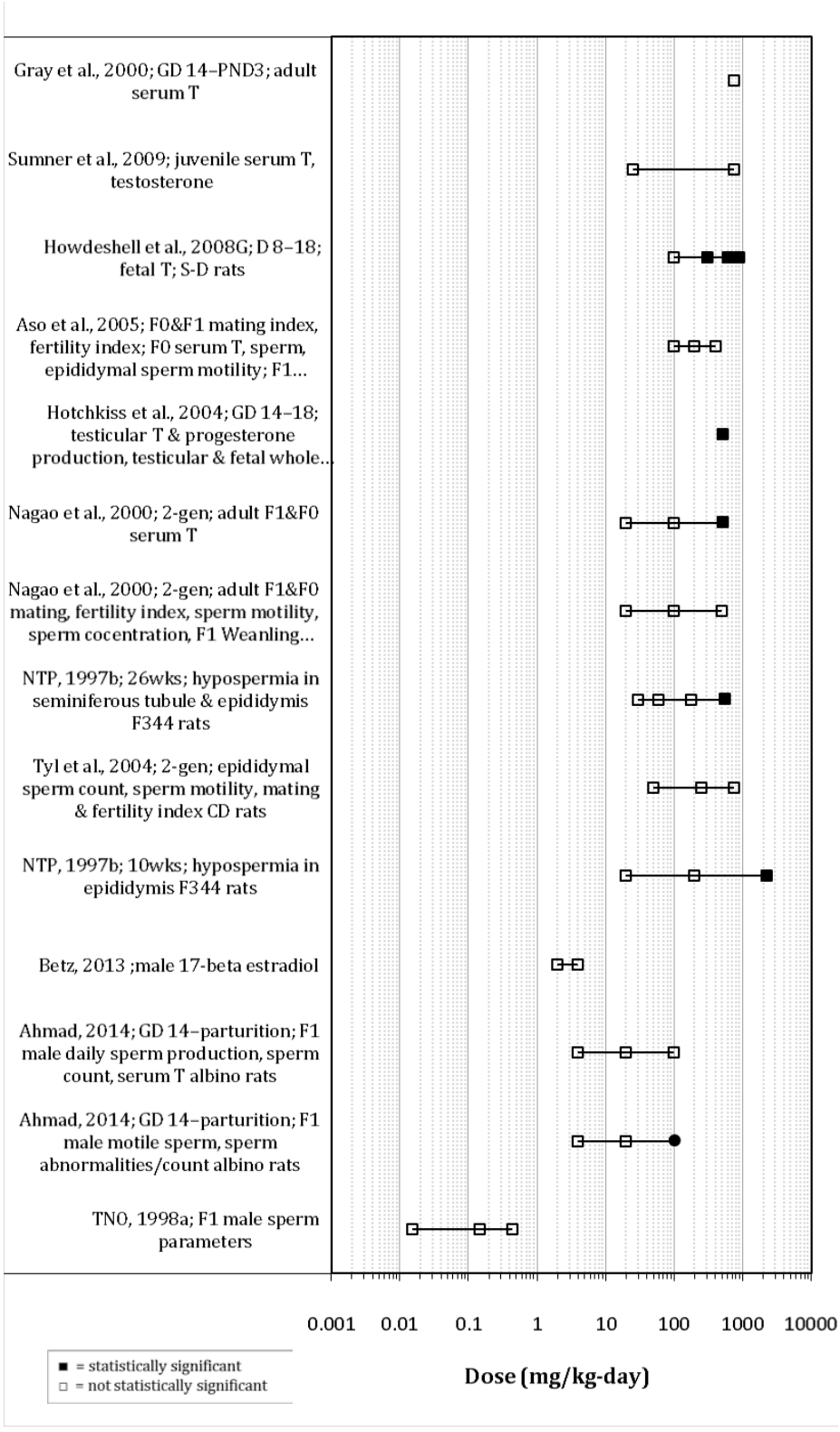


Figure 3-2. Exposure-response array of male reproductive toxicity following oral exposure to BBP: alterations in hormone concentrations, mating, and sperm decrements.

Table 3-20. Evidence pertaining to male reproductive toxicity following oral exposure to BBP: Histopathological changes and malformations in adults and offspring

Reference and study design	Results						
NTP (1997b)	**Testes and epididymal histopathology** *(percent incidence)*						
Rat (F344); 15 males/dose	mg/kg-day (F0 males)	0		20	200		2,200
0, 300, 2,800, 25,000 ppm 0, 20, 200, 2,200 mg/kg-day	*atrophic seminiferous tubules*	0		7	0		100*
Diet	*seminiferous tubule, giant cells*	0		0	0		67*
10-week modified mating study	*seminiferous tubule necrosis*	0		0	0		20
	epididymal hypospermia	0		7	0		100*
	chronic inflammation of epididymal tail	0		0	0		27*
	epididymal tail detritus	0		0	0		73*
NTP (1997b)	**Testes and epididymal histopathology** *(percent incidence)*						
Rat (F344); 15/dose	mg/kg-day	0	30	60	180	550	High
0, 300, 900, 2,800, 8,300, 25,000 ppm 0, 30, 60, 180, 550, "high" mg/kg-day[a]	*atrophic seminiferous tubules*	0	0	0	7	0	100*
Diet	*seminiferous tubule, giant cells*	0	0	0	0	0	33*
26 weeks	*epididymal tail detritus*	0	0	0	7	0	87*
Tyl et al. (2004)	**Malformations and histopathological changes** *(percent incidence)*						
Rat (CD); 30 F0 and 30 F1 parental rats/sex/dose	mg/kg-day (F1 parental males)	0		50	250		750
0, 750, 3,750, 11,250 ppm 0, 50, 250, 750 mg/kg-day[a]	*number of F1 weanlings with at least 1 reproductive tract malformation*	0		0	0		25*
Diet	*percentage of F1 weanlings with at least 1 reproductive tract malformation*	0		0	0		33*
Multigenerational study	*adult F1 testicular lesions*	10		0	14		82
	adult F1 epididymal lesions	7		0	11		54

Reference and study design	Results				
Hotchkiss et al. (2004)	**Malformations** *(percent incidence)*				
Rat (Sprague-Dawley), 6 pregnant females/dose	mg/kg-day (F1 males with malformations)	0			500
0, 500 mg/kg-day	*ventral prostate*	0			2.9
Gavage	*seminal vesicle*	0			11.8
GDs 14–18	*epididymis*	0			11.8
	testes	0			11.8
	Note: No significant effects of gestational BBP exposure on the incidence of external or internal reproductive malformations.				
Gray et al. (2000)	**Malformations** *(percent incidence)*				
Rat (Sprague-Dawley); 13–19 pregnant females/dose	mg/kg-day (F1 males)	0			750
	cleft phallus	ND			29
0, 750 mg/kg-day	*hypospadias*	ND			29
Diet	*vaginal pouch*	ND			16
GD 14–PND 3	*ventral prostate agenesis*	ND			27
	seminal vesicle agenesis	ND			38
	epididymides agenesis	ND			67
	fluid-filled testes	ND			67
	undescended testes	ND			22
	absent testes	ND			9
	absent gubernacular cord	ND			57
	Note: Data in Figure 6 shown only for exposure groups; no data (ND) for controls; statistical significance not noted by study authors.				
Piersma et al. (1995)	**Histopathological changes** *(percent incidence)*				
Rat (WU); 10/sex/dose	mg/kg-day (F0 males)	0	250	500	1,000
0, 250, 500, 1,000 mg/kg-day	*testicular degeneration accompanied by leydig cell hyperplasia and appearance of cellular debris*	10	30	30	100*
Gavage					
Reproductive toxicity study					

Reference and study design	Results				
Nagao et al. (2000)	**Histopathological changes** *(percent incidence)*				
Rat (Sprague-Dawley); 25/sex/dose	mg/kg-day	0	20	100	500
0, 20, 100, 500 mg/kg-day	Adult F0 males				
Gavage	*atrophic seminiferous tubules (bilateral)*	10	NE	NE	0
Multigenerational study	*epididymal cell debris (bilateral)*	10	NE	NE	0
	lymphocytic infiltration of prostate interstitium	40	NE	NE	40
	lymphocytic/ neutrophilic infiltration of prostate epithelium	10	NE	NE	10
	Weanling F1 males				
	atrophic seminiferous tubules (bilateral)	0	0	0	10
	decreased spermatocytes in seminiferous tubules (bilateral)	0	0	0	90*
	decreased spermatogonia in seminiferous tubules (bilateral)	0	0	0	30
	leydig cell hyperplasia (bilateral)	0	0	0	10
	epididymal abnormality	0	NE	NE	0
	prostate abnormality	0	NE	NE	0
	seminal vesicle and coagulating gland abnormality	0	NE	NE	0
	Adult F1 males				
	atrophic seminiferous tubules (right side)	0	0	0	60*
	atrophic seminiferous tubules (left side)	0	0	0	30
	decreased germ cells in seminiferous tubules (right side)	0	0	0	40*

Reference and study design	Results				
	decreased germ cells in seminiferous tubules (left side)	0	0	0	10
	diffuse dilatation of seminiferous tubule (left side)	0	0	0	10
	testicular interstitial edema (right side)	0	0	0	40*
	testicular defect (right side)	0	0	0	10
	spermatic granuloma of the rete testis (right side)	0	0	0	10
	multinucleated giant cell seminiferous tubule (left side)	0	0	0	10
	epididymal lesions	0	0	0	50*
	lymphocytic infiltration of prostate interstitium	30	NE	NE	40
	lymphocytic/plasma cell infiltration of the prostate epithelium	20	NE	NE	20
Aso et al. (2005)	**Histopathological changes** *(percent incidence)*				
Rat (Crj:CD(SD)IGS); 24/sex/dose	mg/kg-day (adult F1 males)	0	100	200	400
0, 100, 200, 400 mg/kg-day	*softening of testis*	0	4	8	17
Gavage	*aplasia of epididymis*	0	0	0	4
Multigenerational study	*hypoplasia of epididymis*	0	0	0	17
	leydig cell hyperplasia	0	4	0	21*
	atrophy of seminiferous tubules	4	4	13	38*
	residue germ cells in epididymis lumen	0	4	13	4
	aplasia of epididymis (unilateral)	0	0	0	8
	partial aplasia of epididymis (unilateral)	0	0	0	13
	partial aplasia of epididymis (bilateral)	0	0	0	4

Reference and study design	Results				
	Note: Incidence of Leydig cell hyperplasia of the testes was increased in F0 adult males in the 400 mg/kg-day group.				
BIBRA (1978) Rat (Wistar); 27/sex/group or 45/sex/group (control); interim sacrifices of 9 controls/sex/group and 6 treated rats/sex/group at 2 and 6 weeks 0, 2,000, 5,000, 12,000 ppm 0, 151, 381, 960 mg/kg-day (males)[c] 0, 171, 422,1,069 mg/kg-day (females) Diet 14 weeks	**Histopathological changes** *(incidence)*				
	mg/kg-day	0	151	381	960
	epididymis; sperm retention cyst histopathology	1/27	-/0	-/0	0/14
	No histological lesions were noted by study authors in the prostrate, seminal vesicles, or testis.				

*Statistically different from controls (p <0.05) as reported by study authors.
[a]The high-dose group corresponds to 25,000 ppm BBP; a reliable estimate of dose could not be calculated. The study authors estimated doses for all but the high-dose group based on measured body weights and food consumption. Food consumption was not measured in the 25,000 ppm BBP group due to excessive scattering of feed and because the mean body weight of this group was 30% lower than controls.

CERHR = Center for the Evaluation of Risks to Human Reproduction; NTP = National Toxicology Program
NE = not examnied

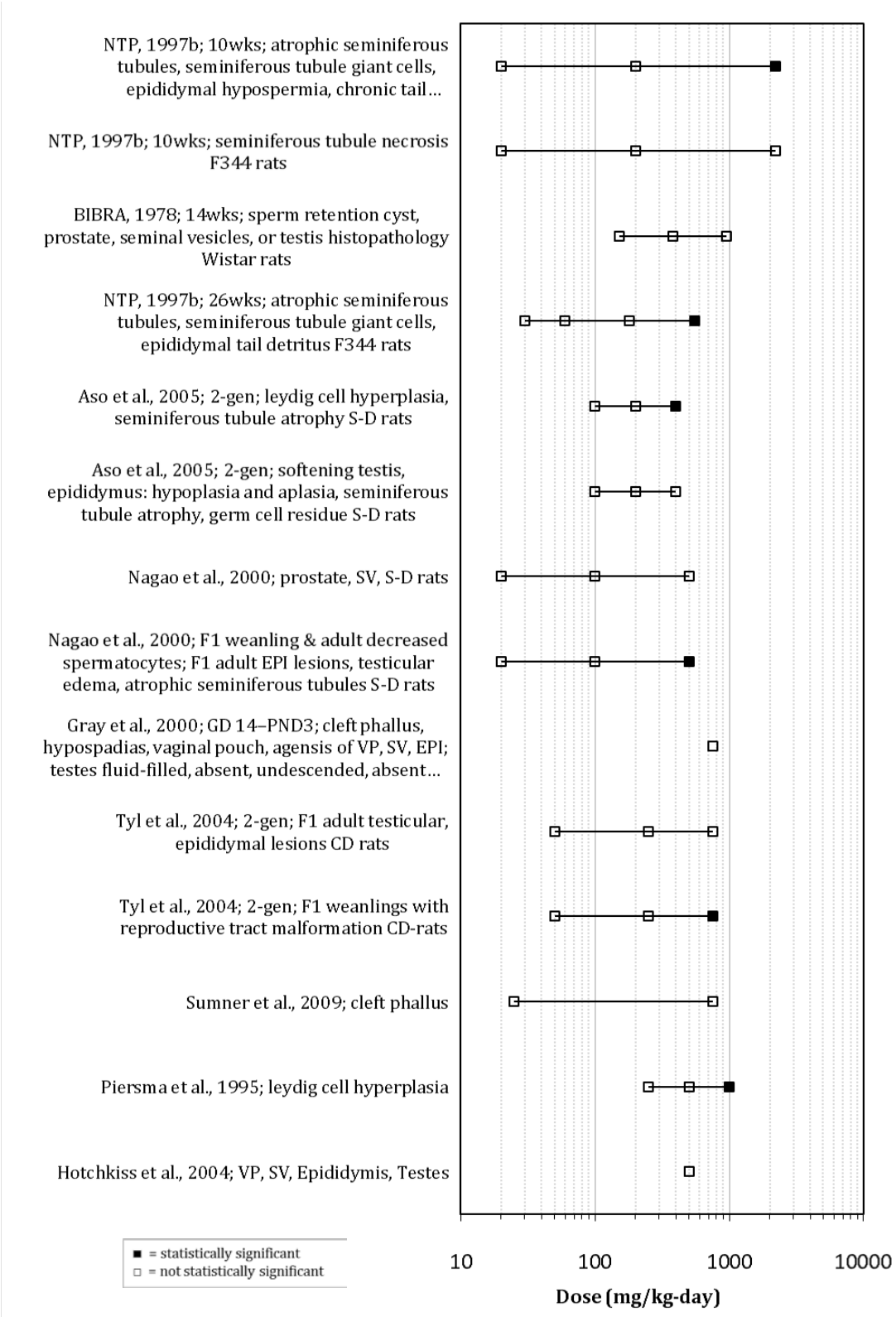


Figure 3-3. Exposure-response array of male reproductive toxicity following oral exposure to BBP: external and internal malformations.

Table 3-21. Evidence pertaining to male reproductive toxicity following oral exposure to BBP: Decrease in androgen-dependent tissue weights

Reference and study design	Results[a]					
NTP (1997b) Rat (F344); 15 males/dose 0, 300, 2,800, 25,000 ppm 0, 20, 200, 2,200 mg/kg-day Diet 10-week modified mating study	mg/kg-day	0	20	200	2,200	
	Absolute weight *(percent change compared to control)*					
	ventral prostate	0	1	−1	−55*	
	right testes	0	−8	0	−70*	
	right epididymis	0	−7	−10	−57*	
	right cauda	0	−11	−19	−69*	
	Relative weight *(percent change compared to control)*					
	ventral prostate	0	1	1	−36*	
	right testes	0	−8	3	−58*	
NTP (1997b) Rat (F344); 15 males/dose 0, 300, 900, 2,800, 8,300, 25,000 ppm 0, 30, 60, 180, 550, "high" mg/kg-day[b] Diet 26 weeks	mg/kg-day	0	30	60	180	550	'High'
	Absolute weight *(percent change compared to control)*						
	right testes	0	4	7	3	5	−70*
	right epididymis	0	3	ND	ND	5	−47*
	right cauda epididymis	0	−13	ND	ND	−7	−52*
	Relative weight (*p*ercent change compared to control)						
	right testes	0	−2	−3	1	2	−56*
Tyl et al. (2004) Rat (CD); 30 F0 and 30 F1 parental rats/sex/dose 0, 750, 3,750, 11,250 ppm 0, 50, 250, 750 mg/kg-day Diet Multigenerational study	*Percent change compared to control*					
	mg/kg-day	0	50	250	750	
	Absolute weight (F1 males)					
	ventral prostate	0	−12	−7	−26*	
	seminal vesicles	0	1	−1	−18*	
	paired testes	0	1	1	−21*	
	paired epididymis	0	2	3	−11*	
	weanling testes	0	3	8*	−26*	
	Relative weight (F1 males)					
	ventral prostate	0	−13	−10	−18*	
	weanling testes	0	3	7*	−10*	

Reference and study design	Results[a]			
Hotchkiss et al. (2004)	**Absolute weight** *(percent change compared to control)*			
Rat (Sprague-Dawley); 6 pregnant females/dose	mg/kg-day	0		500
	glans penis	0		−3
0, 500 mg/kg-day	*ventral prostate*	0		−14
Gavage	*seminal vesicles*	0		−6
GDs 14–18	*paired testes*	0		−1
	whole epididymis	0		−2
	whole cauda epididymis	0		−4
	caput corpus epididymis	0		−4
	LABC	0		−10*
	Note: Tissue weight data adjusted for body weights were not reported.			
Gray et al. (2000)	**Absolute weight** *(percent change compared to control)*			
Rat (Sprague-Dawley); 13–19 pregnant females/dose	mg/kg-day	0		750
	ventral prostate	0		−42*
0, 750 mg/kg-day	*seminal vesicles with coagulating glands*	0		−38*
Gavage				
GD 14–PND 3	*glans penis*	0		−19*
	LABC	0		−34*
	testes	0		−23* (−35* reduction at PND 2)
	paired epididymis	0		−25*
	cauda epididymis	0		−42*
	caput corpus epididymis	0		−26*
	Note: Tissue weight data adjusted for body weights not reported.			
Piersma et al. (1995)	**Absolute weight** *(percent change compared to control)*			
Rat (WU); 10/sex/dose	mg/kg-day	0	250	500	1,000
0, 250, 500, 1,000 mg/kg-day	Adult F0 males				
Gavage	*testes and epididymis*	0	−2	−2	−14*
Reproductive toxicity study					

Reference and study design	Results[a]				
Nagao et al. (2000)	**Absolute weight** *(percent change compared to control)*				
Rat (Sprague-Dawley); 25/sex/dose	mg/kg-day	0	20	100	500
0, 20, 100, 500 mg/kg-day	Adult male F0				
Gavage	*testes*	0	−1	3	−2
Multigenerational study	*paired epididymis*	0	−2	1	−3
	ventral prostate	0	3	7	1
	Seminal vesicle	0	−2	−2	−3
	Weanling male F1 offspring				
	testes	0	4	0	−12*
	paired epididymis	0	7	−1	−9*
	prostate and seminal vesicle	0	3	−1	−9
	Adult male F1 offspring (postweaning)				
	testes	0	0	−3	−12*
	paired epididymis	0	−3	−5	−21*
	ventral prostate	0	−3	−7	−14*
	seminal vesicle	0	−3	−1	−10
	Relative weight *(percent change compared to control)*				
	Adult male F0				
	testes	0	0	2	5
	paired epididymis	0	0	0	5
	ventral prostate	0	0	0	8
	seminal vesicle	0	0	−3	3
	Weanling male F1 offspring				
	testes	0	2	−1	−6*
	paired epididymis	0	5	−2	−3
	Adult male F1 offspring (postweaning)				
	testes	0	4	5	0
	paired epididymis	0	0	0	−10
	ventral prostate	0	0	0	−9
	seminal vesicle	0	3	7	3

Reference and study design	Results[a]				
Aso et al. (2005)	**Absolute weight** *(percent change compared to control)*				
Rat (Crj:CD(SD)IGS); 24/sex/dose	mg/kg-day	0	100	200	400
0, 100, 200, 400 mg/kg-day	Adult male F0				
Gavage	*right testes*	0	5	4	−1
Multigenerational study	*left testes*	0	3	4	−2
	right epididymis	0	3	2	−5
	left epididymis	0	2	2	−6*
	ventral prostate	0	−13	−4	−18
	seminal vesicle	0	−2	0	−7
	Adult male F1 offspring (postweaning)				
	right testes	0	−1	−1	−5
	left testes	0	1	−3	−5
	right epididymis	0	−1	−7	−17*
	left epididymis	0	−7	−12*	−16*
	ventral prostate	0	1	−9	−13
	seminal vesicle	0	−5	−9	−13*
	Relative weight *(percent change compared to control)*				
	Adult male F0				
	right testes	0	3	0	0
	left testes	0	0	0	−3
	right epididymis	0	9	0	0
	left epididymis	0	0	0	0
	ventral prostate	0	−15	−8	−15
	seminal vesicle	0	−3	−3	−9
	Adult male F1 offspring (postweaning)				
	right testes	0	0	3	0
	left testes	0	0	0	−3
	right epididymis	0	0	0	−9
	left epididymis	0	0	−9	−9
	ventral prostate	0	0	−9	−9
	seminal vesicle	0	−3	−7	−10
	Autopsy findings *(percent incidence)*				
	Adult male F1 offspring (postweaning)				

Reference and study design	Results[a]				
	small testis	0	0	0	25*
	small epididymis	0	0	0	13
TNO (1998a)	*Percent change compared to control*				
Rat (Wistar); P0, female (28/group)	mg/kg-day	0	0.015	0.147	0.442
0, 100, 1,000, 3,000 µg/L (equivalent to 0.016, 0.171, 0.489 mg/kg-day, average of reported intake over premating, gestation, and lactation)	*F1 male caudal epididymis, absolute weight (left)*	0	−3	−1	−4
Drinking water	*F1 male caudal epididymis, relative weight (left)*	0	−1	−1	3
F0 females: 2 weeks prior to mating, through mating, gestation, and lactation; F0 males: during mating; F1 animals were not treated after weaning	*F1 male epididymis, relative weight*	0	0	−1	−1
	F1 male epididymis absolute weight	0	0	−1	−2
	F1 male prostate, relative weight	0	−4	−3	−4
	F1 male prostate, absolute weight	0	−4	−2	−4
	F1 male seminal vesicles, absolute weight	0	−5	1	−3
	F1 male seminal vesicles, relative weight	0	−4	0	−2
	F1 male testis, absolute weight (left)	0	0	−3	−3
	F1 male testis, relative weight (left)	0	0	−3	−3
Ahmad et al. (2014)	**Absolute weight** *(percent change compared to control)*				
Rat (Albino); P0, female (6/group)	mg/kg-day	0	4	20	100
0, 4, 20, 100 mg/kg	*F1 male epididymis*	0	−3	−4	−13*
Gavage	*F1 male prostrate*	0	−2	−2	−12*
GD 14 to parturition	*F1 male seminal vesicle*	0	−1	−1	−11
	F1 male testis	0	−1	−1	−2

Reference and study design	Results[a]				
BIBRA (1978)	*Percent change compared to control*				
Rat (Wistar); 27/sex/group or 45/sex/group (control); interim sacrifices of 9 controls/sex/group and 6 treated rats/sex/group at 2 and 6 weeks 0, 2,000, 5,000, 12,000 ppm 0, 151, 381, 960 mg/kg-day (males)[d] 0, 171, 422, 1,069 mg/kg-day (females) Diet 14 weeks	mg/kg-day	0	151	381	960
	male gonad relative weight	0	7	8	7
	male gonad weight	0	−2	0	−1

*Statistically different from controls (p <0.05) as reported by study authors.
[a]Percent change compared to control calculated as 100 × ((treated value − control value) ÷ control value).
[b]The high-dose group corresponds to 25,000 ppm BBP; a reliable estimate of dose could not be calculated. The study authors estimated doses for all but the high-dose group based on measured body weights and food consumption. Food consumption was not measured in the 25,000 ppm BBP group due to excessive scattering of feed, and because the mean body weight of this group was 30% lower than controls.

LABC = levator ani bulbocavernosus; ND = not determined

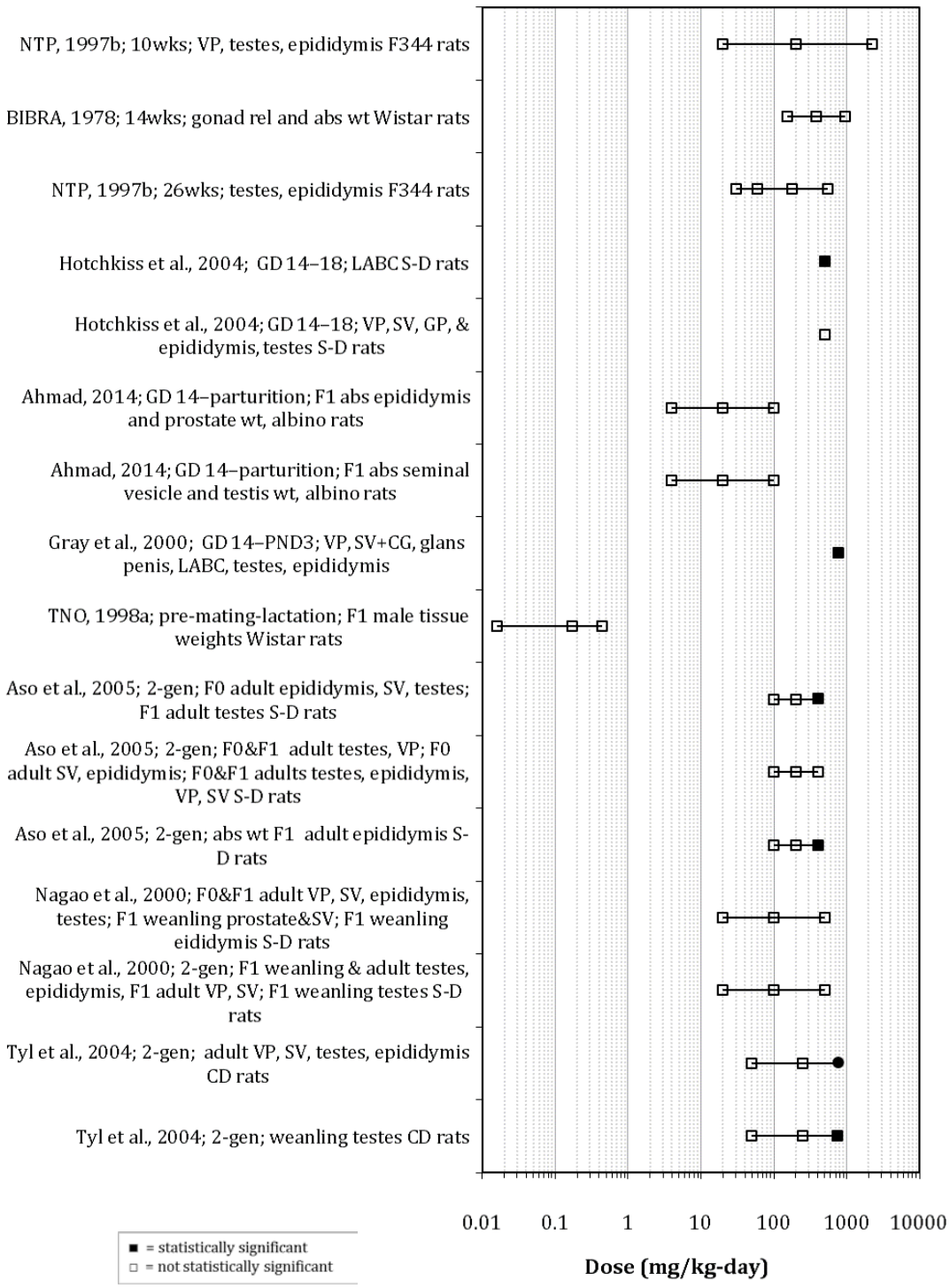


Figure 3-4. Exposure-response array of male reproductive toxicity following oral exposure to BBP: decrease in androgen-dependent tissue weights.

3.3.2. Female Reproductive Effects

Table 3-22. Evidence pertaining to female reproductive toxicity following oral exposure to BBP

Reference and study design	Results[a]				
Reproductive tissue weights					
Moral et al. (2007) Rat (Sprague-Dawley CD); 10 pregnant females/dose 0, 500 mg/kg-day from PND 2 to 20 Gavage Female offspring were evaluated at 21, 35, 50, and 100 days	**Absolute uterine weight** *(percent change compared to control)*				
	mg/kg-day	0			500
	day 21	0			20
	day 35	0			24
	day 50	0			11
	day 100	0			5
	Relative uterine weight *(percent change compared to control)*				
	day 21	0			27*
	day 35	0			23
	day 50	0			11
	day 100	0			6
Götz et al. (2001) Rat (Wistar (Crl:WI)); 10–15/group 0, 10 mg/L BBP to pregnant females during the whole pregnancy and during lactation Drinking water	***Absolute weight*** *(percent change compared to control*				
	mg/L	0			10
	ovarian weight	0			−40*
Nagao et al. (2000) Rat (Sprague-Dawley); 20–25 breeding pairs/group/generation; organ weights assessed in 20–24 F0 females/group and 41–46 F1 female weanlings/group 0, 20, 100, 500 mg/kg-day Gavage Multigenerational study	**Absolute weight** *(percent change compared to control)*				
	mg/kg-day	0	20	100	500
	F0 ovaries	0	0	−4	−11*
	F1 ovaries	0	2	−7	−16*
	F0 uterus	0	−8	10	18
	F1 uterus	0	−2	3	2
	Relative weight *(percent change compared to control)*				
	F0 ovaries	0	2	−3	−11*
	F1 uterus	0	−4	4	13*
	F0 uterus	0	0	18	18
	F1 ovaries	0	0	−6	−9

Reference and study design	Results[a]				
Tyl et al. (2004)	**Absolute weight** *(percent change compared to control)*				
Rat (CD); 30 breeding pairs/group/generation; organ weights assessed in 30 F0 females/group, 30 F1 adult females/group, 67–81 F1 female weanlings/group, and 43–87 F2 female weanlings/group	mg/kg-day	0	50	250	750
	F0 adults ovaries	0	8	3	−13*
	F0 adult uterus	0	−1	3	−75*
	F1 weanlings ovaries	0	6	3	−24*
0, 750, 3,750, 11,250 ppm 0, 50, 250, 750 mg/kg-day[b]	*F1 weanlings uterus*	0	−2	4	−20*
Diet	*F1 adults ovaries*	0	3	3	2
Multigenerational study	*F1 adults uterus*	0	0	9	20*
	F2 weanlings ovaries	0	0	−6	−19*
	F2 weanlings uterus	0	5	16*	−14
	Relative weight *(percent change compared to control)*				
	F0 adults ovaries	0	−3	−7	−19*
	F0 adults uterus	0	−1	3	−17*
	F1 weanlings ovaries	0	4	3	−4
	F1 weanlings uterus	0	−4	4	3
	F1 adults ovaries	0	2	0	9*
	F1 adults uterus	0	−1	6	28*
	F2 weanlings ovaries	0	−2	−6	−8
	F2 weanlings uterus	0	4	13	−2
Aso et al. (2005)	mg/kg-day	0	100	200	400
Rat (Crj:CD(SD)IGS); 24 breeding pairs/group/generation; organ weights assessed in 19–20 F0 females/group and 12–19 F1 females/group	**Absolute weight** *(percent change compared to control)*				
	F0 right ovary	0	−4	1	−7
	F0 left ovary	0	0	−3	−4
0, 100, 200, 400 mg/kg-day	*F0 uterus*	0	−8	−9	−4
Gavage	*F1 right ovary*	0	12	3	−8
Multigenerational study	*F1 left ovary*	0	10	2	−5
	F0 uterus	0	1	8	12
	Relative weight *(percent change compared to control)*				
	F0 right ovary	0	−4	−4	−7
	F0 left ovary	0	−1	−8	−4
	F0 uterus	0	−8	−15*	−4

Reference and study design	Results[a]				
	F1 right ovary	0	7	−3	−9
	F1 left ovary	0	6	−3	−7
	F1 uterus	0	−4	0	8
NTP (1989) Rat (Sprague-Dawley); 27−30 pregnant females/dose 0, 420, 1,100, 1,640 mg/kg-day Diet GDs 6−15; dams sacrificed on GD 20	*Percent change compared to control*				
	mg/kg-day	0	420	1,100	1,640
	gravid uterine weight	0	4	0	−42*
NTP (1990) Mouse (CD-1); 27−30 pregnant females/dose (except n = 14 in the high-dose group) 0, 182, 910, 2,330, 4,121 mg/kg-day Diet GDs 6−15; dams sacrificed on GD 17	*Percent change compared to control*				
	mg/kg-day	0	182	910	2,330
	gravid uterine weight	0	3	−7	−85*
	Note: The 4,121 mg/kg-day group was eliminated after evaluation of 14 dams since all litters were completely resorbed.				
Ema et al. (1998) Rat (Wistar); 7−10 pregnant females/dose 0, 250, 500, 750, 1,000 mg/kg-day Gavage GDs 0−8; dams sacrificed on GD 20	*Percent change compared to control*				
	mg/kg-day	0	250	500	750	1,000
	ovary weight (day 9 pseudopregnancy)[c]	0	−2	−9	−13*	−17*
	uterine weight (day 9 pseudopregnancy)[c]	0	1	−34	−42*	−47*
BIBRA (1978) Rat (Wistar); 27/sex/group or 45/sex/group (control); interim sacrifices of 9 controls/sex/group and 6 treated rats/sex/group at 2 and 6 weeks 0, 2,000, 5,000, 12,000 ppm 0, 151, 381, 960 mg/kg-day (males)[b] 0, 171, 422, 1,069 mg/kg-day (females)[b] Diet 14 weeks	*Percent change compared to control*				
	mg/kg-day	0	171	422	1069
	female gonad relative weight	0	0	8	−5
	female gonad absolute weight	0	0	8	−8

Reference and study design	Results[a]				
TNO (1998a)	*Percent change compared to control*				
Rat (Wistar); P0, female (28/group)	mg/kg-day	0	0.016	0.171	0.489
0, 100, 1,000, 3,000 µg/L (equivalent to 0.016, 0.171, 0.489 mg/kg−day, average of reported intake over premating, gestation, and lactation)	*F1 female absolute ovary weight*	0	6	−1	3
	F1 female absolute uterus weight	0	−3	−2	1
Drinking water	*F1 female relative ovary weight*	0	3	−3	1
F0 females: 2 weeks prior to mating, through mating, gestation, and lactation; F0 males: during mating; F1 animals were not treated after weaning	*F1 female relative uterus weight*	0	−5	−4	0
Gross necropsy of reproductive organs					
Tyl et al. (2004)	*Percent incidence*				
Rat (CD); 30 breeding pairs/group/generation; gross necropsy performed in 30 adult females/generation	mg/kg-day	0	50	250	750
	F0 fluid-filled uterus	0	3	0	0
	F1 fluid-filled uterus	0	0	3	10
0, 750, 3,750, 11,250 ppm 0, 50, 250, 750 mg/kg-day[b]	Note: Study authors report that the consequence of this finding is unknown, as the affected females were in estrus at sacrifice. They also state that increased uterine weight in F1 adults is likely due to increased incidence of fluid filled uteri.				
Diet					
Multigenerational study					
BIBRA (1978)	*Response incidence*				
Rat (Wistar); 27/sex/group or 45/sex/group (control); interim sacrifices of 9 controls/sex/group and 6 treated rats/sex/group at 2 and 6 weeks	mg/kg-day	0	171	422	1069
	female uterus distended	0	–	–	1
0, 2,000, 5,000, 12,000 ppm 0, 151, 381, 960 mg/kg-day (males)[b] 0, 171, 422, 1,069 mg/kg-day (females)[b]	*female ovary histopathology*	No histological lesions were noted in the ovaries			
Diet					
14 weeks					

Reference and study design	Results[a]			
Puberty				
Tyl et al. (2004) Rat (CD); 30 breeding pairs/group/generation; onset of puberty assessed in 26–28 F1 litters/group 0, 750, 3,750, 11,250 ppm 0, 50, 250, 750 mg/kg-day[b] Diet Multigenerational study	*Percent change compared to control*			
	mg/kg-day	0	50	250	750
	F1 age at vaginal opening	0	2	−1	9*
	F1 age at vaginal opening adjusted for body weight	0	0	−1	9*
Moral et al. (2011) Rat (Sprague-Dawley CD); 10 pregnant females/dose 0, 12, 500 mg BBP/kg-day from day 10 post-conception to delivery Gavage Litters were euthanized at 21, 35, 50 and 100 days	*Percent change compared to control*			
	mg/kg-day	0	120	500
	day of vaginal opening	0	−1	6*
	body weight (g) at day of vaginal opening	0	0	2
Moral et al. (2007) Rat (Sprague-Dawley CD); 10 pregnant females/dose 0, 500 mg/kg-day from PND 2 to 20 Gavage Female offspring were evaluated at 21, 35, 50, and 100 days	**Development of the mammary gland** *(number of terminal end buds)*			
	mg/kg-day	0	500	
	day 21	0	1	
	day 35	0	−1	
	day 50	0	24	
	day 100	0	82	
	Development of the mammary gland *(number of terminal ducts)*			
	day 21	0	6	
	day 35	0	−12	
	day 50	0	13	
	day 100	0	8	
	Development of the mammary gland *(number of alveolar buds)*			
	day 21	0	−29	
	day 35	0	−8	
	day 50	0	−12	
	day 100	0	0	

Reference and study design	Results[a]			
	Development of the mammary gland *(number of type 1 lobules)*			
	day 21	0		0
	day 35	0		30
	day 50	0		−1
	day 100	0		8
Nagao et al. (2000) Rat (Sprague-Dawley):, 20–25 breeding pairs/group/generation; onset of puberty assessed in 39–48 F1 females/group (2 pups per litter) 0, 20, 100, 500 mg/kg-day Gavage Multigenerational study	*Percent change compared to control*			
	mg/kg-day	0	20	100	500
	F1 age at vaginal opening	0	2	1	3
TNO (1998a) Rat (Wistar); P0, female (28/group) 0, 100, 1,000, 3,000 µg/L (equivalent to 0.016, 0.171, 0.489 mg/kg-day, average of reported intake over premating, gestation, and lactation) Drinking water F0 females: 2 weeks prior to mating, through mating, gestation, and lactation; F0 males: during mating; F1 animals were not treated after weaning	No significant difference in F1 female sexual maturation as measured by vaginal opening from PND 32 to 45			
Reproductive performance				
Götz et al. (2001) Rat (Wistar (Crl:WI)), 10–15 pregnant females/group 0, 10 mg/L BBP to pregnant females during the whole pregnancy and during lactation Drinking water	*Percent change compared to control*			
	mg/L	0		10
	% of estrus days during a period of 12 days	12.7		19.7
	No change in fertility between groups (quantitative data not reported by authors).			

Reference and study design	Results[a]				
Tyl et al. (2004)	**Mating or fertility index** *(percent change compared to control)*				
Rat (CD); 30 breeding pairs/group/generation	mg/kg-day	0	50	250	750
0, 750, 3,750, 11,250 ppm 0, 50, 250, 750 mg/kg-day[b]	*F0 mating index*	0	−3	0	0
Diet	*F0 fertility index*	0	7	4	4
Multigenerational study	*F1 mating index*	0	0	−4	−28*
	F1 fertility index	0	−3	−7	−19*
Bayer (1998)	**Mating or fertility index** *(percent change compared to control)*				
Rat (Wistar), 28/sex/group	Drinking water				
0, 1, 3 ppm 0, 0.11, 0.35 mg/kg-day for drinking water 0, 0.09, 0.28 mg/kg-day for diet	mg/kg-day	0	0.11		0.35
	Gestation index	0	0		0
	Fertility index	0	5		14
Drinking water and diet	Diet				
Females dosed through mating, gestation, and lactation (males only through cohabitation with females)	mg/kg-day	0	0.9		0.28
	Gestation index	0	0		0
	Fertility index	0	22		9
Nagao et al. (2000)	**Mating or fertility index** *(raw percentages)*				
Rat (Sprague-Dawley); 20–25 breeding pairs/group/ generation; F0 reproductive performance assessed in 25 breeding pairs/group; F1 reproductive performance assessed in 20–24 breeding pairs/group	mg/kg-day	0	20	100	500
	F0 mating index (%)	96	96	96	100
	F0 fertility index (%)	91.7	83.3	95.8	96
	F1 mating index (%)	100	94.7	90.9	91.7
	F1 fertility index (%)	77.3	77.8	95	77.3
0, 20, 100, 500 mg/kg-day Gavage Multigenerational study					
Aso et al. (2005)	**Mating or fertility index** *(percent change compared to control)*				
Rat (Crj:CD(SD)IGS); 24 breeding pairs/group/generation	mg/kg-day	0	100	200	400
0, 100, 200, 400 mg/kg-day	*F0 mating index*	0	−8	−4	−4
Gavage	*F0 fertility index*	0	4	9	10
Multigenerational study	*F1 mating index*	0	0	−9	−9
	F1 fertility index	0	25	12	−15

Reference and study design	Results[a]				
Piersma et al. (1995)	**Mating or fertility index** *(raw percentages)*				
Rat (WU); 10 breeding pairs/dose	mg/kg-day	0	250	500	1,000
0, 250, 500, 1,000 mg/kg-day	*F0 mating index (%)*	100	100	90	90
Gavage	*F0 fertility index (%)*	90	80	78	44
Males: 29 days (14 days premating, up to 14 days mating); females: up to 55 days (14 days premating through PND 6)					
TNO (1998b)	*Percent change compared to control*				
Rat (Wistar); P0, female (28/group)	mg/kg-day	0	0.190		0.280
0, 1,000, 3,000 µg/L (equivalent to 0.190, 0.280 mg/kg-day during premating as calculated by study authors)	*P0 female duration of gestation*	0	0		1
	P0 female fecundity index (%)	96	82		96
Drinking water	*P0 female fertility index (%)*	93	82		93
F0 females: 2 weeks prior to mating, through mating, gestation and lactation; F0 males: mating period only; F1: did not receive additional treatment after weaning	*P0 female gestation index (%)*	100	96		92
	P0 female mating index (%)	96	100		96
	P0 female pre-coital time	0	7		23
TNO (1998a)	*Percent change compared to control*				
Rat (Wistar); P0, female (28/group)	mg/kg-day	0	0.016	0.171	0.489
0, 100, 1,000, 3,000 µg/L (equivalent to 0.016, 0.171, 0.489 mg/kg-day, average of reported intake over premating, gestation, and lactation)	*P0 female duration of gestation*	0	0	1	0
	F1 female estrus cycle length	0	−4	−4	−5
Drinking water	*P0 female pre-coital time*	0	8	−14	−6
F0 females: 2 weeks prior to mating, through mating, gestation, and lactation; F0 males: during mating; F1 animals were not treated after weaning	*Raw percentages*				
	P0 female fecundity index (%)	96	82	88	86
	P0 female fertility index (%)	89	82	82	86
	P0 female gestation index (%)	96	100	96	100
	P0 female mating index (%)	93	100	93	100

Reference and study design	Results[a]				
	Response				
	P0 females pregnant	25/26	23/28	23/26	24/28
Monsanto (1993) Rat (Wistar); 12 males/group 0, 0.2, 0.4, 0.8% BBP or 0, 116, 235, 458 mg/kg-day (F) and 0, 252, 580, 1,078 mg/kg-day (M) Diet Multigenerational study	**Fertility index** *(raw percentages)*				
	mg/kg-day	0	116	235	458
	litter 1	92	79	83	75
	litter 2	88	96	88	92
Ahmad et al. (2014) Rat (Albino); P0, female (6/group) 0, 4, 20, 100 mg/kg Gavage GD 14 to parturition	P0 female gestation length was significantly longer in all BBP-treated groups (graphical presentation reported by study authors)				
Saillenfait et al. (2003) Rat (Sprague-Dawley); P0, female (9–10/group) 0, 1.8, 3.6, 5.4 mmol/kg (equivalent to 560, 1,120, 1,690 mg/kg as calculated by study authors) Gavage Single dose on GD 10; sacrificed GD 21	**Percent pregnant** *(raw percentages)*				
	mg/kg-day	0	560	1,120	1,690
	P0 female percent pregnant	100	78	90	100
	Note: statistical significance not evaluated by study authors				
Saillenfait et al. (2003) Mouse (OF-1); P0, female (22–24/group) 0, 0.9, 1.8, 3.6, 5.4 mmol/kg (equivalent to 280, 560, 1,120, 1,690 mg/kg as calculated by study authors) Gavage Single dose on GD 8; sacrificed GD 18	**Percent pregnant** *(raw percentages)*				
	mg/kg-day	0	280	560	1,120	1,690
	P0 female percent pregnant	82	83	70	83	68
	Note: Statistical significance not evaluated by study authors					

Reference and study design	Results[a]				
Biomarkers of reproductive development					
Aso et al. (2005) Rat (Crj:CD(SD)IGS); 24 breeding pairs/group/generation; AGD assessed in 19–21 F1 litters/group and 13–20 F2 litters/group 0, 100, 200, 400 mg/kg-day Gavage Multigenerational study	**AGD** *(percent change compared to control)*				
	mg/kg-day	0	100	200	400
	F1 AGD at PND 4	0	10*	8	6
	F1 AGD/BW$^{1/3}$ at PND 4	0	10*	9*	8*
	F2 AGD at PND 4	0	−9	−6	−3
	F2 AGD/BW$^{1/3}$ at PND 4	0	−5	−9	1
Nagao et al. (2000) Rat (Sprague-Dawley); 20–25 breeding pairs/group/generation; AGD assessed in 128–167 F1 female pups/group 0, 20, 100, 500 mg/kg-day Gavage Multigenerational study	**AGD** *(percent change compared to control)*				
	mg/kg-day	0	20	100	500
	F1 AGD at birth	0	−8	0	0*
	Note: F1 AGD at birth reported as significantly increased at 500 mg/kg-day by study authors (pg. 518), but data reported in table do not indicate an increase.				
Tyl et al. (2004) Rat (CD); 30 breeding pairs/group/generation; AGD assessed in 26–28 F1 litters/group and 17–29 F2 litters/group 0, 750, 3,750, 11,250 ppm 0, 50, 250, 750 mg/kg-day[b] Diet Multigenerational study	***AGD*** *(percent change compared to control)*				
	mg/kg-day	0	50	250	750
	F1 AGD at PND 0	0	1	−4	−4
	F2 AGD at PND 0	0	−1	−2	1
Pregnancy outcomes					
Nagao et al. (2000) Rat (Sprague-Dawley); 20–25 breeding pairs/group/generation 0, 20, 100, 500 mg/kg-day Gavage Multigenerational study	mg/kg-day	0	20	100	500
	Number of implantations/litter *(percent change compared to control)*				
	F0 dams for F1 litter	0	6	11	6
	F1 dams for F2 litter	0	5	−4	−6
	Number of live pups/litter *(percent change compared to control)*				
	F0 dams for F1 litter	0	6	14	7
	F1 dams for F2 litter	0	4	−9	−11
	Viability during PNDs 0–4 (%) *(raw percentages)*				

Reference and study design	Results[a]				
	F0 dams for F1 litter	100	99	99.5	96.7*
	F1 dams for F2 litter	97.8	95.4	99.7	97.6
	mg/kg-day	0	50	250	750
	Number of implantations/litter *(percent change compared to control)*				
	F0 dams for F1 litter	0	−11	−5	−10
	F1 dams for F2 litter	0	−5	−4	−22*
	Number of live pups/litter (PND 0) *(percent change compared to control)*				
	F0 dams for F1 litter	0	−8	1	−2
	F1 dams for F2 litter	0	−1	0	−20*
	4-Ray survival index (%) *(raw percentages)*				
	F0 dams for F1 litter	97.2	96.3	97.5	92.6
	F1 dams for F2 litter	98.3	98.1	96.9	95.4
Piersma et al. (1995)	*Percent change compared to control*				
Rat (WU); 10 breeding pairs/dose 0, 250, 500, 1,000 mg/kg-day Gavage Males: 29 days (14 days premating, up to 14 days mating); Females: up to 55 days (14 days premating through PND 6)	mg/kg-day	0	250	500	1,000
	number of implantations/dam	0	19	−6	37
	number of live pups/litter	0	21	−11	−84*
	Raw percentages				
	postnatal mortality PNDs 1−6 (%)	2.1	2.6	4.8	46.7
Aso et al. (2005) Rat (Crj:CD(SD)IGS); 24 breeding pairs/group/generation 0, 100, 200, 400 mg/kg-day Gavage Multigenerational study	mg/kg-day	0	100	200	400
	Number of implantations/litter *(percent change compared to control)*				
	F0 dams for F1 litter	0	−13	−6	−6
	F1 dams for F2 litter	0	6	−19	−4
Saillenfait et al. (2003)	*Percent change compared to control*				
Rat (Sprague-Dawley); P0, female (9−10/group) 0, 1.8, 3.6, 5.4 mmol/kg (equivalent to 560, 1,120, 1,690 mg/kg as calculated by study authors) Gavage	mg/kg-day	0	560	1,120	1,690	1,690
	P0 female implants/litter	0	9	2	1	22

Reference and study design	Results[a]				
Single dose on GD 10; sacrificed GD 21					
Bayer (1998) Rat (Wistar), 28/sex/group 0, 1, 3 ppm 0, 0.11, 0.35 mg/kg-day for drinking water 0, 0.09, 0.28 mg/kg-day for diet Drinking water and diet Females dosed through mating, gestation, and lactation (males only through cohabitation with females)	**Lacation index** *(percent change compared to control)*				
	Drinking water				
	mg/kg-day	0	0.11	0.35	
		0	0	-6	
	Diet				
	mg/kg-day	0	0.09	0.28	
		0	-8	-3	
Monsanto (1993) Rat (Wistar); 12 males/group 0, 0.2, 0.4, 0.8% BBP or 0, 116, 235, 458 mg/kg-day (F) and 0, 252, 580, 1,078 mg/kg-day (M) Diet Multigenerational study	**Live birth index** *(raw percentages)*				
	mg/kg-day	0	116	235	458
	litter 1	97	98	100	99
	litter 2	98	98	99	99
	Viability index *(raw percentages)*				
	litter 1	100	97	100	97
	litter 2	98	96	100	99
Saillenfait et al. (2003) Mouse (OF-1); P0, female (22–24/group) 0, 0.9, 1.8, 3.6, 5.4 mmol/kg (equivalent to 280, 560, 1,120, 1,690 mg/kg as calculated by study authors) Gavage Single dose on GD 8; sacrificed GD 18	*Percent change compared to control*				
	mg/kg-day	0	280	560	1,120	1,690
	P0 female implants/ litter	0	−3	−9	−4	9
Ahmad et al. (2014) Rat (Albino); P0, female (6/group) 0, 4, 20, 100 mg/kg Gavage GD 14 to parturition	*Percent change compared to control*				
	mg/kg-day	0	4	20	100
	F1 combined litter size	0	−1	−5	15

*Statistically different from controls (p <0.05), as reported by study authors.
[a]Percent change compared to control calculated as 100 × ((treated value − control value) ÷ control value).
[b] Calculated as follows: [% in diet × intake food/water (mg)] ÷ body weight (kg) = mg/kg-day.

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

Mating index = (number copulated/number cohabitated) × 100; fertility index = (number of pregnant/number copulated) × 100, ; gestation index = (number of pregnant females/number of sperm-positive females) × 100; lactation index = (number of live pups after three weeks/number of live pups after four days (after culling)) × 100; fecundity index = (number of females pregnant/number of females mated) × 100; viability index = (number of live pups on day 21/number of live pups on day 4 (after culling)) × 100

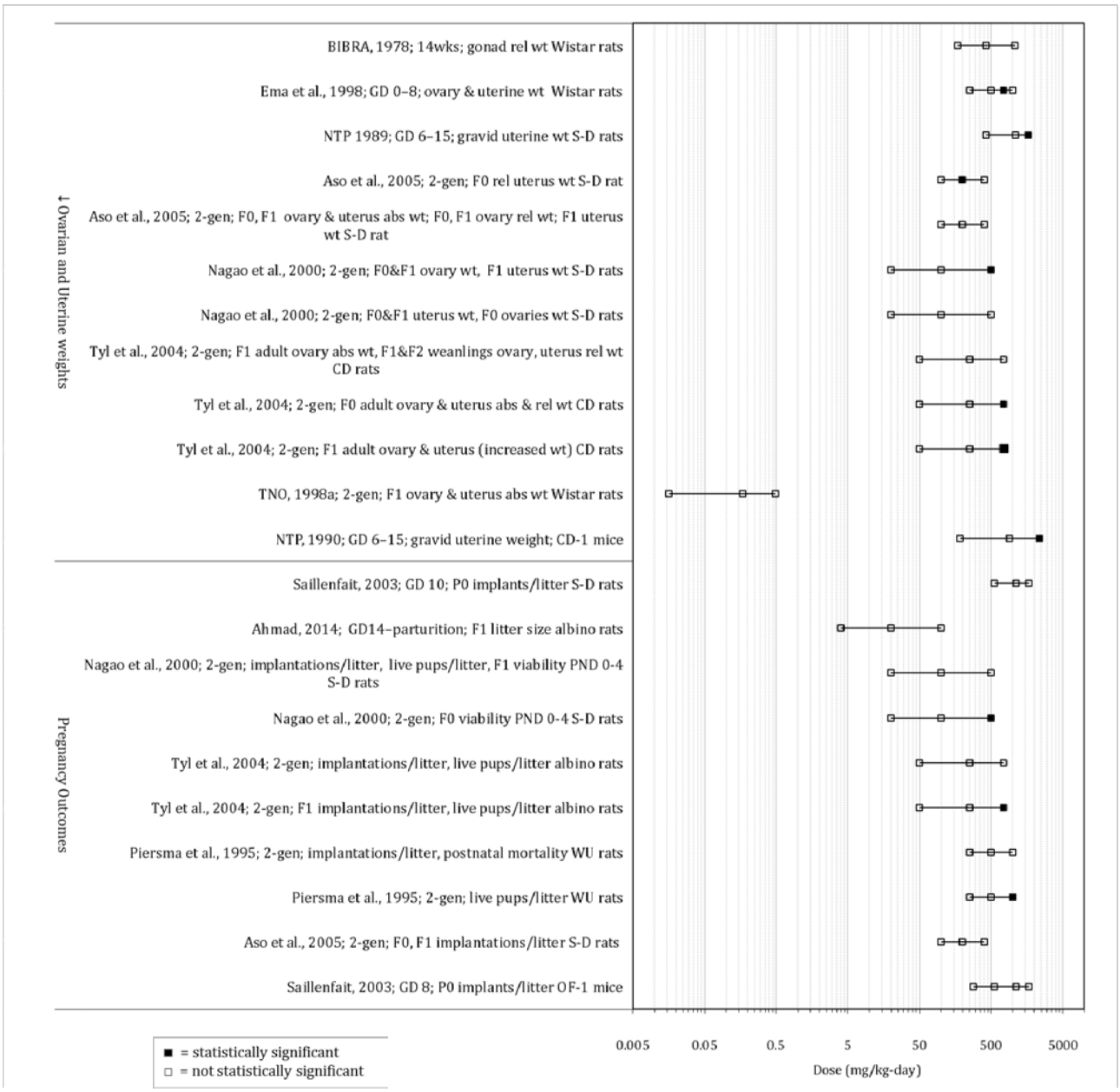


Figure 3-5. Exposure response array of female reproductive toxicity following oral exposure to BBP: weights and pregnancy outcomes.

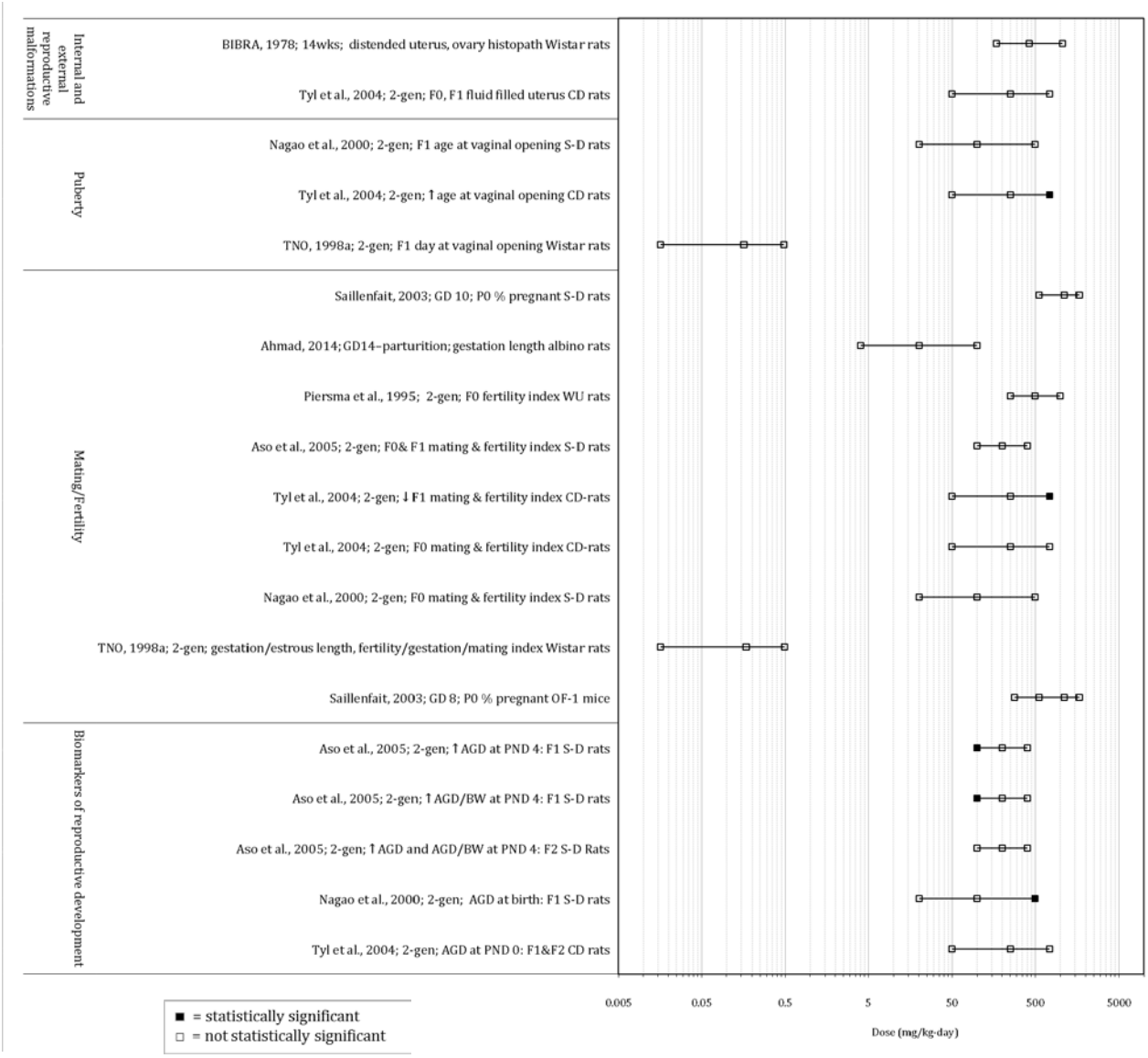


Figure 3-6. Exposure response array of other female reproductive parameters following oral exposure to BBP.

Table 3-23. Evidence pertaining to pregnancy outcomes following oral exposure to BBP: Measures of embryotoxicity

Reference and study design	Results[a]				
NTP (1989) Rat (Sprague-Dawley); 27–30 pregnant females/dose 0, 420, 1,100, 1,640 mg/kg-day Diet GDs 6–15; dams sacrificed on GD 20	*Raw percentages*				
	mg/kg-day	0	420	1,100	1,640
	resorptions/litter (%)	3.5	3.8	3.8	40.2*
	litters with resorptions (%)	32.1	44.4	43.3	86.2*
	Percent change compared to control				
	number of live fetuses/litter	0	5	2	−33*
Ema et al. (1990) Rat (Wistar); 13–17 pregnant females/dose 0, 0.25, 0.5, 1.0, 2.0% 0, 185, 375, 654, 974 mg/kg-day Diet GDs 0–20; dams sacrificed on GD 20	*Raw percentages or ratios*				
	mg/kg-day	0	185	375	654	974
	postimplantation loss/litter (%)	7.6	9.0	16.4	12.1	100*
	total loss/litter (%)	12.7	13.6	25.4	19.8	100*
	sex ratio (M:F)	100:108	110:118	67:102	73:87	NA
	pre-implantation loss/litter (%)	5.6	5.2	10.5	8.8	13.6
	Percent change compared to control					
	number of live fetuses/litter	0	−4	−19*	−12	−100
	Note: All litters were lost at the high dose.					
Ema et al. (1992b) Rat (Wistar); 11 pregnant females/dose 0 [ad libitum controls], 0 [pair fed controls], or 974 mg/kg-day[b] Diet GDs 0–20, 0–11, or 11–20; dams sacrificed on GD 20	*Raw percentages or ratios*					
	mg/kg-day	0 (ad libitum)	0 (pair fed)	974 (GDs 0–20)	974 (GDs 0–11)	974 (GDs 11–20)
	postimplantation loss/litter (%)	9.2	16.7	100*	100*	13.4
	litters resorbed (%)	0	0	100*	100*	0
	sex ratio (M:F)	57:78	64:68	NA	NA	67:67
	pre-implantation loss/litter (%)	6.2	6.4	3.4	7.2	3.9

Reference and study design	Results[a]					
	Percent change compared to ad libitum control					
	number of live fetuses/litter	0	−2	−100*	−100*	−1
Ema et al. (1992a) Rat (Wistar); 11−12 pregnant females/dose 0 [ad libitum controls], 0 [pair fed controls], or 974 mg/kg-day[b] Diet GDs 0−20, 0−7, 7−16, or 16−20; dams sacrificed at GD 20	*Raw percentages or ratios*					
	mg/kg-day	0 (ad libitum)	0 (pair fed)	974 (GDs 0−20)	974 (GDs 0−7)	974 (GDs 7−16)	974 (GDs 16−20)
	postimplantation loss/litter (%)	9.2	16.7	100*	24.8*	55.8*	11.7
	total loss/litter (%)	14.3	22	100*	29.6*	59.1*	17.6
	litters resorbed (%)	0	0	100*	0	17	0
	sex ratio (M:F)	57:78	64:68	NA	54:59	37:36	62:70
	pre-implantation loss/litter (%)	6.2	6.4	3.4	6.7	6.7	4.1
	Percent change compared to ad libitum control						
	Number of live fetuses/litter	0	−2	−100*	−16	−50*	−2
Ema et al. (1992c) Rat (Wistar); 10 pregnant females/dose 0, 500, 750, 1,000 mg/kg-day Gavage GDs 7−15; dams sacrificed at GD 20	*Raw percentages or ratios*				
	mg/kg-day	0	500	750	1,000
	postimplantation loss/litter (%)	8.2	14.7	81.7*	100*
	litters resorbed (%)	0	0	30	100*
	sex ratio (M:F)	57:64	62:58	11:14	NA
	Percent change compared to control				
	number of resorptions and dead fetuses/litter	0	67	833*	1,050*
	number of live fetuses/litter	0	−1	−79*	−100
Ema et al. (1993) Rat (Wistar); 10 pregnant females/dose 0, 600, 750, 1,000 mg/kg-day Gavage GDs 7−9, 10−12, or 13−15; dams sacrificed at GD 20	*Raw percentages or ratios*				
	mg/kg-day	0	600	750	1,000
	Postimplantation loss/litter *(%)*				
	exposed GDs 7−9	15.5	14.3	52.8*	74.3*
	exposed GDs 10−12	13.1	7.8	32.1*	88.7*
	exposed GDs 13−15	11.7	19.5	47.2*	62.3*

Reference and study design	Results[a]				
	Sex ratio (M:F)				
	exposed GDs 7–9	65:60	59:65	36:33	17:21
	exposed GDs 10–12	54:67	48:81	55:44	13:4*
	exposed GDs 13–15	57:71	55:55	41:32	26:29
	Number of resorptions and dead fetuses/litter *(percent change compared to control)*				
	exposed GDs 7–9	0	31	363*	581*
	exposed GDs 10–12	0	−35	176*	659*
	exposed GDs 13–15	0	65	288*	435*
	Number of live fetuses/litter *(percent change compared to control)*				
	exposed GDs 7–9	0	−1	−45*	−70*
	exposed GDs 10–12	0	7	−18	−86*
	exposed GDs 13–15	0	−14	−43*	−57*
	Percentage of litters resorbed *(percent change compared to control)*				
	exposed GDs 7–9	0	0	10	30
	exposed GDs 10–12	0	0	10	70*
	exposed GDs 13–15	0	0	0	20
Ema et al. (1995) Rat (Wistar); 10–12 pregnant females/dose 0, 750, 1,000, 1,250 mg/kg-day Gavage GDs 7–9, 10–12, or 13–15; dams sacrificed at GD 20	*Raw percentages or ratios*				
	mg/kg-day	0	750	1,000	1,250
	Sex ratio *(M:F)*				
	exposed GDs 7–9	68:87	45:44	26:27	NA
	exposed GDs 10–12	68:87	64:60	20:12*	NA
	exposed GDs 13–15	68:87	51:39*	27:29	NA
	Post implantation loss/litter *(%)*				
	exposed GDs 7–9	17.5	49.2*	69.6*	100*
	exposed GDs 10–12	17.5	30.0*	81.8*	100*
	exposed GDs 13–15	17.5	45.9*	68.0*	100*
	Number of live fetuses/litter *(percent change compared to control)*				
	exposed GDs 7–9	0	−43*	−66*	−100*
	exposed GDs 10–12	0	−20	−79*	−100*
	exposed GDs 13–15	0	−42*	−64*	−100*
	Note: All litters were resorbed at the high dose.				

Reference and study design	Results[a]					
Ema et al. (1998) Rat (Wistar); 7–10 pregnant females/dose 0, 250, 500, 750, 1,000, mg/kg-day Gavage GDs 0–8; dams sacrificed on GD 20	*Raw percentages or ratios*					
	mg/kg-day	0	250	500	750	1,000
	pre-implantation loss/litter (%)	4.7	5.5	4.0	8.1	16.9*
	postimplantation loss/litter (%)	7.2	6.5	18.6	29.7*	43.7*
	sex ratio of live fetuses (M:F)	79:62	72:57	55:54	32:40	18:30*
	litters resorbed (%)	0	0	11	0	0
	Percent change compared to control					
	number of live fetuses/litter	0	1	−14	−27	−51*
	number of dead or resorbed fetuses/ litter	0	−9	164	236	409
Piersma et al. (2000) Rat (Harlan Cpb-WU); 4–10 pregnant females/dose 0, 270, 350, 450, 580, 750, 970, 1,250, 1,600, 2,100 mg/kg-day GDs 6–15 or 6–20; dams sacrificed on GD 21	The study authors reported dose-dependent increases in numbers of resorptions for both exposure periods, with 100% resorption at the high-dose (data shown graphically).					
Uriu-Adams et al. (2001) Rat (Wistar); 9–17 pregnant females/dose 0, 250, 1,000, 1,500, 2,000 mg/kg-day Gavage GDs 11–13; dams sacrificed on GD 20	**Resportions** *(raw percentages)*					
	mg/kg-day	0	250	1,000	1,500	2,000
	resorptions (%)	13.08	7.82	11.52	23.84	53.73*
	Percent change compared to control					
	number of resorptions/litter	0	−9	30	247*	653*
	number of live fetuses/litter	0	10	−1	−2	−45*

Reference and study design	Results[a]				
Ema and Miyawaki (2002) Rat (Wistar); 16 pregnant females/dose 0, 250, 500, 1,000 mg/kg-day Gavage GDs 15–17; dams sacrificed on GD 21	*Raw percentages or ratios*				
	mg/kg-day	0	250	500	1,000
	sex ratio (M:F)	127:107	105:111	111:113	108:93
	postimplantation loss/litter (%)	6.4	7.9	7.2	15.2
	Percent change compared to control				
	number of live fetuses/litter	0	−8	−4	−14*
	number of resorptions/litter	0	38	13	138
	number of dead fetuses/litter	0	−50	−50	100
Tyl et al. (2004) Rat (CD); 30 breeding pairs/dose/generation 0, 750, 3,750, 11,250 ppm 0, 50, 250, 750 mg/kg-day[b] Diet Multigenerational study	*Raw percentages*				
	mg/kg-day	0	50	250	750
	F1 post implantation loss/litter (%)	15.79	17.65	8.77	14.18
	F2 post implantation loss/litter (%)	10.02	8.75	6.67	7.06
	Percent change compared to control				
	F1 number of implantations/litter	0	−11	−5	−10
	F2 number of implantations/litter	0	−5	−4	−22*
	F1 number of live pups/litter	0	−8	1	−2
	F2 number of live pups/litter	0	−1	0	−20*
Howdeshell et al. (2008) Rat (Sprague-Dawley); 4–9 pregnant females/dose 0, 100, 300, 600, 900 mg/kg-day Gavage GDs 8–18; dams sacrificed on GD 18	*Raw percentages*					
	mg/kg-day	0	100	300	600	900
	fetal mortality (%)	2.9	0	2.2	12.2*	33.3*
	Percent change compared to control					
	number of implantations/litter	0	9	9	−15	−15

Reference and study design	Results[a]				
	number of live fetuses	0	11	7	−24*	−64*
	total resorptions	0	−100	0	275*	900*
TNO (1998b)	*Response*					
Rat (Wistar); P0, female (28/group)	mg/kg-day	0		0.190		0.280
0, 1,000, 3,000 µg/L (equivalent to 0.190, 0.280 mg/kg-day during premating as calculated by study authors)	*P0 females with all stillborn pups*	0		1		2
Drinking water	*P0 females with stillborn pups*	5		2		4
F0 females: 2 weeks prior to mating, through mating, gestation, and lactation; F0 males: mating period only; F1: did not receive additional treatment after weaning	*PO females, stillborn*	13		8		28*
	P0 female, live born	286		240		249
	number of litters lost entirely days 0−7	1		2		5
	F1 combined sex ratio (number of males)	154		123		128
	Response (% ± SE)					
	P0 female postimplantation loss	10.74 (± 2.823)		11.19 (± 4.423)		17.88 (± 5.563)
	Response (%)					
	F1 combined pup mortality, day 4 (%)	10		4.6*		17*
	F1 combined, Viability index, days 4−7 (%)	100		100		100
	P0 female maternal body weight	No significant effect on female body weight throughout the treatment period				

Reference and study design	Results[a]			
TNO (1998a)	*Response*			
Rat (Wistar); P0, female (28/group)	mg/kg-day	0	0.016	0.171	0.489
0, 100, 1,000, 3,000 µg/L (equivalent to 0.016, 0.171, 0.489 mg/kg-day, average of reported intake over premating, gestation, and lactation)	*P0 females with all stillborn pups*	1	0	0	0
	P0 females with stillborn pups	4	0	0	5
Drinking water					
F0 females: 2 weeks prior to mating, through mating, gestation, and lactation; F0 males: during mating; F1 animals were not treated after weaning	*P0 female, live born*	237	233*	212*	241
	F1 combined pup mortality, day 4 (number of pups)	2	2	30*	29*
	F1 combined sex ratio (number of males)	121	125	106	126
	P0 female, stillborn	15	0*	0*	7
	P0 female, postimplantation loss	16.22 (± 4.273)	9.33 (± 1.883)	13.87 (± 4.421)	11.34 (± 2.755)
Ahmad et al. (2014)	*Response*			
Rat (Albino); P0, females (6/group)	mg/kg-day	0	4	20	100
0, 4, 20, 100 mg/kg	F1 combined sex ratio (M/F)	0.47	0.52	0.55	0.59
Gavage					
GD 14 to parturition	*Response (% ± SE)*			
	F1 combined fetal mortality (%)	4 (± 4)	2.78 (± 2.78)	8.21 (± 5.64)	7.47 (± 3.53)
	F1 combined live birth index (%) PND 1	96 (± 4)	97.22 (± 2.78)	91.79 (± 5.64)	92.53 (± 3.53)
	F1 combined, live pups/litter	8 (± 1.22)	8.17 (± 1.19)	7.4 (± 0.93)	8.83 (± 0.4)
	F1 combined viability index PND 4	94 (± 6)	93.17 (± 3.17)	89.79 (±5.25)	89.19 (± 3.69)
	F1 combined weanling index (%) PND 21	94 (± 6)	80.48 (± 8.01)	81.21 (± 13.4)	89.19 (± 3.69)
	P0 female, maternal body weight gain	Body weight gain was significantly lower in the BBP groups on GD 21 compared to controls			

Reference and study design	Results[a]				
Saillenfait et al. (2003) Rat (Sprague-Dawley); P0, female (9–10/group) 0, 1.8, 3.6, 5.4 mmol/kg (equivalent to 0, 560, 1,120, 1,690 mg/kg as calculated by study authors) Gavage Single dose on GD 10; sacrificed GD 21	*Response (% ± SE) or percent change compared to control*				
	mg/kg-day	0	560	1,120	1,690
	P0 female percent of postimplantation loss/litter	6.06 (± 1.27)	6.62 (± 1.46)	13.86 (± 0.91)	15.55 (± 3.87)
	P0 female percent of resorptions/litter	6.06 (± 1.27)	6.62 (± 1.46)	13.86 (± 0.91)	15.55 (± 3.87)
	P0 female live fetuses/litter	0	9	−7	−9
NTP (1990) Mice (CD-1); 27–30 pregnant females/dose (except n = 14 in the high-dose group) 0, 182, 910, 2,330, 4,121 mg/kg-day Diet GDs 6–15; dams sacrificed on GD 17	*Raw percentages*				
	mg/kg-day	0	182	910	2,330
	litters with resorptions (%)	55	46	63	100*
	resorptions/litter (%)	7	4.7	11.8	91.3*
	Percent change compared to control				
	number of live fetuses per litter	0	4	−9*	−77*
	Note: The 4,121 mg/kg-day group was eliminated after evaluation of 14 dams, since all litters were completely resorbed.				
Saillenfait et al. (2003) Mouse (OF-1); P0, female (22–24/group) 0, 0.9, 1.8, 3.6, 5.4 mmol/kg (equivalent to 0, 280, 560, 1,120, 1,690 mg/kg as calculated by study authors) Gavage Single dose on GD 8; sacrificed on GD 18	*Response (% ± SE) or percent change compared to control*				
	mg/kg-day	0	280	560	1,120	1,690
	P0 female, percent of postimplantation loss/litter	5.85 (± 2.19)	10.89 (± 2.61)	22.27* (± 5.24)	50.41* (± 7.53)	77.40* (± 5.14)
	P0 female percent of resorptions/litter	5.53 (± 2.05)	10.02 (± 4.56)	19.13* (± 4.56)	48.1* (± 7.91)	73.76* (± 4.78)
	P0 female live fetuses/litter	0	−6	−23	−48*	−75*

*Statistically different from controls (p <0.05), as reported by study authors.
[a]Percent change compared to control calculated as 100 × ((treated value − control value) ÷ control value).
[b]Calculated as follows: [% in diet × intake food/water (mg)] ÷ body weight (kg) = mg/kg-day.
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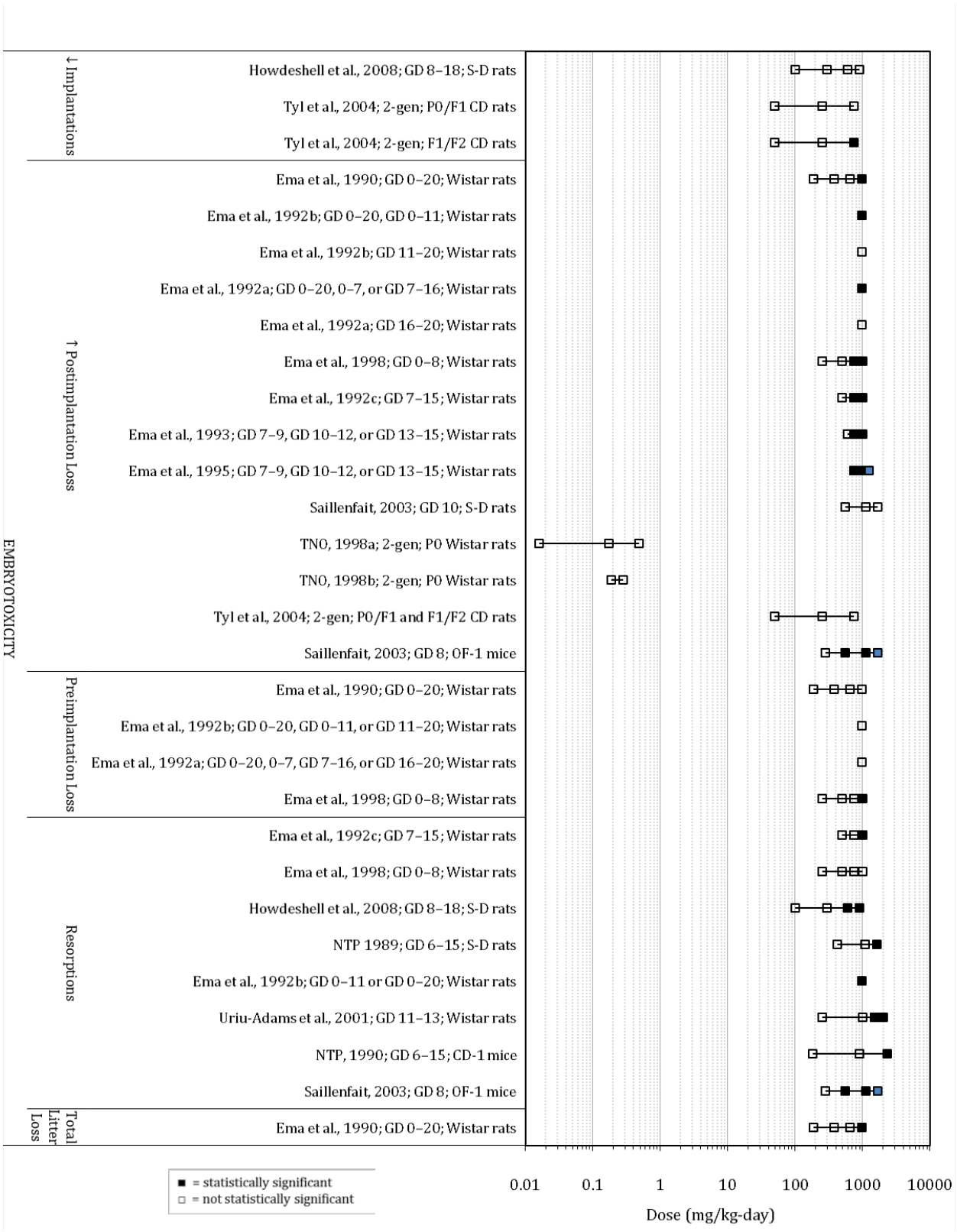

Figure 3-7. Exposure-response array of pregnancy outcomes following oral exposure to BBP.

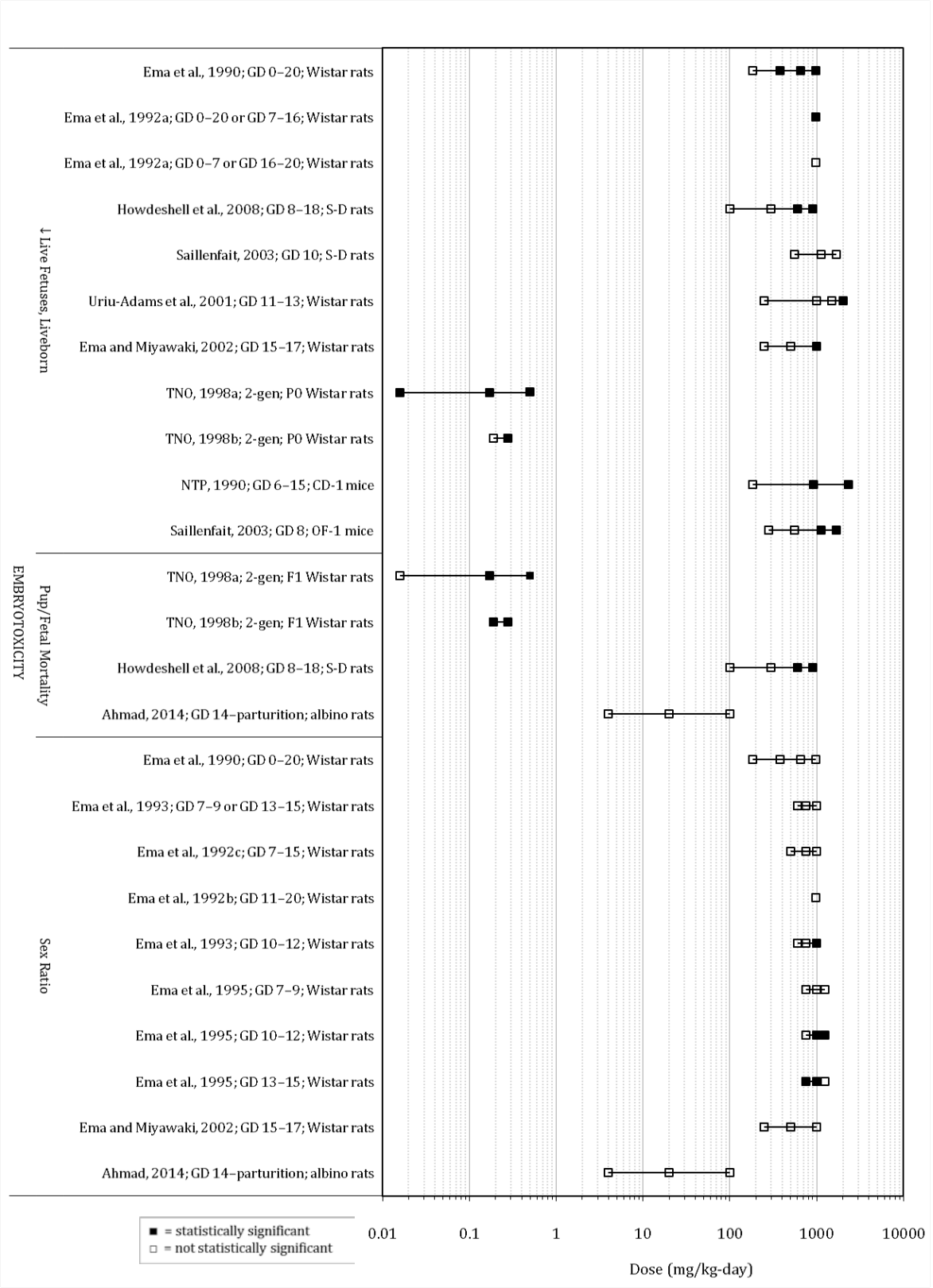

Figure 3-8. Exposure-response array of fetal measures following oral exposure to BBP.

3.3.3. Developmental Effects

Table 3-24. Evidence pertaining to developmental effects following oral exposure to BBP: Teratogenicity

Reference and study design	Results[a]				
NTP (1989) Rat (Sprague-Dawley); 27–30 pregnant females/dose 0, 420, 1,100,1,640 mg/kg-day Diet GDs 6–15; dams sacrificed on GD 20	*Raw percentages*				
	mg/kg-day	0	420	1,100	1,640
	fetuses malformed/litter (%)	2.0	0.9	5.9	52.8*
	litters with malformed fetuses (%)	25.0	14.8	46.7	96.3*
	fetuses with variations/litter (%)	19.0	25.4	41.0*	71.4*
	Percent incidence				
	number of litters with external malformation	0	0	10	52*
	number of litters with skeletal malformations	11	11	30	89*
	number of litters with visceral malformations	18	4	33	78*
Ema et al. (1990) Rat (Wistar); 13–17 pregnant females/dose 0, 0.25, 0.5, 1.0, 2.0% 0, 185, 375, 654, 974 mg/kg-day GDs 0–20; dams sacrificed on GD 20	*Percent incidence*				
	mg/kg-day	0	185	375	654
	number of litters with external anomalies	0	6	0	15
	number of litters with skeletal anomalies	13	6	13	23
	number of litters with skeletal variation	40	47	27	69
	number of litters with delayed ossification in sternebrae	20	35	27	38

Reference and study design	Results[a]					
	number of litters with internal anomalies	0	0	0		8
	Note: All litters were lost at the high dose.					
Ema et al. (1992b) Rat (Wistar); 11 pregnant females/dose; 132–135, 88–89, and 44–46 fetuses/group examined for external, skeletal, and internal malformations, respectively 0 ad libitum controls, 0 pair fed controls, or 974 mg/kg-day[b] Diet GDs 0–20, 0–11, or 11–20; dams sacrificed on GD 20	*Percent litter Incidence*					
	mg/kg-day	0 (ad libitum)	0 (pair fed)	974 (GDs 0–20)	974 (GDs 0–11)	974 (GDs 11–20)
	external malformations	9	0	NA	NA	82*
	cleft palate	0	0	NA	NA	82*
	skeletal malformations	0	18	NA	NA	82*
	fused sternebrae	0	9	NA	NA	73*
	internal malformations	0	0	NA	NA	0
	Percent fetal incidence					
	mg/kg-day	0 (ad libitum)	0 (pair fed)	974 (GDs 0–20)	974 (GDs 0–11)	974 (GDs 11–20)
	all external malformations	1	1	NA	NA	54*
	cleft palate	0	0	NA	NA	54*
	all skeletal malformations	0	2	NA	NA	27*
	fused sternebrae	0	1	NA	NA	25*
	internal malformations	0	0	NA	NA	0
	Note: All litters were lost in groups treated from GDs 0–20 and 0–11.					
Ema et al. (1992a) Rat (Wistar); 11–12 pregnant females/dose; 73–135, 49–90, and 24–46 fetuses/group examined for external, skeletal, and internal malformations, respectively 0 ad libitum controls, 0 pair fed controls, or 974 mg/kg-day[b] Diet GDs 0–20, 0–7, 7–16, or 16–20;	*Percent litter incidence*					
	mg/kg-day	0 (ad libitum)	0 (pair fed)	974 (GDs 0–20)	974 (GDs 0–7)	974 (GDs 7–16)	9974 (GDs 16–20)
	external malformations	9	0	NA	0	100*	0
	cleft palate	0	0	NA	0	100*	0
	skeletal malformations	0	18	NA	9	90*	18

Reference and study design	Results[a]					
dams sacrificed on GD 20	*fused sternebrae*	0	9	NA	0	90*	0
	internal malformations	0	0	NA	0	22	0
	Percent fetal incidence						
	external malformations	1	0	NA	0	93*	0
	cleft palate	0	0	NA	0	93*	0
	skeletal malformations	0	2	NA	1	78*	3
	fused sternebrae	0	1	NA	0	78*	0
	internal malformations	0	0	NA	0	8	0
	Note: All litters were lost in the group treated from GDs 0–20.						
Ema et al. (1992c) Rat (Wistar); 10 pregnant females/dose; 25–121, 16–81, and 9–41 fetuses/group examined for external, skeletal, and internal malformations, respectively 0, 500, 750, 1,000 mg/kg-day Gavage GDs 7–15; dams sacrificed on GD 20	*Percent litter incidence*				
	mg/kg-day	0	500	750	1,000
	external malformations	0	0	100*	NA
	cleft palate	0	0	100*	NA
	skeletal malformations	10	30	57*	NA
	fused sternebrae	0	0	57*	NA
	internal malformations	0	0	60*	NA
	dilation of renal pelvis	0	0	60*	NA
	Percent fetal incidence				
	external malformations	0	0	48*	NA
	cleft palate	0	0	48*	NA
	skeletal malformations	1	4	31*	NA
	fused sternebrae	0	0	25*	NA
	internal malformations	0	0	33*	NA
	dilation of renal pelvis	0	0	33*	NA

Reference and study design	Results[a]				
	Note: All litters were lost at the high dose.				
Ema et al. (1993) Rat (Wistar); 10 pregnant females/dose; 38–125, 25–83, and 13–42 fetuses/group examined for external, skeletal, and internal malformations, respectively 0, 600, 750, 1,000 mg/kg-day Gavage GDs 7–9, 10–12, or 13–15; dams sacrificed on GD 20	*Percent litter incidence*				
	mg/kg-day	0	600	750	1,000
	External malformations				
	GDs 7–9	0	0	0	29
	GDs 10–12	0	0	11	33
	GDs 13–15	0	10	70*	100*
	Skeletal malformations				
	GDs 7–9	10	30	56*	86*
	GDs 10–12	10	20	11	0
	GDs 13–15	0	20	70*	100*
	Internal malformations				
	GDs 7–9	0	0	11	29
	GDs 10–12	0	0	11	0
	GDs 13–15	0	0	0	0
	Percent fetal incidence				
	External malformations				
	GDs 7–9	0	0	0	5
	GDs 10–12	0	0	1	6
	GDs 13–15	0	2	47	82
	Skeletal malformations				
	GDs 7–9	1	5	20	44
	GDs 10–12	1	2	2	0
	GDs 13–15	0	5	42	97
	Internal malformations				
	GDs 7–9	0	0	4	15
	GDs 10–12	0	0	3	0
	GDs 13–15	0	0	0	0
	Note: Specific malformations that were significantly increased included vertebral malformations (GDs 7–9), fusion of sternebrae (GDs 13–15), and cleft palate (GDs 13–15).				

Reference and study design	Results[a]			
Ema et al. (1995)	*Percent litter incidence*			
Rat (Wistar); 10–12 pregnant females/dose; 53–155, 35–102, and 18–53 fetuses/group examined for external, skeletal, and internal malformations, respectively	mg/kg-day	0	750	1,000	1,250
	External malformations				
	GDs 7–9	0	0	33	NA
	GDs 10–12	0	9	40	NA
0, 750, 1,000, or 1,250 mg/kg-day	*GDs 13–15*	0	67*	100*	NA
Gavage	**Skeletal malformations**				
GDs 7–9, 10–12, 13–15; dams sacrificed on GD 20	*GDs 7–9*	8	64*	89*	NA
	GDs 10–12	8	9	0	NA
	GDs 13–15	8	67*	100*	NA
	Internal malformations				
	GDs 7–9	0	18	22	NA
	GDs 10–12	0	9	0	NA
	GDs 13–15	0	0	0	NA
	Percent fetal incidence				
	External malformations				
	GDs 7–9	0	0	6	NA
	GDs 10–12	0	1	6	NA
	GDs 13–15	0	48	82	NA
	Skeletal malformations				
	GDs 7–9	1	19	54	NA
	GDs 10–12	1	1	0	NA
	GDs 13–15	1	44	97	NA
	Internal malformations				
	GDs 7–9	0	7	11	NA
	GDs 10–12	0	2	0	NA
	GDs 13–15	0	0	0	NA
	Note: All litters were resorbed at the high dose. Specific malformations that were significantly increased included vertebral malformations (GDs 7–9), fusion/absence of ribs (GDs 7–9), fusion of sternebrae (GDs 13–15), and cleft palate (GDs 13–15).				

Reference and study design	Results[a]					
Piersma et al. (2000) Rat (Harlan Cpb-WU); 4–10 pregnant females/dose 0, 270, 350, 450, 580, 750, 970, 1,250, 1,600, 2,100 mg/kg-day GDs 6–15 or 6–20; dams sacrificed on GD 21	The study authors reported increased incidences of several skeletal anomalies in the "middle or high doses" (quantitative data not provided). There was a dose-dependent increase in the occurrence of extra 13th lumbar ribs in groups exposed to 270–1,250 mg/kg-day (all litters were resorbed at higher doses); the effect was more pronounced in the group exposed on GDs 6–20 (data shown graphically).					
Uriu-Adams et al. (2001) Rat (Wistar); 9–17 pregnant females/dose; 8–16 litters/dose (36–119 fetuses/dose) were examined for anomalies and malformations 0, 250, 1,000, 1,500, 2,000 mg/kg-day Gavage GDs 11–13; dams sacrificed on GD 20	*Percent change compared to control*					
	mg/kg-day	0	250	100	1,500	2,000
	crown rump length, males	0	1	1	−1	−6*
	crown rump length, females	0	0	1	−2	−10*
	Skeletal malformations					
	ossification sites, metacarpals	0	−5	−4	−9	−32*
	ossification sites, metatarsals	0	−4	−2	−16*	−27*
	ossification sites, sternum	0	−11	−8	−36*	−62*
	number of rudimentary ribs/fetus	0	0	2,150*	6,800*	7,250*
	Raw percentages					
	fetuses with rib anomaly (%)	1.79	2.38	23.30*	82.64*	92.26*
	External malformations					
	fetuses with cleft palate/litter (%)	0	0	2.3	27.5*	52.9*
	Note: Study authors did not report whether the litter or the fetus was the statistical unit of comparison.					
Saillenfait et al. (2003) Rat (Sprague-Dawley); F1, combined (100–123/group) 0, 1.8, 3.6, 5.4 mmol/kg (equivalent to 0, 560, 1,120, 1,690 mg/kg as calculated by study authors)	*Response (%)*					
	mg/kg-day	0	560	1,120	1,690	
	F1 combined percent of malformed fetuses	0	0*	0.9*	5*	

Reference and study design	Results[a]				
Gavage Single dose on GD 10; sacrificed GD 21					
Saillenfait et al. (2003) Mouse (OF-1); F1, combined (35–221/group) 0, 0.9, 1.8, 3.6, 5.4 mmol/kg (equivalent to 0, 280, 560, 1,120, and 1,690 mg/kg as calculated by study authors) Gavage Single dose on GD 8; sacrificed GD 18	*Response (%)*				
	mg/kg-day	0	280	560	1,120	1,690
	F1 combined, percent of malformed fetuses	0	0*	2.1*	9.1*	42.9*
NTP (1990) Mouse (CD-1); 27–30 pregnant females/dose (except n = 14 in the high-dose group) 0, 182, 910, 2,330, 4,121 mg/kg-day Diet GDs 6–15; dams sacrificed on GD 17	mg/kg-day	0	182	910	2,330
	Raw percentages				
	litters with gross malformations (%)	10	0	27	67*
	litters with skeletal malformations (%)	21	11	43	100*
	litters with visceral malformations (%)	7	7	23	33
	malformed fetuses/litter (%)	4.4	2.4	13.6*	89.3*
	litters with malformed fetuses (%)	31	18	60*	100*
	fetuses with variations per litter (%)	29	26.2	35.9	98.4*
	litters with variations (%)	86	82	97	100
	Note: The 4,121 mg/kg-day group was eliminated after evaluation of 14 dams, since all litters were completely resorbed.				

*Statistically different from controls (p <0.05), as reported by study authors.
[a]Percent change compared to control calculated as 100 × ((treated value − control value) ÷ control value).
[b]Calculated as follows: [% in diet × intake food/water (mg)] ÷ body weight (kg) = mg/kg-day.

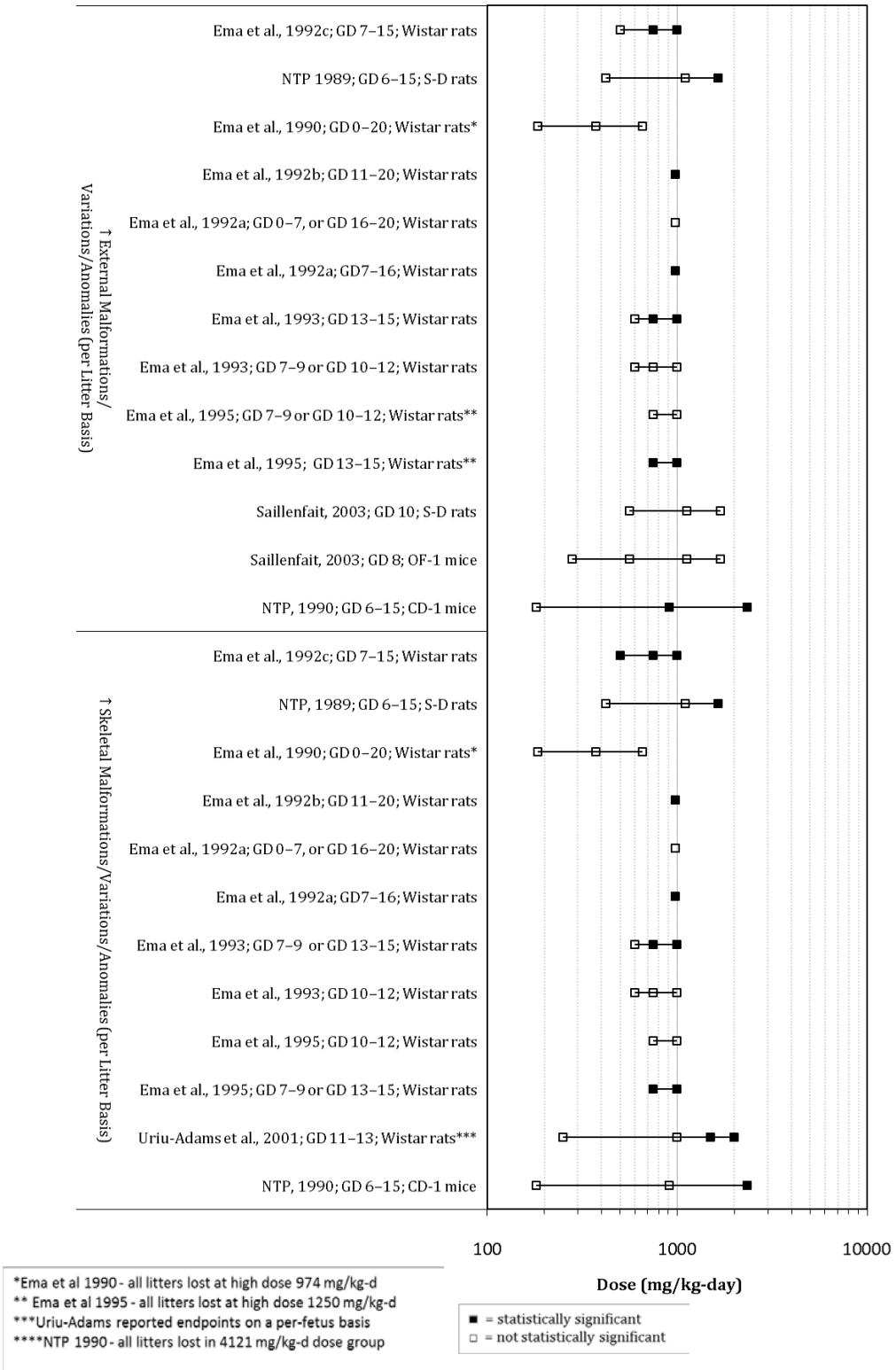

Figure 3-9. Exposure-response array of developmental effects following oral exposure to BBP: teratogenicity.

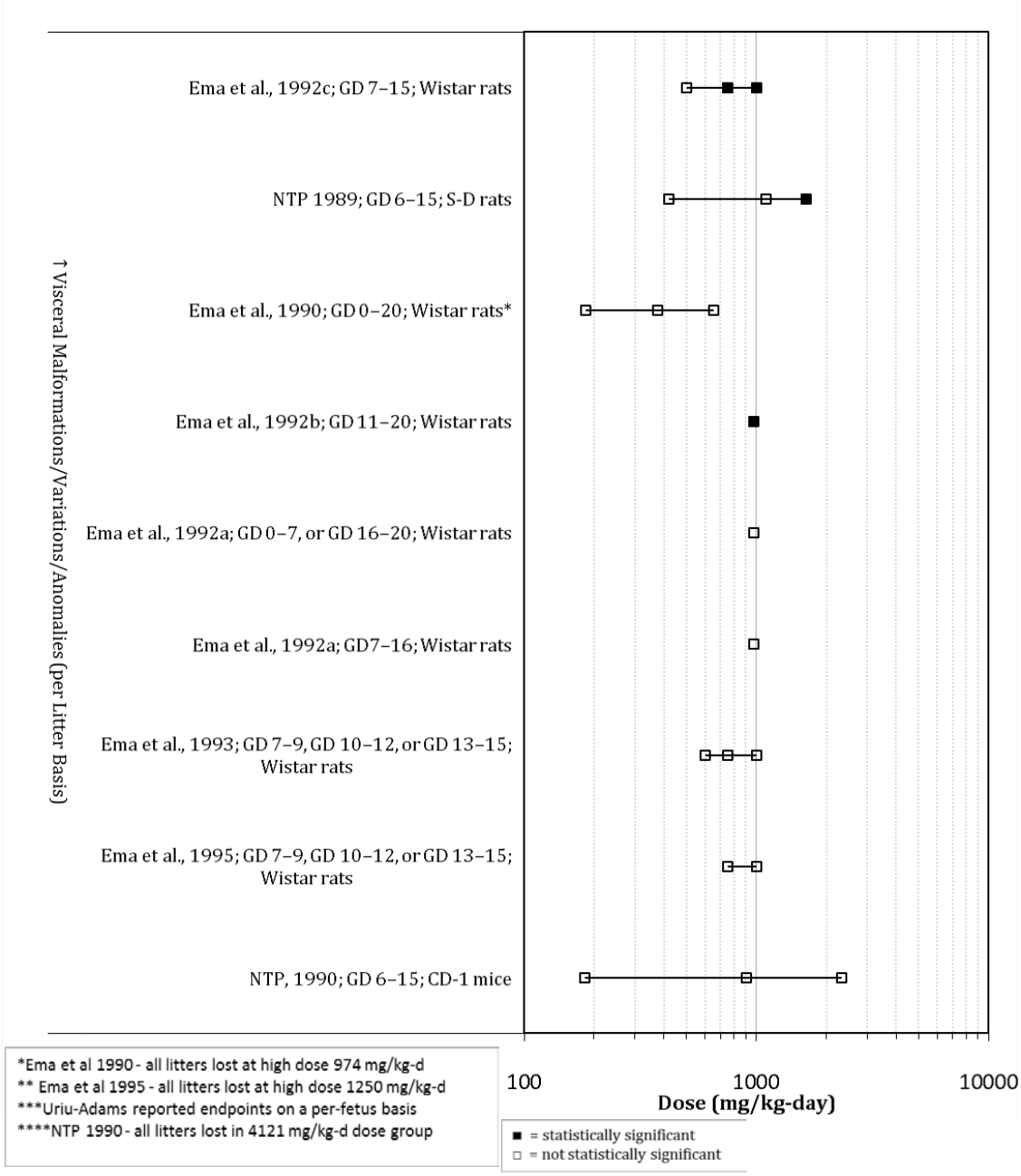

Figure 3-10. Exposure-response array of developmental effects following oral exposure to BBP: malformations.

Table 3-25. Evidence pertaining to developmental effects following oral exposure to BBP: offspring body weight

Reference and study design	Results[a]				
Fetal body weight					
NTP (1989) Rat (Sprague-Dawley CD); 27–30 pregnant females/dose 0, 420, 1,100, 1,640 mg/kg-day Diet GDs 6–15; dams sacrificed on GD 20	*Percent change compared to control*				
	mg/kg-day	0	420	1,100	1,640
	Fetal body weight (litter means)				
	all	0	−3	−3	−21*
	males	0	−3	−3	−20*
	females	0	0	−3	−21*
Ema et al. (1990) Rat (Sprague-Dawley); 13–17 pregnant females/dose 0, 0.25, 0.5, 1.0, 2.0% 0, 185, 375, 654, 974 mg/kg-day Diet GDs 0–20; dams sacrificed on GD 20	*Percent change compared to control*				
	mg/kg-day	0	185	375	654	974
	Fetal body weight (litter means)					
	males	0	2	5*	−7*	NA
	females	0	2	3*	−7*	NA
	Note: All litters were lost at the high dose.					
Ema et al. (1992b) Rat (Wistar); 11 pregnant females/dose 0 ad libitum controls, 0 pair fed controls, or 974 mg/kg-day Diet GDs 0–20, 0–11, or 11–20; dams sacrificed on GD 20	*Percent change compared to control*				
	mg/kg-day	0 (ad libitum)	0 (pair fed)	974 (GDs 0–20)	974 (GDs 0–11)	974 (GDs 11–20)
	Fetal body weight (litter means)					
	males	0	−8*	NA	NA	−22*
	females	0	−10*	NA	NA	−19*
	Note: Statistical results are shown for comparison to ad libitum control group. Fetal body weights in the group treated on GDs 11–20 were also significantly lower than pair fed controls. All litters were lost in groups treated on GDs 0–20 and GD 0–11.					

Reference and study design	Results[a]						
Ema et al. (1992a) Rat (Wistar); 11–12 pregnant females/dose 0 ad libitum controls, 0 pair fed controls, or 974 mg/kg-day Diet GDs 0–20, 0–7, 7–16, or 16–20; dams sacrificed on GD 20	*Percent change compared to control*						
	mg/kg-day	0 (ad libitum)	0 (pair fed)	974 (GDs 0–20)	974 (GDs 0–7)	974 (GDs 7–16)	974 (GDs 16–20)
	Fetal body weight (litter means)						
	males	0	−8*	NA	−7*	−11*	−17*
	females	0	−10*	NA	−9*	−12*	−18*
	Note: Statistical results are shown for comparison to ad libitum control group. Fetal body weights in the groups treated on GDs 16–20 were also significantly lower than pair fed controls. All litters were lost in the group treated on GDs 0–20.						
Ema et al. (1992c) Rat (Wistar); 10 pregnant females/dose 0, 500, 750, 1,000 mg/kg-day Gavage GDs 7–15; dams sacrificed on GD 20	*Percent change compared to control*						
	mg/kg-day	0	500	750	1,000		
	Fetal body weight (litter means)						
	males	0	−5	−18*	NA		
	females	0	−4	−18*	NA		
	Note: All litters were lost at the high dose.						
Ema et al. (1993) Rat (Wistar); 10 pregnant females/dose 0, 600, 750, 1,000 mg/kg–day Gavage GDs 7–9, 10–12, or 13–15; dams sacrificed on GD 20	*Percent change compared to control*						
	mg/kg-day	0	600	750	1,000		
	Male fetal body weight (litter means)						
	exposed GDs 7–9	0	−3	−15*	−18*		
	exposed GDs 10–12	0	5	−6	−14*		
	exposed GDs 13–15	0	3	−2	−5		
	Female fetal body weight (litter means)						
	exposed GDs 7–9	0	−3	−16*	−16*		
	exposed GDs 10–12	0	4	−4	−9		
	exposed GDs 13–15	0	−1	−5	−6		

Reference and study design	Results[a]							
Ema et al. (1995) Rat (Wistar); 10–12 pregnant females/dose 0, 750, 1,000, 1,250 mg/kg-day Gavage GDs 7–9, 10–12, or 13–15; dams sacrificed on GD 20	*Percent change compared to control*							
	mg/kg-day	0	750	1,000	1,250			
	Male fetal body weight (litter means)							
	exposed GDs 7–9	0	−14*	−17*	NA			
	exposed GDs 10–12	0	−5	−14*	NA			
	exposed GDs 13–15	0	−3	−8	NA			
	Female fetal body weight (litter means)							
	exposed GDs 7–9	0	−16*	−17*	NA			
	exposed GDs 10–12	0	−5	−15*	NA			
	exposed GDs 13–15	0	−3	−5	NA			
	Note: All litters were lost at the high dose.							
Ema et al. (1998) Rat (Wistar); 7–10 pregnant females/dose 0, 250, 500, 750, 1,000 mg/kg-day Gavage GDs 0–8; dams sacrificed on GD 20	*Percent change compared to control*							
	mg/kg-day	0	250	500	750	1,000		
	Fetal body weight (litter means)							
	males	0	0	−14*	−32*	−45*		
	females	0	−2	−14*	−33*	−40*		
Piersma et al. (2000) Rat (Harlan Cpb-WU); 4–10 pregnant females/dose 0, 270, 350, 450, 580, 750, 970, 1,250, 1,600, 2,100 mg/kg-day Gavage GD 6–15 or GD 6–20 ; dams sacrificed on GD 21	*Percent change compared to control*							
	mg/kg-day	0	270	350	450	580	750	970	1250
	fetal weight[b]	0	−4	−5	−5	−7	−15	−22	−28
	Note: The study authors reported a dose-dependent decrease in fetal weight for both exposure periods. All litters were resorbed in the 1,600 and 2,100 mg/kg-day groups.								
Uriu-Adams et al. (2001) Rat (Wistar); 9–17 pregnant females/dose 0, 250, 1,000, 1,500, 2,000 mg/kg-day Gavage	*Percent change compared to control*							
	mg/kg-day	0	250	1,000	1,500	2,000		
	Fetal body weight (litter means)							
	males	0	2	4	−7*	−18*		

Reference and study design	Results[a]				
GDs 11–13; dams sacrificed on GD 20	*females*	0	1	3	−9*	−22*
Ema and Miyawaki (2002)	*Percent change compared to control*				
Rat (Wistar); 16 pregnant females/dose	mg/kg-day	0	250	500	1,000
0, 250, 500, 1,000 mg/kg-day	**Fetal body weight (litter means)**				
Gavage	*males*	0	4	0	−17*
GDs 15–17; dams sacrificed on GD 21	*females*	0	4	−1	−14*
NTP (1990)	*Percent change compared to control*				
Mouse (CD-1); 27–30 pregnant females/dose (except n = 14 in the high-dose group)	mg/kg-day	0	182	910	2,330
0, 182, 910, 2,330, 4,121 mg/kg-day	**Fetal body weight (litter means)**				
Diet	*All*	0	1	−4	−17*
	males	0	2	−3	−16*
	females	0	2	−3	−14*
GDs 6–15; dams sacrificed on GD 17	Note: The 4,121 mg/kg-day group was eliminated after evaluation of 14 dams, since all litters were completely resorbed.				
Saillenfait et al. (2003)	*Percent change compared to control*				
Mouse (OF-1); F1, combined (35–221/group)	mg/kg-day	0	280	560	1,120	1,690
0, 0.9, 1.8, 3.6, 5.4 mmol/kg (equivalent to 0, 280, 560, 1,120, 1,690 mg/kg as calculated by study authors)	*F1 combined, mean fetal weight/litter*	0	−2	−2	−8	16*
Gavage						
Single dose on GD 8; sacrificed GD 18						
Pup body weight						
Piersma et al. (1995)	*Percent change compared to control*				
Rat (WU); 10 breeding pairs/dose	mg/kg-day	0	250	500	1,000
0, 250, 500, 1,000 mg/kg-day	*mean pup weight on PND 1*	0	−1	−7*	−29*
Gavage					
Males: 29 days (14 days premating, up to 14 days mating); females: up	*mean pup weight on PND 6*	0	3	−1	−43*

Reference and study design	Results[a]				
to 55 days (14 days premating through PND 6)	Note: The statistical unit of comparison (litter or individual pup) was not reported.				
Bayer (1998) Rat (Wistar), 28/sex/group 0, 1, 3 ppm 0, 0.11, 0.35 mg/kg-day for drinking water 0, 0.09, 0.28 mg/kg-day for diet Drinking water and diet Females dosed through mating, gestation, and lactation (males only through cohabitation with females)	*Percent change compared to control*				
	Drinking water				
	mg/kg-day	0	0.11	0.35	
	mean pup weight on PND 0				
	Males	0	0	3	
	Females	0	0	4	
	mean pup weight on PND 21				
	Males	0	2	5	
	Females	0	3	6	
	Diet				
	mg/kg-day	0	0.09	0.28	
	mean pup weight on PND 0				
	Males	0	2	3	
	Females	0	2	4	
	mean pup weight on PND 21				
	Males	0	-3	0.4	
	Females	0	-3	-0.7	
Nagao et al. (2000) Rat (Sprague-Dawley); 20–25 breeding pairs/group/ generation 0, 20, 100, 500 mg/kg-day Gavage Multigenerational study	*Percent change compared to control*				
	mg/kg-day	0	20	100	500
	F1 mean pup weight				
	males PND 0	0	0	−6*	−7*
	females PND 0	0	2	−6*	−6*
	males PND 14	0	0	−1	−8*
	females PND 14	0	1	−3	−8*
	males PND 21	0	1	−1	−7*
	females PND 21	0	1	−2	−7*
	Note: There were no significant differences in F1 body weight at PND 4 or PND 7; there were no significant differences in F2 body weight at any time point. The study authors did not state whether the litter or the individual was the statistical unit of comparison.				
Tyl et al. (2004) Rat (CD); 30 breeding pairs/group/generation	*Percent change compared to control*				
	mg/kg-day	0	50	250	750
	Litter mean pup body weight at PND 0				

Reference and study design	Results[a]				
0, 750, 3,750, 11,250 ppm 0, 50, 250, 750 mg/kg-day[b] Diet Multigenerational study					
	F1 male	0	3	−1	−9*
	F1 female	0	5	1	−7*
	F2 male	0	1	−2	−5
	F2 female	0	2	0	−5
Aso et al. (2005) Rat (Crj:CD(SD)IGS); 24 breeding pairs/group/generation 0, 100, 200, 400 mg/kg-day Gavage Multigenerational study	Note: Study authors report significant lowered bodyweights on PND 0 in F1 males ≥100 mg/kg-day and F2 males and females at 100 and 400 mg/kg-day. (Data shown graphically - Figure 1-4).				
Ahmad et al. (2014) Rat (Albino); P0, female (6/group) 0, 4, 20, 100 mg/kg Gavage GD 14 to parturition	*Percent change compared to control*				
	mg/kg-day	0	4	20	100
	F1 male, pup weight (M) PND 1	0	−3*	−4*	−5*
	F1 male, pup weight (M) PND 21	0	−13*	−22*	−16*
TNO (1998a) Rat (Wistar); P0, female (28/group) 0, 100, 1,000, 3,000 µg/L (equivalent to 0.016, 0.171, 0.489 mg/kg-day, average of reported intake over premating, gestation, and lactation) Drinking water F0 females: 2 weeks prior to mating, through mating, gestation, and lactation; F0 males: during mating; F1 animals were not treated after weaning	*Percent change compared to control*				
	mg/kg-day	0	0.016	0.171	0.489
	F1 combined pup weight PND 1	0	0	3	2
	F1 combined pup weight PND 14	0	−1	1	0
	F1 female, pup weight PND 21	0	−5	1	−3
	F1 male, pup weight PND 21	0	−1	3	0
	F1 combined pup weight preculling	0	0	5	2
	F1 combined pup weight PND 7	0	−1	4	1
TNO (1998b) Rat (Wistar); P0, female (28/group) 0, 1,000, 3,000 µg/L (equivalent to 0.190, 0.280 mg/kg-day during premating as calculated by study authors)	*Percent change compared to control*				
	mg/kg-day	0	0.190	0.280	
	F1 combined, pup weight PND 1	0	2	8	
	F1 combined, pup	0	2	9	

Reference and study design	Results[a]			
Drinking water F0 females: 2 weeks prior to mating, through mating , gestation and lactation; F0 males: mating period only; F1: did not receive additional treatment after weaning	*weight PND 4 preculling* *F1 combined, pup weight PND 7*	0	2	6

*Statistically different from controls (p <0.05), as reported by study authors.
[a]Percent change from controls calculated as 100 × ((treated value − control value) ÷ control value).
[b]Values reported by the study authors were estimated from published graphs using "Grab It!", a Microsoft Excel based free software application used to digitizes data from image files. Publisher: www.datatrendsoftware.com.

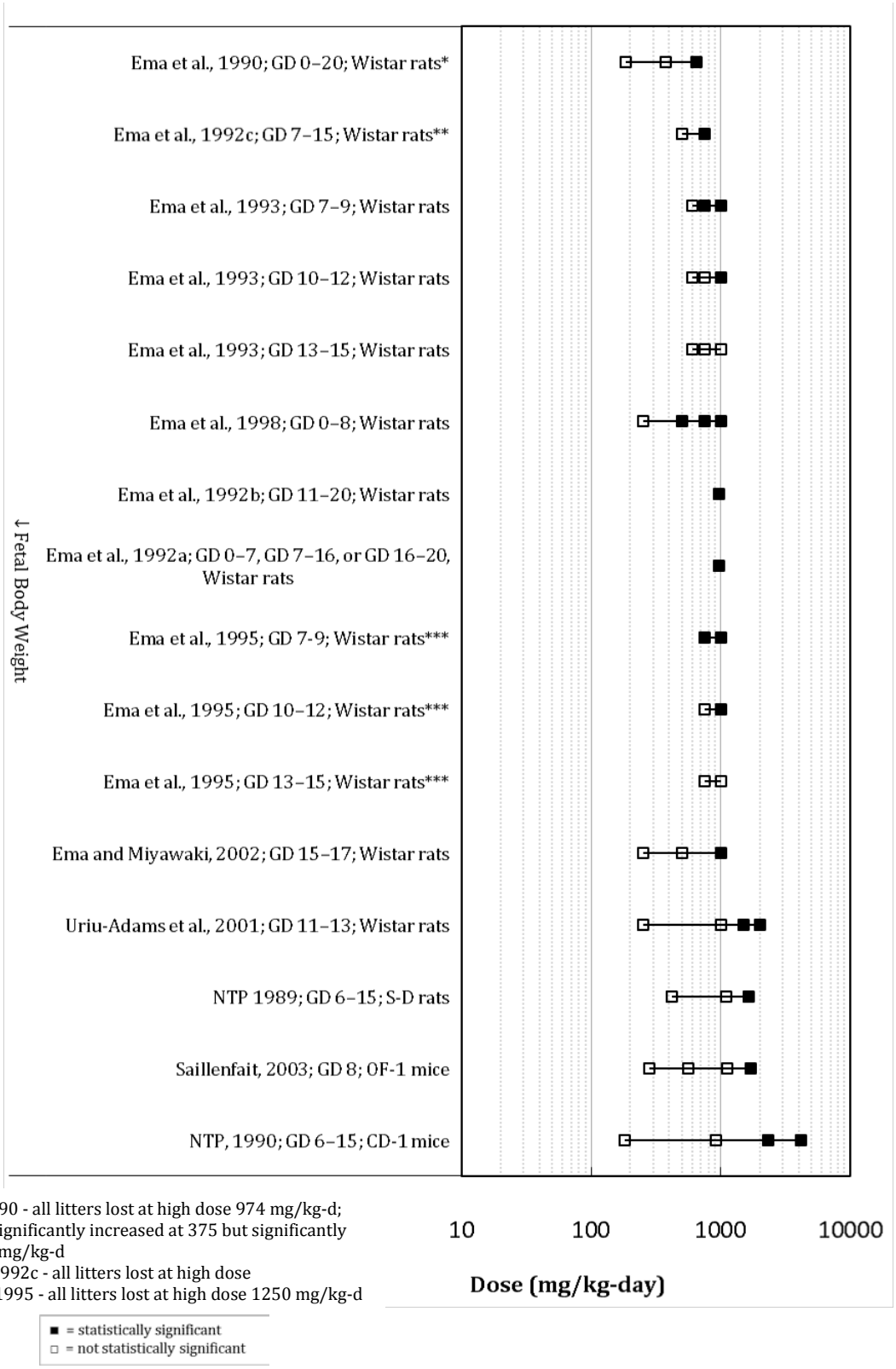

Figure 3-11. Exposure-response array of developmental effects following oral exposure to BBP: fetal body weight.

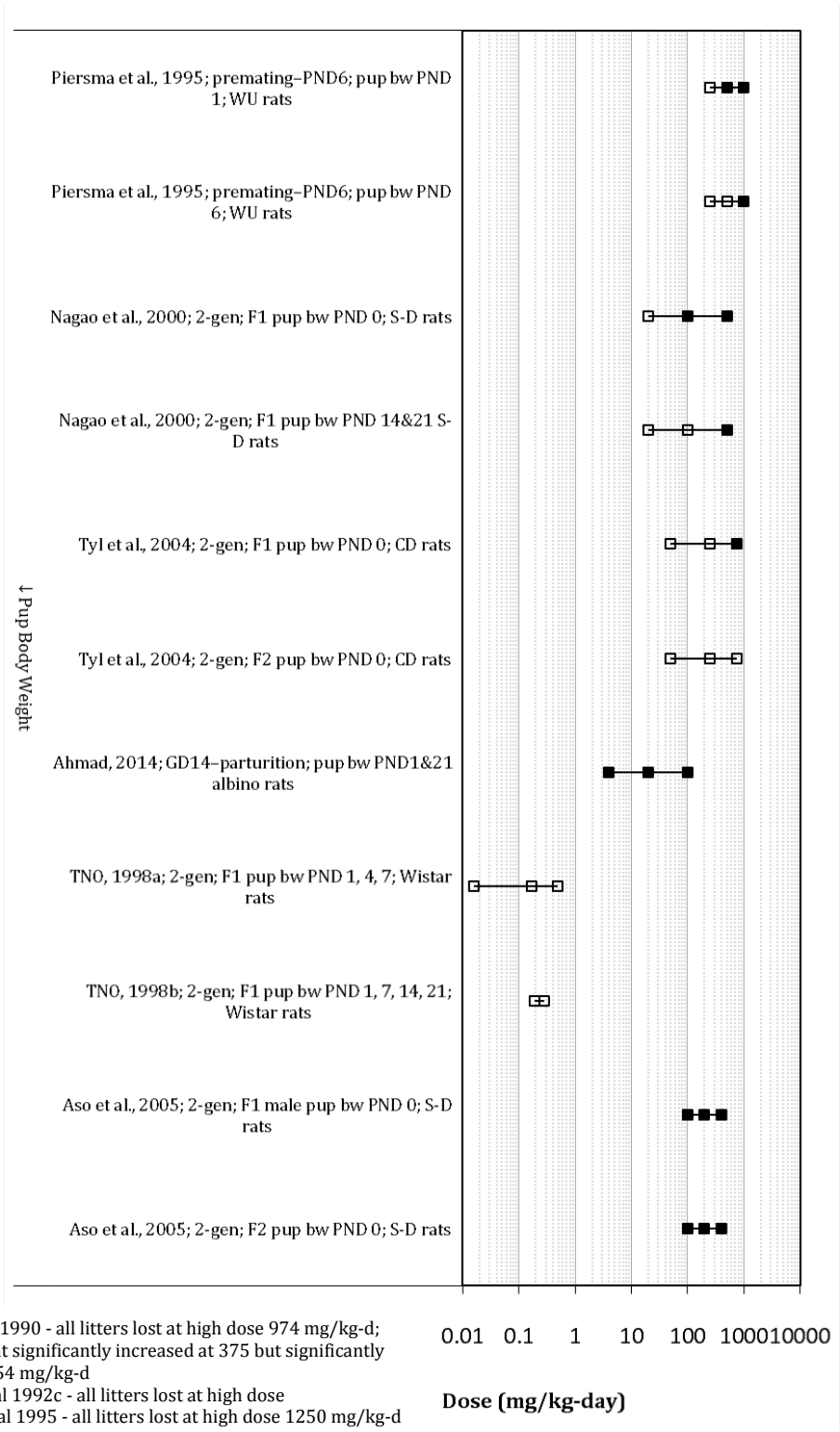

Figure 3-12. Exposure-response array of developmental effects following oral exposure to BBP: pup weight.

3.3.4. Liver Effects

Table 3-26. Evidence pertaining to liver effects in animals following oral and inhalation exposure to BBP

Reference and study design	Results[a]				
Liver weight[b]					
NTP (1989) Rat (Sprague-Dawley CD); 30 females/group 0, 420, 1,100, 1,640 mg/kg-day Diet GDs 6–15	**Maternal liver weight, GD 20** *(percent change compared to control)*				
	mg/kg-day	0	420	1,100	1,640
	absolute weight	0	4	5	1
	relative weight	0	0	7*	13*
BIBRA (1978) Rat (Wistar); 27/sex/group or 45/sex/group (control); interim sacrifices of 9 controls/sex/group and 6 treated rats/sex/group at 2 and 6 weeks 0, 2,000, 5,000 12,000 ppm 0, 151, 381, 960 mg/kg-day (males) 0, 171, 422, 1,069 mg/kg-day (females) Diet 14 weeks	**Liver weight** *(percent change compared to control)*				
	mg/kg-day (M)	0	151	381	960
	absolute weight; 2 weeks	0	0	5	17
	absolute weight; 6 weeks	0	1	−4	5
	absolute weight; 14 weeks	0	−4	−1	18*
	relative weight; 2 weeks	0	3	6	25*
	relative weight; 6 weeks	0	6*	3	19*
	relative weight; 14 weeks	0	4	8*	28*
	mg/kg-day (F)	0	171	422	1,069
	absolute weight; 2 weeks	0	5	5	11
	absolute weight; 6 weeks	0	3	7	11*
	absolute weight; 14 weeks	0	4	3	15*
	relative weight; 2 weeks	0	2	5	19*
	relative weight; 6 weeks	0	0	5	17*
	relative weight; 14 weeks	0	4*	5*	21*

Reference and study design	Results[a]					
NTP (1997b)	**Liver weight** *(percent change compared to control)*					
Rat (F344); 15 males/group	mg/kg-day	0	20	200	2,200	
0, 300, 2,800, 25,000 ppm 0, 20, 200, 2,200 mg/kg-day	*absolute weight*	0	1	0	−24*	
Diet	*relative weight*	0	2	2	6*	
10 weeks						
NTP (1997b)	**Liver weight** *(percent change compared to control)*					
Rat (F344); 15 males/group	mg/kg-day	0	30	60	180	550	ND
0, 300, 900, 2,800, 8,300, 25,000 ppm 0, 30, 60, 180, 550, "high" mg/kg-day[c]	*absolute weight*	0	7	13	3	17*	−3
	relative weight	0	2	3	3	14*	42*
Diet							
26 weeks							
NTP (1997b)	**Liver weight, 15 months** *(percent change compared to control)*					
Rat (F344); 60/sex/group; assessed in 10 rats/sex/group at 15-month interim sacrifice	mg/kg-day (Mal)e	0	120	240	500	
0, 3,000, 6,000, 12,000 ppm (males); 0, 6,000, 12,000, 24,000 ppm (females) 0, 120, 240, 500 mg/kg-day (males); 0 300, 600, 1,200 mg/kg-day (females)	*absolute weight*	0	4	0	2	
	relative weight	0	4	7	12*	
	mg/kg-day (F)	0	300	600	1,200	
	absolute weight	0	2	8	−3	
	relative weight	0	2	6	26*	
Diet						
2 years						
Tyl et al. (2004)	**Liver weight** *(percent change compared to control)*					
Rat (CD); 30 F0 and F1 parental rats/sex/group	mg/kg-day	0	50	250	750	
	Absolute weight					
0, 750, 3,750, 11,250 ppm 0, 50, 250, 750 mg/kg-day	*F0 males*	0	−1	8	13*	
	F1 males	0	1	10*	5	
Diet	*F0 females*	0	4	9	15*	
Multigenerational study	*F1 females*	0	1	8	6	
Exposure 10 weeks prior to mating and through mating, gestation, and lactation periods (females) or 21 days after mating (males)	Relative weight					
	F0 males	0	1	4	16*	
	F1 males	0	0	6	16*	
	F0 females	0	4	9	19*	

Reference and study design	Results[a]				
	F1 females	0	0	4	6
Nagao et al. (2000)	**Liver weight** *(percent change compared to control)*				
Rat (Sprague-Dawley); 25 sex/generation/group	mg/kg-day	0	20	100	500
	Absolute weight				
0, 20, 100, 500 mg/kg-day	*F0 males*	0	−3	1	11*
Gavage	*F1 males*	0	0	−8	0
Multigenerational study	*F0 females*	0	1	2	6
F0 males and females: exposure for 12 weeks prior to mating, 2 weeks cohabitation, and until necropsy at 23 weeks of age (males) or postpartum day 22 (females); F1 animals: from weaning until necropsy at PND 22	*F1 females*	0	0	−2	1
	Relative weight				
	F0 males	0	−1	1	20*
	F1 males	0	4	−1	15*
	F0 females	0	2	2	5
	F1 females	0	−1	−3	0
Aso et al. (2005)	**Liver weight** *(percent change compared to control)*				
Rat (Crj:CD(SD)IGS); 24 sex/generation/group	mg/kg-day	0	100	200	400
	Absolute weight				
0, 100, 200, 400 mg/kg-day	*F0 males*	0	5	9	14
Gavage	*F1 males*	0	5	5	12
Multigenerational study	*F0 females*	0	3	12*	11*
F0 and F1 exposed for 4 weeks prior to mating, through mating for 10 weeks, and until weaning of offspring (females) or necropsy (males)	*F1 females*	0	3	7	10
	Relative weight				
	F0 males	0	3	5	14*
	F1 males	0	5	8*	18*
	F0 females	0	3	6*	10*
	F1 females	0	−1	1	8*
Monsanto (1983)	**Liver weight** *(percent change compared to control)*				
Rat (Sprague-Dawley); 25/sex/group; interim sacrifice of 10 rats/sex/group at 7 weeks	mg/kg-day	0	51	218	789
	Absolute weight				
0, 51, 218, 789 mg/m^3	*male (7 weeks)*	0	0	7	18*
Inhalation (whole-body)	*female (7 weeks)*	0	1	4	17*
13 weeks	*male (13 weeks)*	0	9	9	24*
	female (13 weeks)	0	4	5	11*
	Relative weight				
	male (7 weeks)	0	0	10*	18*

Reference and study design	Results[a]									
	female (7 weeks)	0		1		1		13*		
	male (13 weeks)	0		7		6		21*		
	female (13 weeks)	0		4		5		12*		
NTP (1990) Mouse (Swiss albino CD-1); 28–30 females/group (except n = 14 in 4,121 group) 0, 182, 910, 2,330, 4,121 mg/kg-day Diet GDs 6–15	**Liver weight, GD 17** *(percent change compared to control)*									
	mg/kg-day	0	182	910	2,330	4,121				
	absolute weight	0	0	−1	−15*	NE				
	relative weight	0	0	2	26*	NE				
NTP (1997a) Rat (F344); 50–60/sex/group; interim sacrifice of 10 rats/sex/group at 15 months 0, 12,000 ppm (males); 0, 24,000 ppm (females) 0, 500 mg/kg-day (males); 0, 1,200 mg/kg-day (females) Diet 4 exposure protocols: ad libitum feeding, weight-matched controls, restricted feed (2 years), and restricted feed (lifetime) 2 years to lifetime	**Liver weight, ad libitum and weight-matched** *(percent change compared to control*									
	mg/kg-day (M)	0 (ad libitum)	500 (ad libitum)	0 (weight-matched)	500 (weight-matched)					
	absolute weight	0	2	0	20*					
	relative weight	0	12*	0	22*					
	mg/kg-day (F)	0 (ad libitum)	1,200 (ad libitum)	0 (weight-matched)	1,200 (weight-matched)					
	absolute weight	0	−3	0	64*					
	relative weight	0	26*	0	51*					
	Feed-restricted 2 years or lifetime *(percent change compared to control)*									
	mg/kg-day (M)	0	500							
	absolute weight	0	6							
	relative weight	0	11*							
	mg/kg-day (F)	0	1,200							
	absolute weight	0	−1							
	relative weight	0	20*							
Piersma et al. (2000) Rat (Harlan Cpb-WU); 10 females/group 0, 270, 350, 450, 580, 750, 970, 1,250, 1,600, 2,100 mg/kg-day Gavage	**Liver weight** *(percent change compared to control)*									
	mg/kg-day	0	270	350	450	580	750	970	1,250	1,600	2,100
	Relative liver weight[d]										
	short	0	8	6	6	6	11	11	19	13	22

Reference and study design	Results[a]									
GD 6–15 or 6–20	*exposure (GDs 6–15)*									
	long exposure (GDs 6–20)	0	1	5	7	13	1	16	18	31	30
	Note: No data with respect to absolute liver weight were provided by study authors.										
Ahmad et al. (2014) Rat (Albino); P0, female (6/group) 0, 4, 20, 100 mg/kg Gavage GD 14 to parturition	**Liver weight** *(percent change compared to control)*									
	mg/kg-day	0		4			20			100
	F1 male absolute liver weight	0		−3			−3			−6
TNO (1998a) Rat (Wistar); P0, female (28/group) 0, 100, 1,000, 3,000 µg/L (equivalent to 0.016, 0.171, 0.489 mg/kg-day, average of reported intake over premating, gestation, and lactation) Drinking water F0 females: 2 weeks prior to mating, through mating, gestation, and lactation; F0 males: during mating; F1 animals were not treated after weaning	**Liver weight** *(percent change compared to control)*									
	mg/kg-day	0		0.016			0.171			0.489
	Absolute weight									
	F1 female	0		3			4			2
	F1 male	0		0			4			0
	Relative weight									
	F1 female	0		1			2			1
	F1 male	0		1			3			1
Liver histopathology										
NTP (1989) Rat (Sprague-Dawley CD); 30 females/dose 0, 420, 1,100, 1,640 mg/kg-day Diet GDs 6–15	No histopathological effects were observed in the livers of control or high-dose dams (10/group); other groups were not examined.									
BIBRA (1978) Rat (Wistar); 27/sex/dose or	*Percent incidence*									
	mg/kg-day (M)	0		151			281			960

Reference and study design	Results[a]				
45/sex/group (control)	**Individual cell or focal necrosis**				
0, 2,000, 5,000, 12,000 ppm 0, 151, 381, 960 mg/kg-day (males); 0, 171, 422, 1,069 mg/kg-day (females); interim sacrifices of 9 controls/sex/group and 6 treated rats/sex/group at 2 and 6 weeks Diet 14 weeks	*2 weeks*	0	33	0	0
	6 weeks	0	17	0	83*
	14 weeks	11	7	13	50*
	Inflammatory cells				
	2 weeks	11	17	67*	0
	6 weeks	78	17*	67	67
	14 weeks	78	80	80	71
	Bile duct hyperplasia				
	6 weeks	0	17	33	33
	14 weeks	4	7	27	0
	Portal vacuolation/fatty change				
	2 weeks	0	0	0	0
	14 weeks	11	0	7	0
	Occasional foci of hemorrhage				
	14 weeks	0	0	7	0
	Percent incidence				
	mg/kg-day (F)	0	171	422	1,069
	Individual cell or focal necrosis				
	2 weeks	0	0	0	0
	6 weeks	0	0	0	0
	14 weeks	0	13	0	0
	Inflammatory cells				
	2 weeks	67	50	33	50
	6 weeks	89	50	33*	67
	14 weeks	56	67	73	53
	Bile duct hyperplasia				
	6 weeks	0	0	0	0
	14 weeks	0	0	0	0
	Portal vacuolation/fatty change				
	2 weeks	11	0	0	0
	14 weeks	11	7	0	0
	Occasional foci of hemorrhage				

Reference and study design	Results[a]				
	14 weeks	0	0	0	0
NTP (1997b) Rat (F344); 15 males/group 0, 300, 2,800, 25,000 ppm 0, 20, 200, 2,200 mg/kg-day Diet 10 weeks	No significant effects were reported by study authors in control or high-dose animals (quantitative data not shown).				
NTP (1997b) Rat (F344); 15 males/dose 0, 300, 900, 2,800, 8,300, 25,000 ppm 0, 30, 60, 180, 550, "high" mg/kg-day[c] Diet 26 weeks	No significant effects were reported by study authors in control or high-dose animals (quantitative data not shown).				
NTP (1997b) Rat (F344); 60/sex/group 0, 3,000, 6,000, 12,000 ppm (males); 0, 6,000, 12,000, 24,000 ppm (females) 0, 120, 240, 500 mg/kg-day (males); 0 300, 600, 1,200 mg/kg-day (females) Diet 2 years	*Percent incidence at study termination*				
	mg/kg-day (M)	0	120	240	500
	granuloma	0	0	0	14
	mg/kg-day (F)	0	300	600	1,200
	cytoplasmic vacuolization of hepatocytes	14	12	4	0
	Note: At 2 years, the incidences of granulomas (in males) and cytoplasmic vacuolization of hepatocytes (in females) were not considered significant by the study authors.				
Tyl et al. (2004) Rat (CD); 30 F0 F1 parental rats/sex/dose 0, 750, 3,750, 11,250 ppm 0, 50, 250, 750 mg/kg-day Diet Multigenerational study Exposure 10 weeks prior to mating and through mating, gestation, and lactation periods (females) or through 21 days after end of mating (males)	*Percent incidence at study termination*				
	mg/kg-day	0	50	250	750
	Histopathological lesions[e]				
	F0 males	0	0	0	28
	F1 males	0	0	0	0
	F0 females	3	0	7	30
	F1 females	0	0	0	17

Reference and study design	Results[a]				
Nagao et al. (2000) Rat (Sprague-Dawley); 25 sex/generation/group; assessed in 10 control and high-dose rats/sex/group 0, 20, 100, 500 mg/kg-day Gavage Multigenerational study F0 males and females: exposure for 12 weeks prior to mating, 2 weeks cohabitation, and until necropsy at 23 weeks of age (males) or postpartum day 22 (females); F1 animals: exposure from weaning until necropsy	*Percent incidence*				
	mg/kg-day	0	20	100	500
	Fatty change; periportal				
	F0 males	30	NE	NE	0
	F1 males	20	NE	NE	0
	Fibrosis; capsule/subcapsule; diaphragmatic nodule				
	F0 females	10	NE	NE	0
	Granulation; subcapsule; focal				
	F0 females	10	NE	NE	0
	F1 females	10	NE	NE	0
Aso et al. (2005) Rat (Crj:CD(SD)IGS); 24 sex/generation/group 0, 100, 200, 400 mg/kg-day Gavage Multigenerational study F0 and F1 exposed for 4 weeks prior to mating, through mating for 10 weeks, and until weaning of offspring (females) or necropsy (males)	No significant treatment-related effects were observed by the study authors in F0 or F1 parental males or females (quantitative data not reported).				
Monsanto (1983) Rat (Sprague-Dawley); 25/sex/group; interim sacrifice of 10 rats/sex/group at 7 weeks 0, 51, 218, 789 mg/m^3 Inhalation (whole-body) 13 weeks	*Percent incidence*				
	mg/kg-day (M)	0	51	218	789
	tiny granulomas, 7 weeks	20	30	20	0
	tiny granulomas, 13 weeks	7	0	7	7
	focal necrosis, 7 weeks	0	0	0	0
	lymphoid focus, 7 weeks	0	0	10	0
	mg/kg-day (F)				
	tiny granulomas, 7 weeks	30	20	10	0

Reference and study design	Results[a]			
	tiny granulomas, 13 weeks (focal)	0	7	0	7
	focal necrosis, 7 weeks	0	10	0	0
	lymphoid focus, 7 weeks	0	0	0	0
NTP (1990) Mouse (Swiss albino CD-1); 28–30 females/group (except n = 14 in 4,121 group); assessed in 10 dams/group (except the high-dose) 0, 182, 910, 2,330, 4,121 mg/kg-day Diet GDs 6–15; necropsy at GD 17	No significant treatment-related effects were observed by study authors (quantitative data not reported).			
NTP (1997a) Rat (F344); 50–60/sex/group; interim sacrifice of 10 rats/sex/group at 15 months 0, 12,000 ppm (males); 0, 24,000 ppm (females) 0, 500 mg/kg-day (males); 0, 1,200 mg/kg-day (females) Diet 4 exposure protocols: ad libitum feeding, weight-matched controls, restricted feed (2 years), and restricted feed (lifetime) 2 years to lifetime	*Percent incidence (ad libitum and weight-matched protocols)*			
	mg/kg-day (M)	0 (ad libitum)	0 (weight-matched)	500
	15 months			
	basophilic focus	60	20	10
	granuloma	0	0	10
	inflammation; subacute	0	10	10
	hepatocyte; cytoplasmic vacuolization	20	30	0
	lobules, necrosis	0	0	20
	2 years			
	basophilic focus	44	40	28
	granuloma	0	0	14
	inflammation; subacute	0	0	8
	hepatocyte; cytoplasmic vacuolization	12	18	8
	lobules, necrosis	4	4	2
	Percent incidence (ad libitum and weight-matched protocols)			

Reference and study design	Results[a]			
	mg/kg-day (F)	0 (ad libitum)	0 (weight-matched)	1,200
	15 months			
	basophilic focus	100	70	90
	granuloma	10	20	0
	2 years			
	centrilobular; necrosis	2	4	0
	hepatocyte; vacuolization cytoplasmic	14	2	0
	lobules, necrosis	12	2	12
	Percent incidence (Feed-restricted; 2 years or lifetime protocols)			
	mg/kg-day (M)	0 (2 years)	500 (2 years)	0 (lifetime)	500 (lifetime)
	15 months				
	basophilic focus	10	0	NA	NA
	granuloma	0	10	NA	NA
	hepatocyte; vacuolization cytoplasmic	20	0	NA	NA
	At study termination (2 years or lifetime)				
	basophilic focus	32	30	14	24
	granuloma	2	0	2	6
	inflammation; subacute	4	4	0	0
	hepatocyte; vacuolization cytoplasmic	8	0	4	8
	lobules, necrosis	2	6	10	10
	Percent incidence (Feed-restricted; 2 years or lifetime protocols)				
	mg/kg-day (F)	0 (2 years)	1,200 (2 years)	0 (lifetime)	1,200 (lifetime)
	15 months				
	basophilic focus	100	30	NA	NA
	granuloma	10	0	NA	NA
	inflammation; subacute	10	0	NA	NA

Reference and study design	Results[a]				
	At study termination (2 years or lifetime)				
	basophilic focus	80	82	64	76
	granuloma	16	16	22	10
	inflammation; subacute	6	6	2	0
	centrilobular; necrosis	0	0	2	0
	hepatocyte; vacuolization cytoplasmic	0	2	12	0
	lobules, necrosis	12	4	8	8
NTP (1982)	*Percent incidence*				
F344 rats; 50 sex/group	mg/kg-day (F)	0	550	1,100	
0, 6,000, 12,000 ppm 0, 474, 947 mg/kg-day (males); 0, 550, 1,100 mg/kg-day (females)	*necrosis; NOS*	0	2	0	
	necrosis; focal	4	0	4	
	necrosis; diffuse	0	2	0	
Diet	*basophilic cyto change*	88	69	70	
28 weeks (males) or 103 weeks (females)	Note: Males were not examined histopathologically.				
NTP (1982)	*Percent incidence at study termination*				
B6C3F$_1$ mice; 50 sex/group	mg/kg-day (M)	0	474	947	
0, 6,000, 12,000 ppm 0, 474, 947 mg/kg-day (males); 0, 550, 1,100 mg/kg-day (females)	*necrosis; focal*	2	0	0	
	necrosis; hemorrhagic	0	2	0	
Diet	mg/kg-day (F)	0	550	1,100	
103 weeks	*necrosis; NOS*	0	0	2	
	necrosis; focal	2	0	0	

*Statistically significant (p <0.05) relative to controls based on statistics performed by the study authors.
[a]Percent change compared to control calculated as 100 × ([treated value − control value] ÷ control value).
[b]All studies reported relative weight in addition to absolute weight; where patterns were similar only relative weight is included in this table.
[c]The high-dose group corresponds to 25,000 ppm BBP; a reliable estimate of dose could not be calculated. The study authors estimated doses for all but the high-dose group based on measured body weights and food consumption. Food consumption was not measured in the 25,000 ppm BBP group due to excessive scattering of feed, and because the mean body weight of this group was 30% lower than controls.
[d] Values reported by the study authors were estimated from published graphs using "Grab It!", a Microsoft Excel based free software application used to digitizes data from image files. Publisher: www.datatrendsoftware.com.

[e]Histopathology reported by (Tyl et al. (2004)) includes: subtle to slight changes including diffuse cytomegaly, variable karyomegaly, reduced cytoplasmic glycogen, increased cytoplasmic eosinophilia (increased numbers of peroxisomes), increased cytoplasmic granularity.

F = female(s); M = male(s); ND = not determined; NE = not examined; NA = not applicable, NOS = not otherwise specified

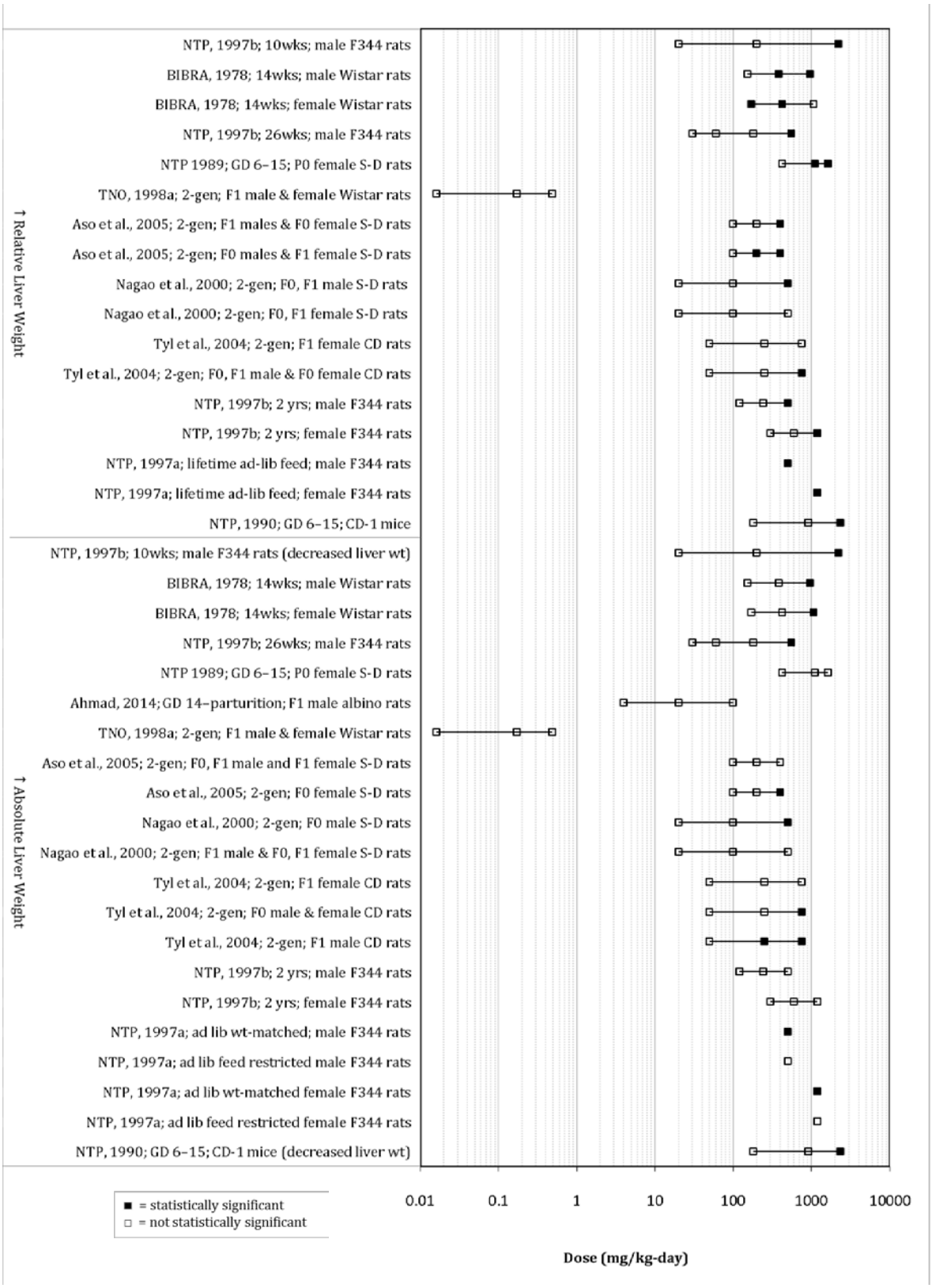

Figure 3-13. Exposure-response array of liver weight effects following oral exposure to BBP.

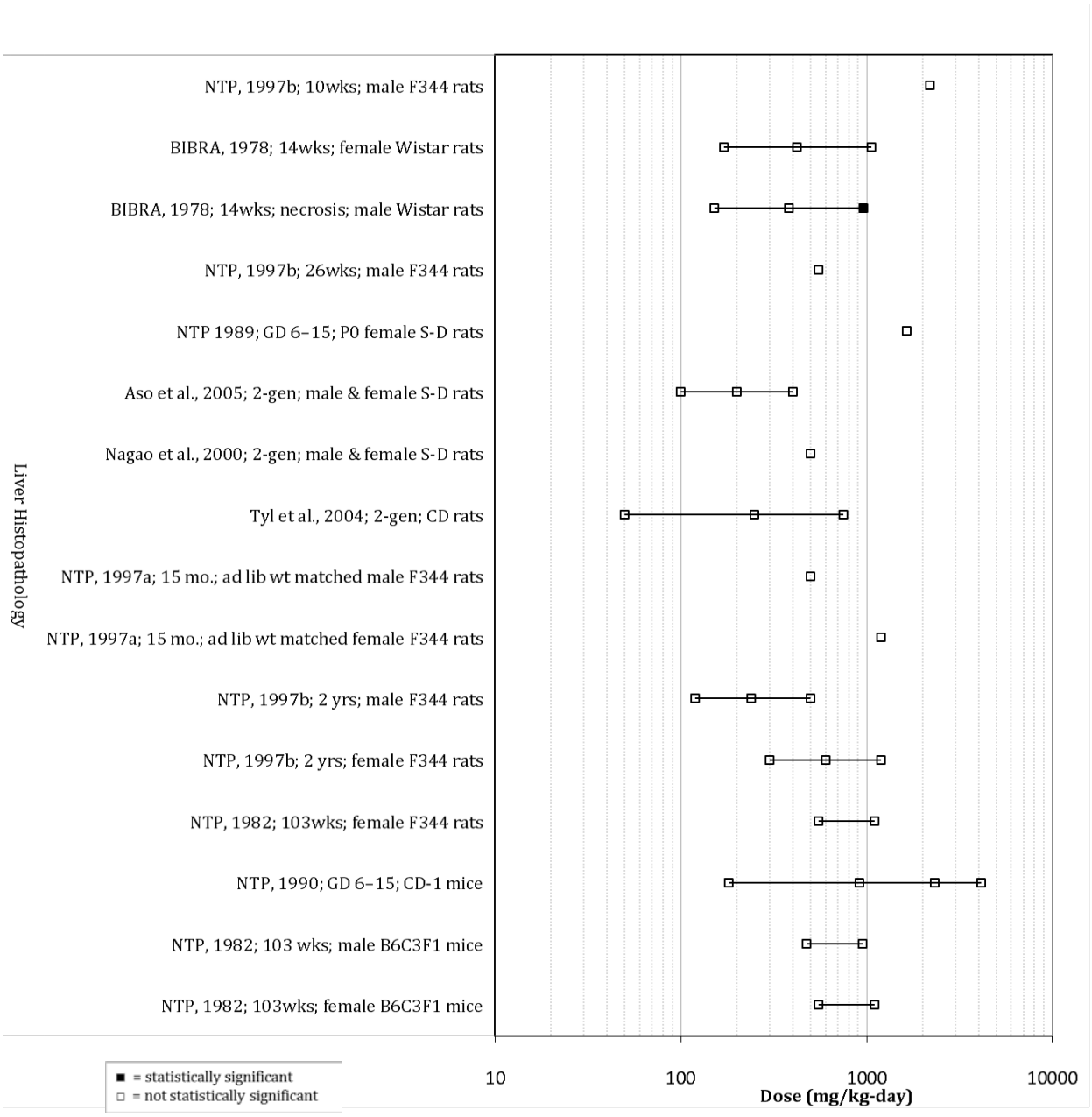

Figure 3-14. Exposure-response array of liver histopathological effects following oral exposure to BBP.

3.3.5. Kidney Effects

Table 3-27. Evidence pertaining to kidney effects in animals following oral and inhalation exposure to BBP

Reference and study design	Results				
Kidney weight[a,b]					
BIBRA (1978) Rat (Wistar); 27/sex/dose or 45/sex/group (control); interim sacrifices of 9 controls/sex/group and 6 treated rats/sex/group at 2 and 6 weeks 0, 2,000, 5,000, 12,000 ppm 0, 151, 381, 960 mg/kg-day (males); 0, 171, 422, 1,069 mg/kg-day (females) Diet 14 weeks	**Kidney weight** *(percent change compared to control)*				
	mg/kg-day (M)	0	151	381	960
	absolute weight, 2 weeks	0	3	6	1
	absolute weight, 6 weeks	0	2	0	−5
	absolute weight, 14 weeks	0	−2	1	4
	relative weight, 2 weeks	0	6	7*	6
	relative weight, 6 weeks	0	7*	7*	8*
	relative weight, 14 weeks	0	6	8*	12*
	mg/kg-day (F)	0	171	422	1,069
	absolute weight, 2 weeks	0	7	3	−1
	absolute weight, 6 weeks	0	7	6	5
	absolute weight, 14 weeks	0	2	6	12*
	relative weight, 2 weeks	0	3	3	6
	relative weight, 6 weeks	0	4	3	10*
	relative weight, 14 weeks	0	3	8*	19*
NTP (1997b) Rat (F344); 15 males/group 0, 300, 2,800, 25,000 ppm 0, 20, 200, 2,200 mg/kg-day Diet 10 weeks	**Right kidney weight** *(percent change compared to control)*				
	mg/kg-day	0	20	200	2,200
	absolute weight	0	−2	3	−25*
	relative weight	0	−1	5	6

Reference and study design	Results						
NTP (1997b) Rat (F344); 15 males/group 0, 300, 900, 2,800, 8,300, 25,000 ppm 0, 30, 60, 180, 550, "high" mg/kg-day[d] Diet 26 weeks	**Right kidney weight** *(percent change compared to control)*						
	mg/kg-day	0	30	60	180	550	ND
	absolute weight	0	0	7	−2	11	−20*
	relative weight	0	−5	−2	−3	8	18*
NTP (1997b) Rat (F344); 60/sex/group; assessed in 10 rats/sex/group at 15-month interim sacrifice 0, 3,000, 6,000, 12,000 ppm (males); 0, 6,000, 12,000, 24,000 ppm (females) 0, 120, 240, 500 mg/kg-day (males); 0 300, 600, 1,200 mg/kg-day (females) Diet 2 years	**Right kidney weight, 15 months** *(percent change compared to control)*						
	mg/kg-day (M)	0		120		240	500
	absolute weight	0		10		4	6
	relative weight	0		9*		10*	16*
	mg/kg-day (F)	0		300		600	1,200
	absolute weight	0		8		9*	−7
	relative weight	0		8		7	21*
Tyl et al. (2004) Rat (CD); 30 F0 and F1 parental rats/sex/group 0, 750, 3,750, 11,250 ppm 0, 50, 250, 750 mg/kg-day Diet Multigenerational study Exposure 10 weeks prior to mating and through mating, gestation, and lactation (females) or through 21 days after end of mating (males)	**Kidney weight** *(percent change compared to control)*						
	mg/kg-day	0		50		250	750
	Absolute weight						
	F0 males	0		−3		7*	8*
	F1 males	0		3		12*	−4
	F0 females	0		2		6*	6
	F1 females	0		2		8*	6
	Relative weight						
	F0 males	0		−1		3	10*
	F1 males	0		2		7*	5
	F0 females	0		2		6*	9*
	F1 females	0		1		5	4

Reference and study design	Results				
Nagao et al. (2000) Rat (Sprague-Dawley); 25 sex/generation/group 0, 20, 100, 500 mg/kg-day Gavage Multigenerational study F0 males and females: exposure for 12 weeks prior to mating, 2 weeks cohabitation, and until necropsy at 23 weeks of age (males) or postpartum day 22 (females); F1 animals: exposure from weaning until necropsy	**Kidney weight** *(percent change compared to control)*				
	mg/kg-day	0	20	100	500
	Absolute weight				
	F0 males	0	−3	2	7
	F1 males	0	0	1	4
	F0 females	0	3	7*	7*
	F1 females	0	1	6	4
	Relative weight				
	F0 males	0	−2	2	14
	F1 males	0	4	9*	18*
	F0 females	0	5	8*	6*
	F1 females	0	0	5	5
Aso et al. (2005) Rat (Crj:CD(SD)IGS); 24 sex/generation/group 0, 100, 200, 400 mg/kg-day Gavage Multigenerational study F0 and F1 exposed for 4 weeks prior to mating, through mating for 10 weeks, and until weaning of offspring (females) or necropsy (males)	**Kidney weight** *(percent change compared to control)*				
	mg/kg-day	0	100	200	400
	Absolute weight				
	F0 males left kidney	0	6	8*	9*
	F1 males left kidney	0	−1	0	0
	F0 females left kidney	0	17	12*	12*
	F1 females left kidney	0	6	7	6
	F0 males right kidney	0	4	7	8
	F1 males right kidney	0	0	0	0
	F0 females right kidney	0	3	11*	8*
	F1 females right kidney	0	9	12	5
	Relative weight				
	F0 males left kidney	0	3	7	10*
	F1 males left kidney	0	0	0	3
	F0 females left kidney	0	6	6	12*

Reference and study design	Results				
	F1 females left kidney	0	3	3	6
	F0 males right kidney	0	3	3	10
	F1 males right kidney	0	0	0	3
	F0 females right kidney	0	3	6	6*
	F1 females right kidney	0	3	6	3
Monsanto (1983) Rat (Sprague-Dawley); 25/sex/group; interim sacrifice of 10 rats/sex/group at 7 weeks 0, 51, 218, 789 mg/m^3 Inhalation (whole-body) 13 weeks	**Kidney weight** *(percent change compared to control)*				
	mg/kg-day	0	51	218	789
	Absolute weight, left kidney				
	males, 7 weeks	0	2	8	22*
	females, 7 weeks	0	−2	8	13
	males, 13 weeks	0	5	8	18*
	females, 13 weeks	0	3	6	14*
	Absolute weight, right kidney				
	males, 7 weeks	0	1	11*	21*
	females, 7 weeks	0	0	10	12*
	males, 13 weeks	0	1	7	17*
	females, 13 weeks	0	4	7	12*
	Relative weight, left Kidney				
	males, 7 weeks	0	3	11*	22*
	females, 7 weeks	0	−2	4	10
	males, 13 weeks	0	3	5	15*
	females, 13 weeks	0	3	7	15*
	Relative weight, right kidney				
	males, 7 weeks	0	1	13*	20*
	females, 7 weeks	0	0	6	9
	males, 13 weeks	0	0	4	14*
	females, 13 weeks	0	4	8	13*

Reference and study design	Results				
NTP (1989) Rat (Sprague-Dawley CD); 30 females/group 0, 420, 1,100, 1,640 mg/kg-day Diet GDs 6–15	**Kidney weight** *(percent change compared to control)*				
	mg/kg-day (Maternal)	0	420	1,100	16,40
	Absolute weight				
	left kidney	0	1	2	2
	right kidney	0	2	2	2
	Relative weight				
	left kidney	0	0	7	20*
	right kidney	0	0	3	16*
NTP (1990) Mouse (Swiss albino CD-1); 28–30 females/group (except n = 14 in 4,121 mg/kg-day group) 0, 182, 910, 2,330, 4,121 mg/kg-day Diet GDs 6–15	*Right kidney weight, GD 17 (percent change compared to control)*				
	mg/kg-day	0	182	910	2,330	4,121
	absolute weight	0	0	5	10	NE
	relative weight	0	0	8	62*	NE
NTP (1997a) Rat (F344); 50–60/sex/group; interim sacrifice of 10 rats/sex/group at 15 months 0, 12,000 ppm (males); 0, 24,000 ppm (females) 0, 500 mg/kg-day (males); 0, 1,200 mg/kg-day (females) Diet 4 exposure protocols: ad libitum feeding, weight-matched controls, restricted feed (2 years), and restricted feed (lifetime) Diet 2 years	*Kidney weight, ad libitum and weight-matched (percent change compared to control)*				
	mg/kg-day (M)	0 (ad libitum)	500 (ad libitum)	0 (weight matched)	500 (weight matched)
	absolute weight	0	6	0	20*
	relative weight	0	16*	0	15*
	mg/kg-day (F)	0 (ad libitum)	1,200 (ad libitum)	0 (weight matched)	1,200 (weight matched)
	absolute weight	0	−6	0	30*
	relative weight	0	22*	0	20*
	Kidney weight, Feed-restricted; 2 years or lifetime (percent change compared to control)				
	mg/kg-day (M)	0		500	
	absolute weight	0		12*	
	relative weight	0		17*	

Reference and study design	Results									
	mg/kg-day (F)			0				1200		
	absolute weight			0				−4		
	relative weight			0				16*		
Piersma et al. (2000)	*Percent change compared to control*									
Rat (Harlan Cpb-WU); 10 females/group	mg/kg-day	0	270	350	450	580	750	970	1,250	1,600	2,100
1, 270, 350, 450, 580, 750, 970,1,250, 1,600, 2,100 mg/kg-day	Relative kidney weight[c]										
Gavage	*short exposure (GDs 6–15)*	0	2	1	4	10	10	16	20	19	33
GDs 6–15 or 6–20; dams sacrificed on GD 21	*long exposure (GDs 6–20)*	0	−1	−3	2	6	11	14	20	36	24
	Note: No data with respect to absolute kidney weight were provided by study authors.										
Ahmad et al. (2014)	*Kidney weight (percent change compared to control)*										
Rat (Albino); P0, female (6/group)	mg/kg-day			0			4		20		100
0, 4, 20, 100 mg/kg	F1 male absolute weight			0			−1		−1		−11*
Gavage											
GD 14 to parturition											
TNO (1998a)	*Kidney weight (percent change compared to control)*										
Rat (Wistar); P0, female (28/group)	mg/kg-day			0			0.016		0.160		0.481
0, 100, 1,000, 3,000 µg/L (equivalent to 0.016, 0.171, 0.489 mg/kg-day, average of reported intake over premating, gestation, and lactation)	Absolute weight										
	F1 female			0			−3		1		1
	F1 male			0			−2		4		1
Drinking water	Relative weight										
F0 females: 2 weeks prior to mating, through mating, gestation, and lactation; F0 males: during mating; F1 animals were not treated after weaning	*F1 female*			0			−4*		−1		0
	F1 male			0			−1		3		2

Reference and study design	Results				
Kidney histopathology					
NTP (1997b) Rat (F344); 60/sex/dose; assessed in 10 rats/sex/group at 15-month interim sacrifice and 50 rats/sex/group at study termination 0, 3,000, 6,000, 12,000 ppm (males); 0, 6,000, 12,000, 24,000 ppm (females) 0, 120, 240, 500 mg/kg-day (males); 0 300, 600, 1,200 mg/kg-day (females) Diet 2 years	*Percent incidence*				
	mg/kg-day (M)	0	120	240	500
	nephropathy, 15 months	100	100	100	90
	renal tubule; pigmentation, 15 months	100	100	100	100
	nephropathy, 2 years	96	94	100	96
	renal tubule; pigmentation, 2 years	98	96	100	100
	mineralization, 2 years	0	2	4	0
	transitional epithelium hyperplasia, 2 years	12	20	12	2
	mg/kg-day (F)	0	300	600	1,200
	nephropathy, 15 months	70	100	100	100
	renal tubule; pigmentation, 15 months	100	100	100	100
	mineralization, 15 months	100	90	90	80
	nephropathy, 2 years	68	94*	86*	90*
	renal tubule; pigmentation, 2 years	98	98	98	94
	mineralization, 2 years	86	68*	74	70*
	transitional epithelium hyperplasia, 2 years	0	6	14*	8
Nagao et al. (2000) Rat (Sprague-Dawley); 25 sex/generation/group; assessed in 10 control and high-dose rats/sex	*Percent incidence*				
	mg/kg-day (M)	0	20	100	500
	Basophilic tubule in cortex				
	F0	NA	NE	NE	NA

Reference and study design	Results				
0, 20, 100, 500 mg/kg-day Gavage Multigenerational study F0 males and females: exposure for 12 weeks prior to mating, 2 weeks cohabitation, and until necropsy at 23 weeks of age (males) or postpartum day 22 (females); F1 animals: exposure from weaning until necropsy	*F1*	100	NE	NE	100*
	Cast, cortex/medulla				
	F0	20	NE	NE	40
	F1	20	NE	NE	40
	Eosinophilic bodies				
	F0	70	NE	NE	50
	F1	30	NE	NE	10
	Mineralization				
	F0	30	NE	NE	0
	F1	40	NE	NE	30
	Cyst; medulla				
	F0	10	NE	NE	0
	Degeneration; vacuolar, with hyaline droplet; proximal tubular epithelium				
	F0	10	NE	NE	0
	Cellular infiltration, lymphocyte, interstitium				
	F1	0	NE	NE	10
	Dilatation, renal pelvis				
	F1	10	NE	NE	10
	Fibrosis; focal, subcapsule				
	F1	10	NE	NE	0
	mg/kg-day (F)	0	20	100	500
	Basophilic tubule in cortex				
	F0	20	NE	NE	50
	F1	40	NE	NE	50
	Fibrosis; focal, subcapsule				
	F0	10	NE	NE	0
	Mineralization; papilla				
	F1	20	NE	NE	0
	Dilatation; renal pelvis; right side				
	F1	10	NE	NE	0
	Dilatation, collecting tubule, medulla, and papilla				
	F1	0	NE	NE	10

Reference and study design	Results				
Hotchkiss et al. (2004) Rat (Sprague-Dawley); 6 litters/group 0, 500 mg/kg-day Gavage GDs 14–18	*Percent incidence in male offspring at 3 months of age*				
	mg/kg-day	0		500	
	hydronephrosis	3		30*	
	Note: Individual percent incidence was calculated on a per animal basis and included both left and right tissues.				
BIBRA (1978) Rat (Wistar); 27/sex/dose or 45/sex/group (control); interim sacrifices of 9 controls/sex/group and 6 treated rats/sex/group at 2 and 6 weeks 0, 2,000, 5,000, 12,000 ppm 0, 151, 381, 960 mg/kg-day (males)[c] 0, 171, 422, 1,069 mg/kg-day (females) Diet 14 weeks	*Percent incidence*				
	mg/kg-day (M)	0	151	381	960
	Early nephrosis				
	2 weeks	33	33	17	0
	6 weeks	67	17	17	17
	14 weeks	33	67	33	14
	Basophilia and tubular hyperplasia				
	2 weeks	44	50	33	17
	6 weeks	0	33	83*	33
	14 weeks	26	0	0	43
	Foci of inflammatory cells				
	2 weeks	0	17	0	0
	6 weeks	0	17	0	0
	14 weeks	0	7	0	7
	Foci of calcium at corticomedullary junction				
	14 weeks	0	0	0	0
	Transitional cell hyperplasia				
	14 weeks	0	7	0	0
	mg/kg-day (F)	0	171	422	1,069
	Early nephrosis				
	2 weeks	0	0	17	17
	6 weeks	0	0	0	0
	14 weeks	7	0	0	0
	Basophilia and tubular hyperplasia				
	2 weeks	33	50	33	33
	6 weeks	11	17	0	0

Reference and study design	Results			
	14 weeks	0	7	13	0
	Foci of inflammatory cells				
	2 weeks	0	0	0	0
	6 weeks	0	0	0	17
	14 weeks	0	0	0	0
	Foci of calcium at corticomedullary junction				
	14 weeks	0	0	0	7
	Transitional cell hyperplasia				
	14 weeks	0	0	0	0
NTP (1997a) Rat (F344); 50–60/sex/group; interim sacrifice of 10 rats/sex/group at 15 months 0, 12,000 ppm (males); 0, 24,000 ppm (females) 0, 500 mg/kg-day (males); 0, 1,200 mg/kg-day (females) Diet 4 exposure protocols: ad libitum feeding, weight-matched controls, restricted feed (2 years), and restricted feed (lifetime) 2 years to lifetime	*Percent incidence*			
	Ad libitum and weight-matched			
	mg/kg-day (M)	0 (ad libitum)	0 (weight matched)	500
	nephropathy, 15 months	100	90	90
	inflammation; suppurative, 2 years	0	2	8
	mineralization, 2 years	0	2	0
	nephropathy, 2 years	96	96	96
	transitional epithelium; hyperplasia, 2 years	12	0	2
	mg/kg-day (F)	0 (ad libitum)	0 (weight matched)	1,200
	mineralization, 15 months	100	90	80
	nephropathy, 15 months	70	20	100
	hydronephrosis, 2 years	0	4	2
	mineralization, 2 years	86	98	70
	nephropathy, 2 years	68	64	90

Reference and study design	Results				
	transitional epithelium; hyperplasia, 2 years	0	8		8
	Feed-restricted; 2 years or lifetime				
	mg/kg-day (M)	0 (2 years)	500 (2 years)	0 (lifetime)	500 (lifetime)
	mineralization, 15 months	0	10	NA	NA
	nephropathy, 15 months	80	100	NA	NA
	hydronephrosis, 2 years	0	0	0	2
	mineralization, 2 years	10	8	12	10
	nephropathy, 2 years	86	92	98	98
	transitional epithelium; hyperplasia, 2 years	2	4	4	2
	Feed-restricted; 2 years or lifetime				
	mg/kg-day (F)	0 (2 years)	1,200 (2 years)	0 (lifetime)	1,200 (lifetime)
	mineralization, 15 months	100	80	NA	NA
	nephropathy, 15 months	100	90	NA	NA
	hydronephrosis, 2 years	0	2	0	0
	inflammation; suppurative	0	0	0	4
	mineralization, 2 years	92	68	90	62
	transitional epithelium; hyperplasia, 2 years	2	40	4	58
Monsanto (1983)	*Percent incidence*				
Rat (Sprague-Dawley); 25/sex/group; interim sacrifice of 10 rats/sex/group at 7 weeks	mg/kg-day (M)	0	51	218	789
	Focal scar				
0, 51, 218, 789 mg/m^3	*6 weeks*	10	0	10	0

Reference and study design	Results				
Inhalation (whole-body)	**Lymphoid foci**				
13 weeks	*6 weeks*	10	0	0	10
	13 weeks	0	7	0	7
	Tubular basophilia				
	6 weeks	20	0	0	0
	13 weeks	7	0	0	0
	Small cysts				
	6 weeks	0	0	0	0
	13 weeks	0	7	0	0
	Pelvic dilation				
	6 weeks	10	0	0	10
	13 weeks	0	0	7	7
	Tiny granuloma				
	13 weeks	0	0	7	0
	Focal interstitial nephritis				
	13 weeks	0	0	0	7
	Percent incidence				
	mg/kg-day (F)	0	51	218	789
	Focal Scar				
	6 weeks	0	0	0	0
	Lymphoid foci				
	6 weeks	0	0	10	0
	13 weeks	0	7	0	0
	Tubular basophilia				
	6 weeks	10	0	0	0
	13 weeks	0	0	0	0
	Small cysts				
	6 weeks	20	0	0	10
	13 weeks	0	7	0	0
	Pelvic dilation				
	6 weeks	10	0	0	10
	13 weeks	7	0	0	0
	Tiny granuloma				

Reference and study design	Results			
	13 weeks	0	0	0	0
	Focal interstitial nephritis				
	13 weeks	0	0	0	0
NTP (1982) B6C3F$_1$ mice, 50/sex/group 0, 6,000, 12,000 ppm 0, 474, 947 mg/kg-day (males); 0, 550, 1,100 mg/kg-day (females) Diet 103 weeks	*Percent incidence*			
	mg/kg-day (M)	0	474	947
	mineralization	2	0	0
	inflammation, interstitial	2	2	21
	nephropathy	0	2	0
	mg/kg-day (F)	0	550	1,100
	mineralization	0	0	2
	inflammation, interstitial;	2	2	6
	nephropathy	2	0	0
	tubule; regeneration; NOS	0	2	0
NTP (1982) F344 rats; 50 sex/group 0, 6,000, 12,000 ppm 0, 474, 947 mg/kg-day (males); 0, 550, 1,100 mg/kg-day (females) Diet 28 weeks (males) or 103 weeks (females)	*Percent incidence*			
	mg/kg-day (F)	0	550	1,100
	mineralization	2	0	2
	hydronephrosis	0	2	0
	inflammation, interstitial;	0	0	2
	nephropathy	68	64	40
	tubule; regeneration; NOS	2	2	0
	Note: Males were not examined histopathologically.			
Tyl et al. (2004) Rat (CD); 30 F0 and F1 parental rats/sex/group 0, 750, 3,750, 11,250 ppm 0, 50, 250, 750 mg/kg-day Diet Multigenerational study	No significant treatment-related effects were observed by study authors in F0 or F1 parental males or females (quantitative data not reported).			

Reference and study design	Results
Exposure 10 weeks prior to mating and through mating, gestation, and lactation (females) or through 21 days after end of mating (males)	
Aso et al. (2005) Rat (Crj:CD(SD)IGS); 24 sex/generation/group 0, 100, 200, 400 mg/kg-day Gavage Multigenerational study F0 and F1 exposed for 4 weeks prior to mating, through mating for 10 weeks, and until weaning of offspring (females) or necropsy (males)	No significant treatment-related effects were observed by study authors in F0 or F1 parental males or females (quantitative data not reported).
NTP (1990) Mouse (Swiss albino CD-1); 28–30 females/group (except n = 14 in 4,121 mg/kg-day group); assessed in 10 dams/group (except the high-dose) 0, 182, 910, 2,330, 4,121 mg/kg-day Diet GDs 6–15	Histopathology at GD 17 was evaluated, but no significant treatment-related effects were observed by study authors (quantitative data not reported).
NTP (1989) Rat (Sprague-Dawley CD); 30 females/group 0, 420, 1,100, 1,640 mg/kg-day Diet GDs 6–15	Histopathology at GD 20 was evaluated, but no histopathological effects were observed in the kidneys of control or high-dose dams (10/group); other groups were not examined.
NTP (1997b) Rat (F344); 15 males/group 0, 300, 2,800, 25,000 ppm 0, 20, 200, 2,200 mg/kg-day Diet 10 weeks	No significant effects reported by study authors in control or high-dose animals (quantitative data not reported).

Reference and study design	Results
NTP (1997b) Rat (F344); 15 males/group 0, 300, 900, 2,800, 8,300, 25,000 ppm 0, 30, 60, 180, 550, "high" mg/kg-day[d] Diet 26 weeks	No significant effects reported by study authors in control or high-dose animals (quantitative data not reported).

*Statistically significant (p <0.05) relative to controls based on statistics performed by the study authors.
[a]Percent change compared to control calculated as 100 × ((treated value − control value) ÷ control value).
[b]All studies reported relative weight in addition to absolute weight; patterns were similar, and only relative weight is included in this table.
[c]Values reported by the study authors were estimated from published graphs using "Grab It!", a Microsoft Excel based free software application used to digitizes data from image files. Publisher: www.datatrendsoftware.com.
[d]The high-dose group corresponds to 25,000 ppm BBP; a reliable estimate of dose could not be calculated. The study authors estimated doses for all but the high-dose group based on measured body weights and food consumption. Food consumption was not measured in the 25,000 ppm BBP group due to excessive scattering of feed, and because the mean body weight of this group was 30% lower than controls.

NE = not examined; NOS = not otherwise specified

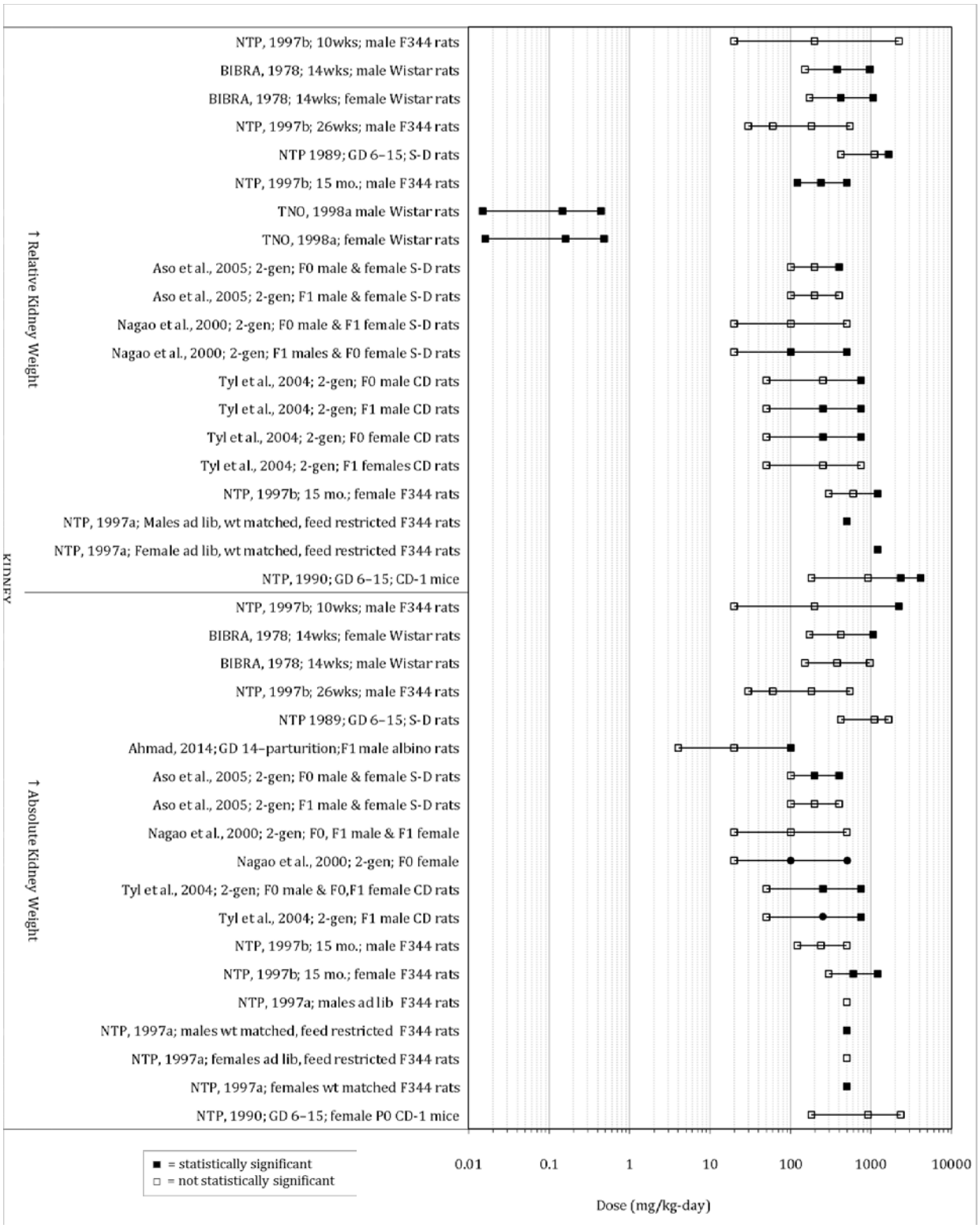

Figure 3-15. Exposure-response array of kidney weight effects following oral exposure to BBP.

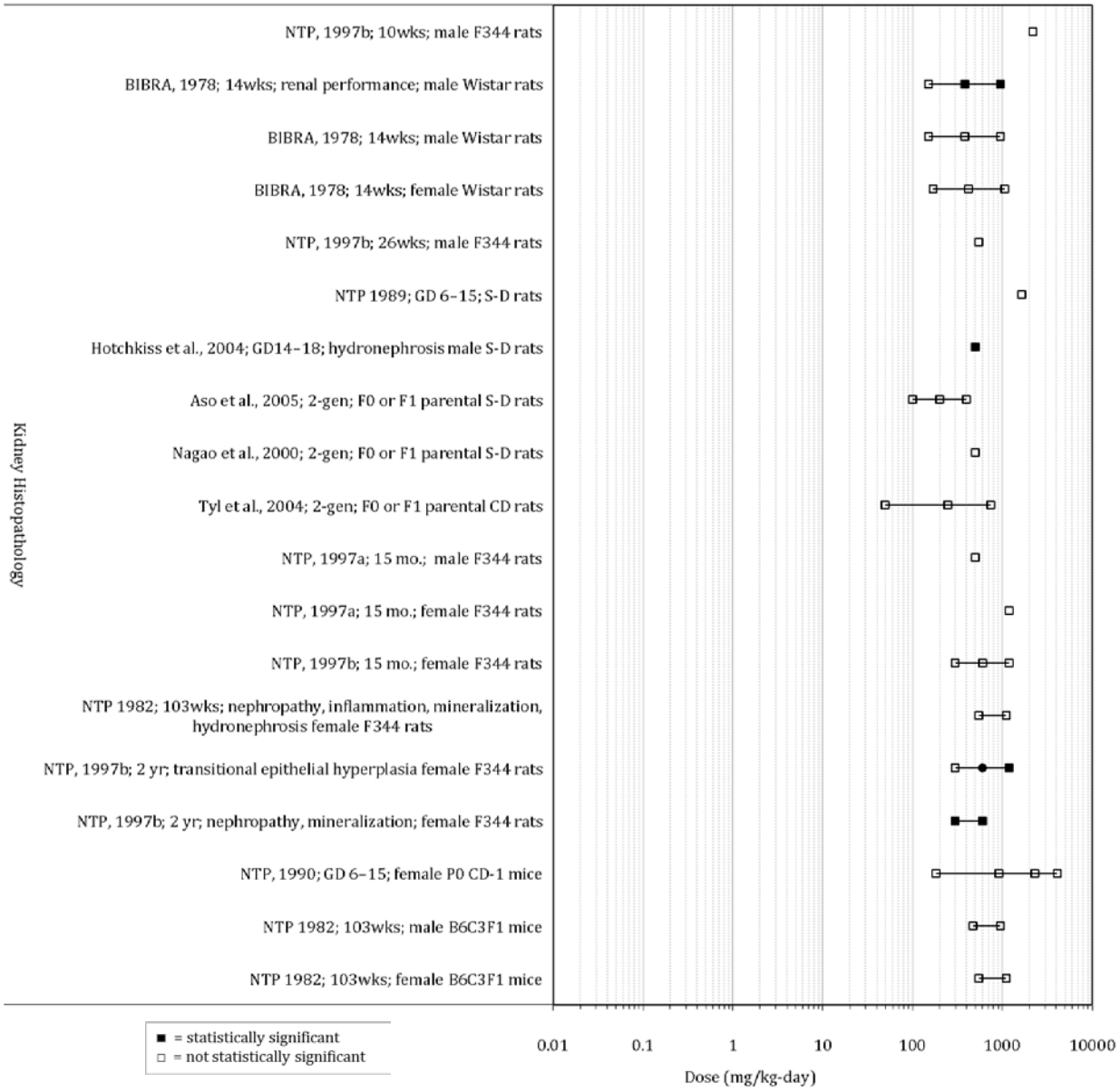

Figure 3-16. Exposure-response array of kidney histopathological effects following oral exposure to BBP.

3.3.6. Pancreatic Effects

Table 3-28. Evidence pertaining to pancreatic effects in animals following oral and inhalation exposure to BBP

Reference and study design	Results				
Pancreas weight[a]					
Tyl et al. (2004) Rat (CD); 30 F0 and F1 parental rats/sex/group 0, 750, 3,750, 11,250 ppm 0, 50, 250, 750 mg/kg-day[b] Diet Multigenerational study Exposure 10 weeks prior to mating and through mating, gestation, and lactation (females) or through 21 days after end of mating (males)	**Pancreas weight** *(percent change compared to control)*				
	mg/kg-day	0	50	250	750
	Absolute weights				
	F0 males	0	−5	−7	−2
	F1 males	0	9	14*	14*
	F0 females	NR	NR	NR	NR
	F1 females	NR	NR	NR	NR
	Relative weights				
	F0 males	0	−3	−10	1
	F1 males	0	9	9	25*
	F0 females	NR	NR	NR	NR
	F1 females	NR	NR	NR	NR
	Note: No effect reported by study authors on female pancreas weights (quantitative data not reported).				
Pancreas histopathology					
BIBRA (1978) Rat (Wistar); 27/sex/treatment group or 45/sex/group (control) 0, 2,000, 5,000, 12,000 ppm 0, 151, 381, 960 mg/kg-day (males)[b]; 0, 171, 422, 1,069 mg/kg-day (females)[b]; interim sacrifices of 9 controls/sex/group and 6 treated rats/sex/group at 2 and 6 weeks Diet 14 weeks	*Percent incidence*				
	mg/kg-day (M)	0	151	381	960
	focus of exocrine hyperplasia; 6 weeks	0	NE	NE	0
	incidental pancreatic lesion; 14 weeks	7	0	7	0
	marginal islet enlargement; 14 weeks	0	57*	20*	0
	pancreatic lesions	0	0	53*	93*
	mg/kg-day (F)	0	171	422	1,069
	focus of exocrine hyperplasia; 6 weeks	11	NE	NE	0

Reference and study design	Results				
	incidental pancreatic lesion; 14 weeks	0	NE	NE	0
	marginal islet enlargement; 14 weeks	0	NE	NE	0
	pancreatic lesions, 14 weeks	0	NE	NE	0
	Lesions include islet enlargement with cell vacuolation, peri-islet congestion, peri-islet inflammatory cell infiltration, and slight fibrosis in the endocrine pancreas; occasional pyknotic nuclei, acinar atrophy, periacinar inflammatory cell infiltrate, and fibrosis observed less frequently in the exocrine pancreas. The severity of these lesions increased in a dose-related manner.				
NTP (1997b) Rat (F344); 15 males/group 0, 300, 2,800, 25,000 ppm 0, 20, 200, 2,200 mg/kg-day[b] Diet 10 weeks	No significant effects reported by study authors in control or high-dose animals (quantitative data not reported).				
NTP (1997b) Rat (F344); 15 males/group 0, 300, 900, 2,800, 8,300, 25,000 ppm 0, 30, 60, 180, 550, "high" mg/kg-day[b] Diet 26 weeks	No significant effects reported by study authors in control or high-dose animals (quantitative data not reported).				
NTP (1997b) Rat (F344); 60/sex/group; assessed in 10 rats/sex/group at 15-month interim sacrifice and 50 rats/sex/group at study termination 0, 3,000, 6,000, 12,000 ppm (males); 0, 6,000, 12,000, 24,000 ppm (females) 0, 120, 240, 500 mg/kg-day (males)[b]; 0 300, 600, 1,200 mg/kg-day (females)[b]	*Percent incidence*				
	mg/kg-day (M)	0	120	240	500
	acinus hyperplasia (severity[b])	8 (2.5)	14 (2.1)	18 (2.3)	24 (2.3)
	acinus adenoma	6	4	6	20
	acinus carcinoma	0	0	0	2
	acinus carcinoma or adenoma	6	4	6	22

Reference and study design	Results				
Diet	Females	0	300	600	1,200
2 years	*acinus hyperplasia (severity[c])*	2 (3.0)	8 (2.5)	4 (2.5)	0 (–)
	acinus adenoma	0	0	0	4
NTP (1982)	*Percent incidence*				
$B6C3F_1$ mice; 50/sex/group	mg/kg-day (M)	0	474	974	
0, 6,000, 12,000 ppm 0, 474, 947 mg/kg-day (males)[b]; 0, 550, 1,100 mg/kg-day (females)[b]	*inflammation; NOS*	0	0	2	
	inflammation; focal	0	2	0	
Diet	*atrophy; NOS*	0	2	2	
103 weeks	*acinus; atrophy, focal*	0	2	0	
	mg/kg-day (F)	0	550	1,100	
	dilatation/ducts	2	0	0	
	cystic ducts	0	2	2	
	inflammation; NOS	0	2	0	
	abscess; NOS	0	2	0	
	atrophy; NOS	0	2	0	
	acinus; atrophy, NOS	5	0	0	
	acinus; atrophy, focal	0	0	2	
	acinar-cell adenoma	0	0	2	
	leiomyosarcoma; metastatic	0	2	0	
NTP (1982)	*Percent incidence*				
F344 rats; 50 sex/group	mg/kg-day (F)	0	550	1,100	
0, 6,000, 12,000 ppm 0, 474, 947 mg/kg-day (males)[b]; 0, 550, 1,100 mg/kg-day (females)[b]	*inflammation; NOS*	0	2	0	
	inflammation; focal	0	0	2	
Diet	*atrophy; NOS*	0	2	2	
28 weeks (males) or 103 weeks (females)	*acinus; atrophy, NOS*	2	0	0	
	acinus; atrophy, focal	6	2	2	
	pancreatic islets; islet-cell adenoma	0	7	0	
	Note: Males were not examined histopathologically.				

Reference and study design	Results			
Monsanto (1983) Rat (Sprague-Dawley); 25/sex/group; interim sacrifice of 10 rats/sex/group at 7 weeks 0, 51, 218, 789 mg/m^3 Inhalation (whole-body) 13 weeks	*Percent incidence*			
	mg/kg-day (M)	0	51	218	789
	yellow pigment; peri-islet; 13 weeks	7	0	0	0
	periacinar round cells; 13 weeks	0	0	0	7
	mg/kg-day (f)	0	51	218	789
	yellow pigment; peri-islet; 13 weeks	0	0	0	0
	periacinar round cells; 13 weeks	0	0	0	0
	Note: No significant histopathological effects were observed by study authors in rats sacrificed at interim.				
NTP (1997a) Rat (F344); 60/sex/group; interim sacrifice of 10 rats/sex/group at 15 months 0, 12,000 ppm (males); 0, 24,000 ppm (females) 0, 500 mg/kg-day (males)[b]; 0, 1,200 mg/kg-day (females)[b] Diet Three studies: (1) ad libitum feeding and weight-matched controls, (2) restricted feed (2 years), and (3) restricted feed (lifetime) Diet 2 years to lifetime	*Percent incidence*			
	Ad libitum and weight-matched			
	mg/kg-day (M)	0 (ad libitum control)	0 (weight-matched control)	500
	acinus; hyperplasia	8	4	24
	acinus; adenoma	6	0	20*
	acinus; carcinoma	0	2	2
	acinus; carcinoma or adenoma	6	2	22
	mg/kg-day (F)	0 (ad libitum control)	0 (weight-matched control)	1,200
	acinar hyperplasia	2	0	0
	acinus, adenoma	0	0	4
	Feed restricted; 2 years			
	mg/kg-day (M)	0		500
	acinus, focal hyperplasia	0		6
	acinus, adenoma	0		0
	mg/kg-day (F)	0		1,200

Reference and study design	Results		
	acinar cell, hyperplasia	0	0
	acinus, adenoma	0	0
	Feed-restricted, lifetime		
	mg/kg-day (M)	0	500
	acinus hyperplasia	0	4
	acinus, adenoma	0	2
	mg/kg-day (F)	0	1,200
	acinar cell, hyperplasia	0	2
	acinus, adenoma	0	2
	There were no significant-treatment-related effects in females relative to ad libitum or weight-matched controls or in males and females in the restricted feed studies compared to their respective control groups.		

*Statistically significant (p <0.05) relative to controls based on statistics performed by the study authors.
[a]Percent change compared to control calculated as 100 × ((treated value − control value) ÷ control value).
[b]Calculated as follows: [% in diet × intake food/water (mg)] ÷ body weight (kg) = mg/kg-day.
[c]Average severity in affected animals where 1 = minimal; 2 = mild; 3 = moderate; 4 = marked.

NE = not examined; NOS = not otherwise specified

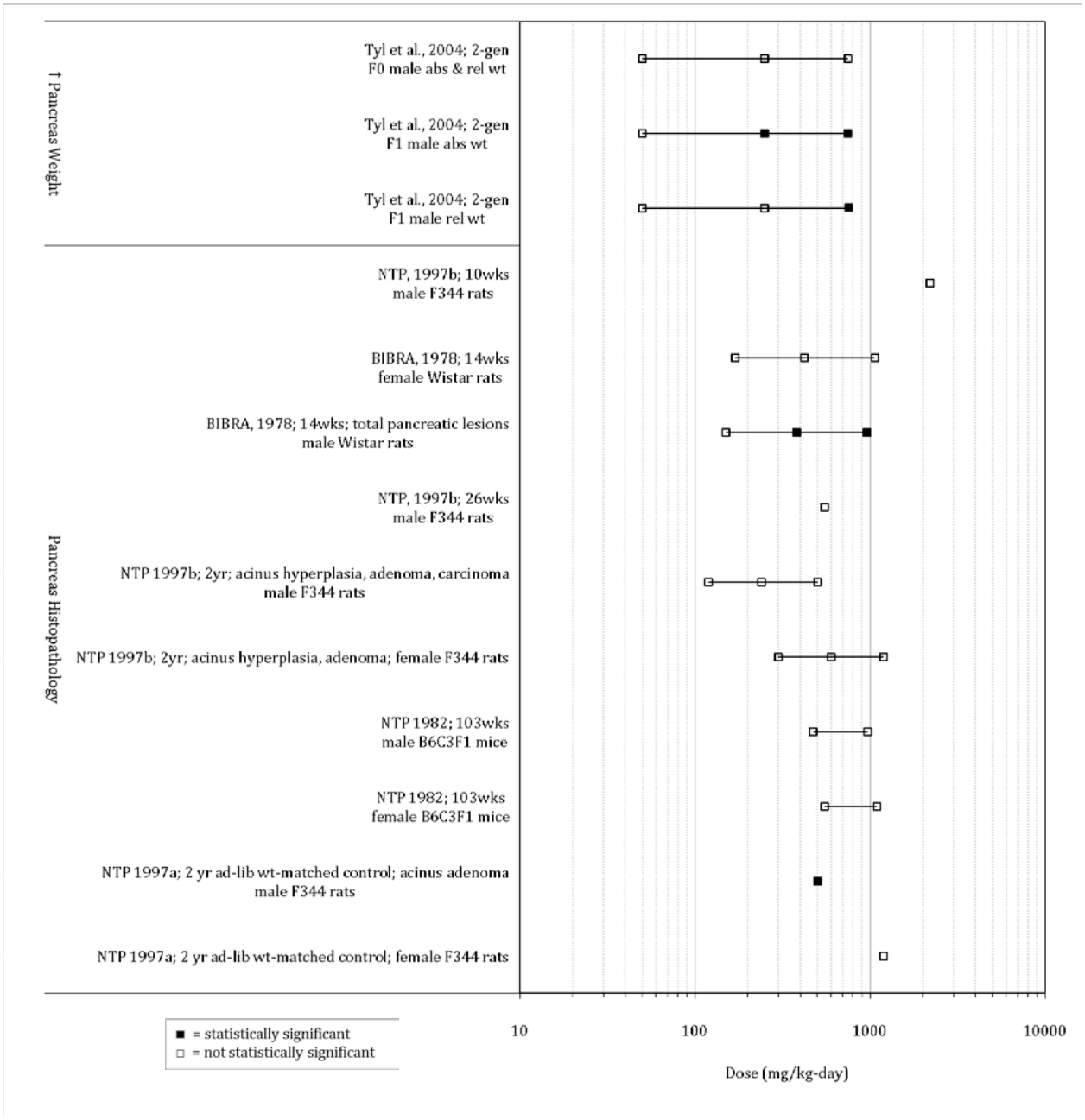

Figure 3-17. Exposure-response array of pancreatic effects following oral exposure to BBP.

3.3.7. Hematopoietic Effects

Table 3-29. Evidence pertaining to hematopoietic effects in animals following oral and inhalation exposure to BBP

Reference and study design	Results				
Spleen weight[a]					
Tyl et al. (2004) Rat (CD); 30 F0 and F1 parental rats/sex/group; assessed in 54–86 male offspring/group and 43–87 female offspring/group (≥3 sex/litter/group if possible) 0, 750, 3,750, 11,250 ppm 0, 50, 250, 750 mg/kg-day[b] Diet Multigenerational study Exposure 10 weeks prior to mating and through mating, gestation, and lactation (females) or through 21 days after end of mating (males)	**Spleen weight, PND 21** *(percent change compared to control)*				
	mg/kg-day	0	50	250	750
	Absolute weight				
	F1 males	0	0	−1	−29*
	F2 males	0	4	1	−27*
	Relative weight				
	F1 males	0	1	−3	−12*
	F2 males	0	4	0	−18*
	Absolute weight				
	F1 females	0	8	−5	−34*
	F2 females	0	8	4	−26*
	Relative weight				
	F1 females	0	6	−4	−14*
	F2 females	0	6	1	−17*
BIBRA (1978) Rat (Wistar); 27/sex/group or 45/sex/group (control); interim sacrifices of 9 controls/sex/group and 6 treated rats/sex/group at 2 and 6 weeks 0, 2,000, 5,000, 12,000 ppm Diet: 0, 151, 381, 960 mg/kg-day (males)[b]; 0, 171, 422, 1,069 mg/kg-day (females)[b] 3 months	**Spleen weight** *(percent change compared to control)*				
	mg/kg-day (M)	0	151	381	960
	Absolute weight				
	2 weeks	0	−6	−2	−19
	6 weeks	0	−7	−10	−24*
	14 weeks	0	−10	−7*	−4
	Relative weight				
	2 weeks	0	0	0	−14*
	6 weeks	0	−5	−5	−14*
	14 weeks	0	−5	0	5
	mg/kg-day (F)	0	171	422	1,069
	Absolute weight				
	2 weeks	0	0	0	−8
	6 weeks	0	0	5	0

Reference and study design	Results				
	14 weeks	0	0	−5	0
	Relative weight				
	2 weeks	0	−3	0	0
	6 weeks	0	−4	0	8
	14 weeks	0	0	−5	5
Aso et al. (2005) Rat (Crj:CD(SD)IGS); 24 sex/generation/group; assessed in male offspring/litter in F1 and F2 offspring 0, 100, 200, 400 mg/kg-day Gavage Multigenerational study F0 and F1 exposed for 4 weeks prior to mating, through mating for 10 weeks, and until weaning of offspring (females) or necropsy (males)	**Spleen weight** *(percent change compared to control)*				
	mg/kg-day	0	100	200	400
	Absolute weight, PND 21				
	F1 males	0	1	3	−16*
	F2 males	0	−12	−8	−25*
	Relative weight, PND 21				
	F1 males	0	−2	4	−13*
	F2 males	0	−9	−8	−20*
	Absolute weight, study termination				
	F0 males	0	−7	−5	−4
	F1 males	0	−6	−7	−8
	F0 females	0	−2	6	−2
	F1 females	0	2	2	−2
	Relative weight, study termination				
	F0 males	0	−7	−7	0
	F1 males	0	−7	−7	−7
	F0 females	0	−6	0	−6
	F1 females	0	−6	−6	−6
Nagao et al. (2000) Rat (Sprague-Dawley); 25 sex/generation/group 0, 20, 100, 500 mg/kg-day Gavage Multigenerational study F0 males and females: Exposure for 12 weeks prior to mating, 2 weeks cohabitation, and until necropsy at 23 weeks of age (males) or until postpartum day 22 (females); F1	**Spleen weight** *(percent change compared to control)*				
	mg/kg-day	0	20	100	500
	Absolute weight				
	F0 males	0	8	4	−1
	F1 males	0	−6	−3	−12*
	F0 females	0	−1	1	−1
	F1 females	0	−4	6	1
	Relative weight				
	F0 males	0	14	7	7
	F1 males	0	0	7	0

Reference and study design	Results					
animals were exposed from weaning until necropsy at PND 22	*F0 females*	0	0	5	0	
	F1 females	0	−5	5	5	
Thymus weights[a]						
NTP (1997b) Rat (F344); 15 males/group 0, 300, 2,800, 25,000 ppm 0, 20, 200, 2,200 mg/kg-day[b] Diet 10 weeks	**Thymus weight** *(percent change compared to control)*					
	mg/kg-day	0	20	200	2,200	
	absolute weight	0	6	−2	−14	
	relative weight	0	6	0	23*	
NTP (1997b) Rat (F344); 15 males/group 0, 300, 900, 2,800, 8,300, 25,000 ppm 0, 30, 60, 180, 550, "high" mg/kg-day[b] Diet 26 weeks	**Thymus weight** *(percent change compared to control)*						
	mg/kg-day	0	30	60	180	550	ND
	absolute weight	0	5	52	3	12	−27
	relative weight	0	1	46	6	12	10
Tyl et al. (2004) Rat (CD); 30 F0 and F1 parental rats/sex/group; assessed in 54−86 male offspring/group and 43−87 female offspring/group (≥3 sex/litter/group if possible) 0, 750, 3,750, 11,250 ppm 0, 50, 250, 750 mg/kg-day[b] Diet Multigenerational study Exposure 10 weeks prior to mating and through mating, gestation, and lactation (females); or for 21 days after mating (males).	**Thymus weight** *(percent change compared to control)*					
	mg/kg-day	0	50	250	750	
	Absolute weight					
	F1 male	0	7	1	−17*	
	F2 male	0	−3	−5	−14*	
	F1 female	0	2	−3	−22*	
	F2 female	0	−3	−5	−15*	
	Relative weight					
	F1 male	0	6	0	2	
	F2 male	0	−2	−6	−2	
	F1 female	0	0	−2	−2	
	F2 female	0	−5	−8	−4	
	Note: Thymus weights were not recorded for F0 or F1 parental animals. There were no significant effects on relative thymus weights of F1 or F2 offspring.					

Reference and study design	Results				
Nagao et al. (2000)	**Thymus weight** *(percent change compared to control)*				
Rat (Sprague-Dawley); 25 sex/generation/group	mg/kg-day	0	20	100	500
	Absolute weight				
0, 20, 100, 500 mg/kg-day	*F0 males*	0	−12	−15	−10
Gavage	*F1 males*	0	−4	−18	−12
Multigenerational study	*F0 females*	0	−10	2	−6
F0 males and females: Exposure for 12 weeks prior to mating, 2 weeks cohabitation, and until necropsy at 23 weeks of age (males) or PND 22 (females); F1 animals: Exposure from weaning until necropsy at PND 22	*F1 females*	0	5	−13	13
	Relative weight				
	F0 males	0	−9	−14	−3
	F1 males	0	0	−12	0
	F0 females	0	−9	2	−7
	F1 females	0	5	−14	13
Aso et al. (2005)	**Thymus weight, PND 21** *(percent change compared to control)*				
Crj:CD(SD)IG rats, 24 rats/sex/generation/group; assessed in 1 male/litter in F1 and F2 offspring	mg/kg-day	0	100	200	400
	Absolute weight				
0, 100, 200, 400 mg/kg-day	*F1 male*	0	6	5	6
Gavage	*F2 male*	0	−1	3	−8
Multigenerational study	Relative weight				
F0 and F1 exposed for 4 weeks prior to mating, through mating for 10 weeks, and until weaning of offspring (females) or necropsy (males).	*F1 male*	0	4	5	9
	F2 male	0	4	2	−2
Other changes					
Piersma et al. (2000)	**Histopathological effects in the spleen at GD 21**				
Rat (Harlan Cpb-WU); 10 females/group	Dose related increase in the extent of extramedullary hematopoiesis (data presented graphically). The severity of the effect was reportedly increased. The effect was classified as normal (0), minimal (1), slight (2), moderate (3), marked (4), or severe (5). It was also noted in the study report that, "pregnant controls showed elevated extramedullary hematopoiesis compared to nonpregnant females (quantitative data not reported), which was further increased after exposure in all dose groups."				
0, 270, 350, 450, 580, 750, 970, 1,250, 1,600, 2,100 mg/kg-day					
Gavage					
GDs 6–15 or 6–20					

Reference and study design	Results				
BIBRA (1978) Rat (Wistar); 27/sex/group or 45/sex/group (control); interim sacrifices of 9 controls/sex/group and 6 treated rats/sex/group at 2 and 6 weeks 0, 2,000, 5,000, 12,000 ppm 0, 151, 381, 960 mg/kg-day (males)[b]; 0, 171, 422, 1,069 mg/kg-day (females)[b] Diet 14 weeks	*Percent incidence*				
	mg/kg-day (M)	0	151	381	960
	Hemorrhage in medulla/congested; thymus				
	6 weeks	22	NE	NE	0
	14 weeks	0	NE	NE	0
	Atrophy of medullas; thymus				
	14 weeks	0	NE	NE	0
	Hemorrhage/congested; lymph nodes				
	14 weeks	7	NE	NE	7
	mg/kg-day (F)	0	171	422	1,069
	Hemorrhage in medulla/congested; thymus				
	6 weeks	22	NE	NE	0
	14 weeks	4	NE	NE	7
	Atrophy of medulla; thymus				
	14 weeks	4	NE	NE	0
	Hemorrhage/congested; lymph nodes				
	14 weeks	4	NE	NE	7
	Note: It is unclear based on the study report if the spleen was examined histopathologically. However, no effects were reported.				
NTP (1997b) Rat (F344); 15 males/group 0, 300, 2,800, 25,000 ppm 0, 20, 200, 2,200 mg/kg-day[b] Diet 10 weeks	Spleen and thymus were examined histopathologically. No significant effects reported in control or high-dose animals (quantitative data not reported).				
NTP (1997b) Rat (F344); 15 males/group 0, 300, 900, 2,800, 8,300, 25,000 ppm 0, 30, 60, 180, 550, "high" mg/kg-day[b] Diet 26 weeks	Spleen and thymus were examined histopathologically. No significant effects reported in control or high-dose animals (quantitative data not reported).				

Reference and study design	Results				
NTP (1997b) Rat (F344), 60/sex/group; assessed in 10 rats/sex/group at 15-month interim sacrifice and 50 rats/sex/group at study termination 0, 3,000, 6,000, 12,000 ppm (males); 0, 6,000, 12,000, 24,000 ppm (females) 0, 120, 240, 500 mg/kg-day (males)[b]; 0 300, 600, 1,200 mg/kg-day (females)[b] Diet 2 years	*Percent incidence*				
	mg/kg-day (M)	0	120	240	500
	15 months				
	lymph node: deep cervical; hemorrhage	50	NE	0	0
	lymph node: mediastinal; hemorrhage	100	NE	100	100
	lymph node: mandibular; hemorrhage	20	0	10	0
	lymph node: mesenteric; hemorrhage	0	0	20	0
	spleen: hematopoietic cell proliferation	20	0	0	10
	spleen: pigmentation; hemosiderin	100	100	100	70
	2 years				
	bone marrow: hypercellularity	2	8	2	0
	lymph node: iliac; hemorrhage	4	0	0	0
	lymph node: mediastinal; hemorrhage	22	23	0	0
	lymph node: pancreatic; hemorrhage	0	5	0	5
	lymph node: mandiubular; congestion	2	4	0	0
	lymph node: mandibular; hemorrhage	8	6	4	12
	lymph node: mesenteric; hemorrhage	2	6	0	8
	spleen: hematopoietic cell proliferation	4	16	10	14

Reference and study design	Results				
	spleen: pigmentation; hemosiderin	28	2	4	12
	thymus: hemorrhage	2	2	0	0
	mg/kg-day (F)	0	300	600	1,200
	15 months				
	lymph node: mediastinal; hemorrhage	NE	100	100	100
	lymph node: mandibular; hemorrhage	0	0	0	10
	spleen: hematopoietic cell proliferation	10	30	30	30
	spleen: pigmentation; hemosiderin	100	100	100	100
	thymus: hemorrhage	0	11	0	0
	2 years				
	bone marrow: hypercellularity	2	4	0	2
	lymph node: mediastinal; hemorrhage	8	9	6	7
	lymph node: pancreatic; hemorrhage	0	0	6	0
	lymph node: renal; hemorrhage	0	18	13	0
	lymph node: mandibular; hemorrhage	10	18	6	10
	lymph node: mesenteric; hemorrhage	6	6	6	4
	spleen: hematopoietic cell proliferation	20	24	16	28
	spleen: pigmentation; hemosiderin	38	40	42	58
	thymus: hemorrhage	2	0	2	2

Reference and study design	Results				
Aso et al. (2005) Crj:CD(SD)IG rats, 24 rats/sex/generation/group; assessed in 1 male/litter in F1 and F2 offspring 0, 100, 200, 400 mg/kg-day Gavage Multigenerational study F0 and F1 exposed for 4 weeks prior to mating, through mating for 10 weeks, and until weaning of offspring (females) or necropsy (males).	Spleen and thymus were examined histopathologically. No significant treatment-related effects observed in F0 or F1 parental males or females (data not provided).				
Monsanto (1983) Rat (Sprague-Dawley); 25/sex/group; interim sacrifice of 10 rats/sex/group at 7 weeks 0, 51, 218, 789 mg/m^3 Inhalation (whole-body) 13 weeks	*Percent incidence*				
	mg/kg-day	0	51	218	789
	Males				
	sinusoidal congestion, 6 weeks	10	0	0	0
	yellow-brown pigment, 13 weeks	0	0	0	0
	Females				
	sinusoidal congestion, 6 weeks	20	0	0	0
	yellow-brown pigment, 13 weeks	0	0	0	7
NTP (1997a) Rat (F344); 50–60/sex/group; interim sacrifice of 10 rats/sex/group at 15 months 0, 12,000 ppm (males); 0, 24,000 ppm (females) 0, 500 mg/kg-day (males)[b]; 0, 1,200 mg/kg-day (females)[b] Diet 4 exposure protocols: ad libitum feeding, weight-matched controls, restricted feed (2 years), and restricted feed (lifetime) Diet	*Percent incidence*				
	Ad libitum and weight matched				
	mg/kg-day (M)	0 (ad libitum)	0 (weight-matched)	500	
	lymph node: deep cervical; hemorrhage, 15 months	50	NE	0	
	lymph node: mediastinal; hemorrhage, 15 months	100	NE	100	
	lymph node:	20	20	0	

Reference and study design	Results			
2 years to lifetime	*mandibular; hemorrhage, 15 months*			
	lymph node: mesenteric; hemorrhage, 15 months	0	0	0
	spleen: hematopoietic cell proliferation, 15 months	20	0	10
	spleen: pigmentation; hemosiderin, 15 months	100	90	70
	bone marrow: hypercellularity, 2 years	2	4	0
	lymph node: iliac; hemorrhage, 2 years	4	0	0
	lymph node: mediastinal; hemorrhage, 2 years	22	29	0
	lymph node: pancreatic; hemorrhage, 2 years	0	0	5
	lymph node: mandiubular; congestion, 2 years	2	0	0
	lymph node: mandibular; hemorrhage, 2 years	8	17	12
	lymph node: mesenteric; hemorrhage, 2 years	2	6	8
	spleen: hematopoietic cell proliferation, 2 years	4	12	14
	spleen: pigmentation; hemosiderin, 2 years	28	4	12
	thymus: hemorrhage, 2 years	2	0	0
	mg/kg-day (F)	0 (ad libitum)	0 (weight-matched)	1,200

Reference and study design	Results			
	lymph node: mediastinal; hemorrhage, 15 months	NE	NE	100
	lymph node: mandibular; hemorrhage, 15 months	0	0	10
	spleen: hematopoietic cell proliferation, 15 months	10	10	30
	spleen: pigmentation; hemosiderin, 15 months	100	100	100
	bone marrow: hypercellularity, 2 years	2	4	2
	lymph node: mediastinal; hemorrhage, 2 years	8	23	7
	lymph node: renal; hemorrhage, 2 years	0	8	0
	lymph node: mandibular; hemorrhage, 2 years	10	16	10
	lymph node: mesenteric; hemorrhage, 2 years	6	4	4
	spleen: hematopoietic cell proliferation, 2 years	20	8	28
	spleen: pigmentation; hemosiderin, 2 years	38	26	58
	thymus: hemorrhage, 2 years	2	0	2
	Feed-restricted, 2 years or lifetime			
	mg/kg-day (M)	0 (2 years)	500 (2 years)	0 (lifetime)	500 (lifetime)
	lymph node: mediastinal; hemorrhage, 15 months	100	NE	NA	NA

Reference and study design	Results				
	lymph node: mandibular; hemorrhage, 15 months	10	10	NA	NA
	spleen: pigmentation; hemosiderin, 15 months	0	10	NA	NA
	thymus: hemorrhage, 15 months	10	10	NA	NA
	bone marrow: hypercellularity, 2 years	4	4	2	4
	lymph node: deep cervical; hemorrhage, 2 years	0	0	4	0
	lymph node: iliac; hemorrhage, 2 years	0	0	0	4
	lymph node: mediastinal; hemorrhage, 2 years	8	11	0	9
	lymph node: pancreatic; hemorrhage, 2 years	0	5	4	0
	lymph node: mandibular; hemorrhage, 2 years	10	15	12	10
	lymph node: mesenteric; hemorrhage, 2 years	4	2	0	4
	spleen: hematopoietic cell proliferation, 2 years	10	8	16	8
	spleen: pigmentation; hemosiderin, 2 years	12	8	16	6
	mg/kg-day (F)	0 (2 years)	1,200 (2 years)	0 (lifetime)	1,200 (lifetime)
	lymph node: mediastinal; hemorrhage, 15 months	100	0	NA	NA
	lymph node: mandibular; hemorrhage, 15 months	0	30	NA	NA

Reference and study design	Results				
	lymph node: mesenteric; hemorrhage, 15 months	0	10	NA	NA
	spleen: hematopoietic cell proliferation, 15 months	30	10	NA	NA
	spleen: pigmentation; hemosiderin, 15 months	90	90	NA	NA
	bone marrow: hypercellularity, 2 years	0	2	4	2
	lymph node: mediastinal; hemorrhage, 2 years	10	13	5	6
	lymph node: renal; hemorrhage, 2 years	10	13	0	0
	lymph node: mandibular; hemorrhage, 2 years	10	14	12	14
	lymph node: mesenteric; hemorrhage, 2 years	4	4	4	4
	spleen: hematopoietic cell proliferation, 2 years	26	16	26	16
	spleen: pigmentation; hemosiderin, 2 years	42	36	36	48
	thymus: atrophy, 2 years	0	2	0	0
	thymus: hemorrhage, 2 years	0	0	2	0
NTP (1982)	*Percent incidence*				
F344 rats; 50/sex/group	mg/kg-day (F)	0		550	1,100
0, 6,000, 12,000 ppm 0, 474, 947 mg/kg-day (males)[b]; 0, 550, 1,100 mg/kg-day (females)[b] Diet	*bone marrow: hypoplasia*	0		4	0
	spleen: pigmentation; NOS	0		2	0

Reference and study design	Results			
28 weeks (males) or 103 weeks (females)	*spleen: hemosiderosis*	6	4	8
	lymph node: mediastinal; hemorrhage	0	0	2
	lymph node: pancreatic; hemorrhage	0	0	2
	lymph node: mesenteric; hemorrhage	0	0	4
	thymus: hemorrhage	0	4	4
	thymus: atrophy	0	4	7
	Note: Males were not examined histopathologically.			
NTP (1982)	*Percent incidence*			
$B6C3F_1$ mice; 50/sex/group	mg/kg-day (M)	0	474	947
0, 6,000, 12,000 ppm 0, 474, 947 mg/kg-day (males)[b]; 0, 550, 1,100 mg/kg-day (females)[b]	*bone marrow: hyperplasia; hematopoietic*	0	2	0
Diet	*lymph node: mesenteric; hemorrhage*	0	4	14
103 weeks	*thymus: atrophy*	0	0	5
	mg/kg-day (F)	0	550	1,100
	bone marrow: hyperplasia; hematopoietic	6	2	2
	spleen: congestion; nos	0	0	2
	spleen: hyperplasia; hematopoietic	4	2	0
	thymus: atrophy	5	0	0
BIBRA (1978)	*Percent change compared to control*			
Rat (Wistar); 27/sex/group or 45/sex/group (control); interim sacrifices of 9 controls/sex/group and 6 treated rats/sex/group at 2 and 6 weeks	mg/kg-day (F)	0	171	422	1,069
	hemoglobin concentration	0	0	2	4
0, 2,000, 5,000, 12,000 ppm 0, 151, 381, 960 mg/kg-day (males)[b] 0, 171, 422, 1,069 mg/kg-day (females)[b]	*hematocrit (packed cell volume)*	0	0	2	0
	spleen histopathology	No lesions were noted in the spleen			
	mg/kg-day (M)	0	151	381	960

Reference and study design	Results				
Diet 14 weeks	*hemoglobin concentration*	0	2	2	−6
	hematocrit (packed cell volume)	0	0	0	−9*
	spleen histopathology	No lesions were noted in the spleen			
Mononuclear cell leukemia					
NTP (1982) $B6C3F_1$ mice; 50/sex/group 0, 6,000, 12,000 ppm 0, 474, 947 mg/kg-day (males)[b]; 0, 550, 1,100 mg/kg-day (females)[b] Diet 103 weeks	*Percent incidence*				
	mg/kg-day (M)	0	474	947	
	leukemia, multiple organs	2	0	0	
	mg/kg-day (F)	0	550	1,100	
	leukemia, liver	0	0	2	
NTP (1982) F344 rats; 50/sex/group 0, 6,000, 12,000 ppm 0, 474, 947 mg/kg-day (males)[b]; 0, 550, 1,100 mg/kg-day (females)[b] Diet 28 weeks (males) or 103 weeks (females)	*Percent incidence*				
	mg/kg-day (M)	0	474	947	
	mononuclear cell leukemia	NE	NE	NE	
	mg/kg-day (F)	0	550	1,100	
	mononuclear cell leukemia, total	14	14	36	
	multiple organs	12	12	34	
	spleen	0	2	2	
	liver	2	0	0	
NTP (1997b) F344 rats; 60/sex/group; assessed in 10 rats/sex/group at 15-month interim sacrifice and 50 rats/sex/group at study termination 0, 3,000, 6,000, 12,000 ppm (males); 0, 6,000, 12,000, 24,000 ppm (females) 0, 120, 240, 500 mg/kg-day (males)[b]; 0 300, 600, 1,200 mg/kg-day (females)[b] Diet 2 years	*Percent incidence at study termination*				
	mg/kg-day (M)	0	120	240	500
	mononuclear cell leukemia	62	56	68	60
	mg/kg-day (F)	0	300	600	1,200
	mononuclear cell leukemia	42	40	42	38

Reference and study design	Results			
NTP (1997a) F344 rats; 50–60/sex/group; interim sacrifice of 10 rats/sex/group at 15 months 0, 12,000 ppm (males); 0, 24,000 ppm (females) 0, 500 mg/kg-day (males)[b]; 0, 1,200 mg/kg-day (females)[b] Diet 4 exposure protocols: ad libitum feeding, weight-matched controls, restricted feed (2 years), and restricted feed (lifetime) 2 years to lifetime	*Percent incidence at study termination*			
	Ad libitum and weight-matched			
	mg/kg-day (M)	0 (ad libitum)	0 (weight-matched)	500
	mononuclear cell leukemia	62	30	60
	mg/kg-day (F)	0 (ad libitum)	0 (weight-matched)	1,200
	mononuclear cell leukemia	42	26	38
	Feed restricted 2-year exposure			
	mg/kg-day (M)	0		500
	mononuclear cell leukemia	42		54
	mg/kg-day (F)	0		1,200
	mononuclear cell leukemia	32		36
	Feed restricted lifetime exposure			
	mg/kg-day (M)	0		500
	mononuclear cell leukemia	78		72
	mg/kg-day (F)	0		1,200
	mononuclear cell leukemia	58		78

*Statistically significant (p <0.05) relative to controls based on statistics performed by the study authors.
[a]Percent change compared to control calculated as 100 × ([treated value − control value] ÷ control value).
[b]Calculated as follows: [% in diet × intake food/water (mg)] ÷ body weight (kg) = mg/kg-day.

NE = not examined; NOS = not otherwise specified

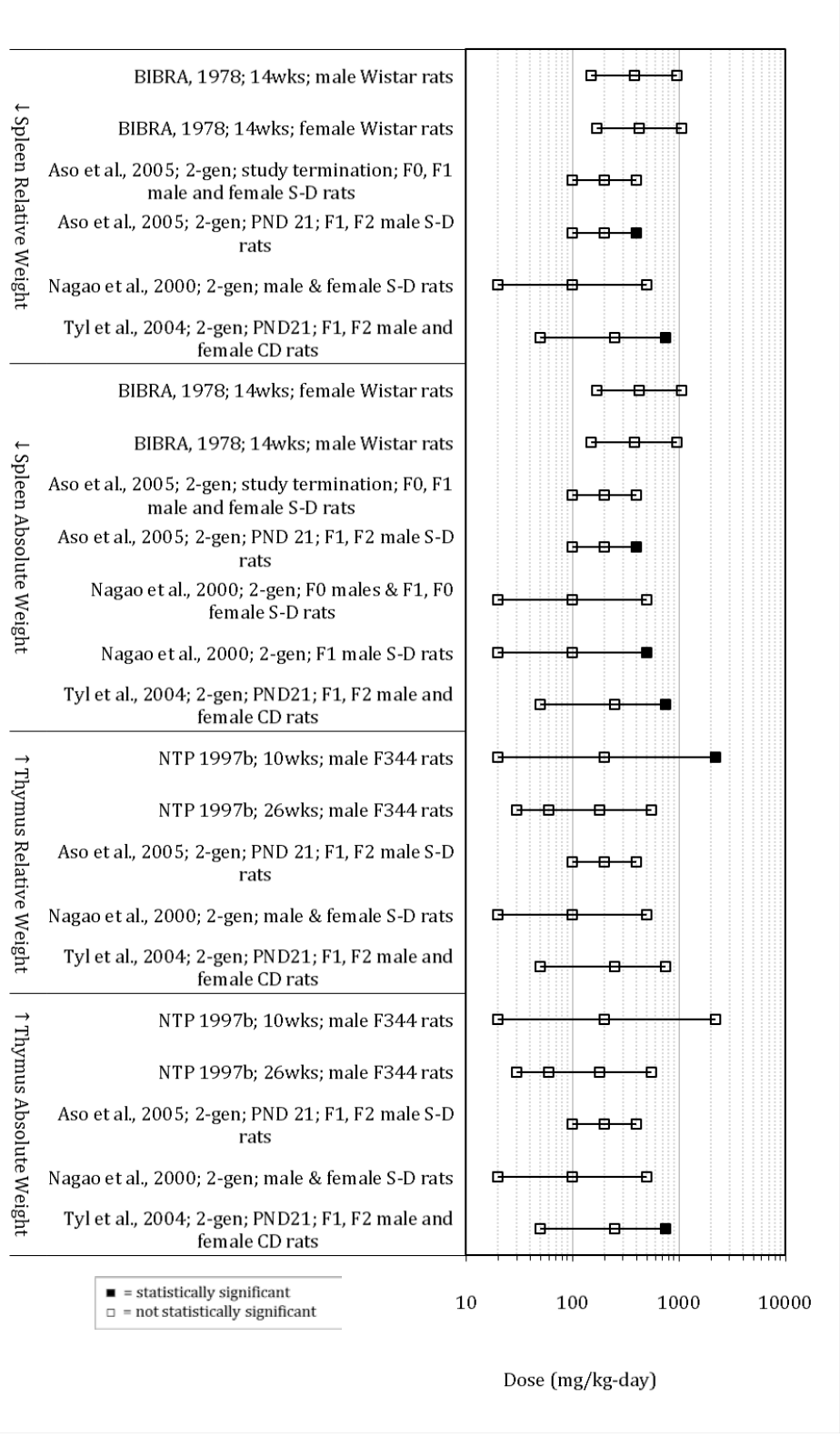

Figure 3-18. Exposure-response array of hematopoietic effects following oral exposure to BBP: spleen and thymus weights.

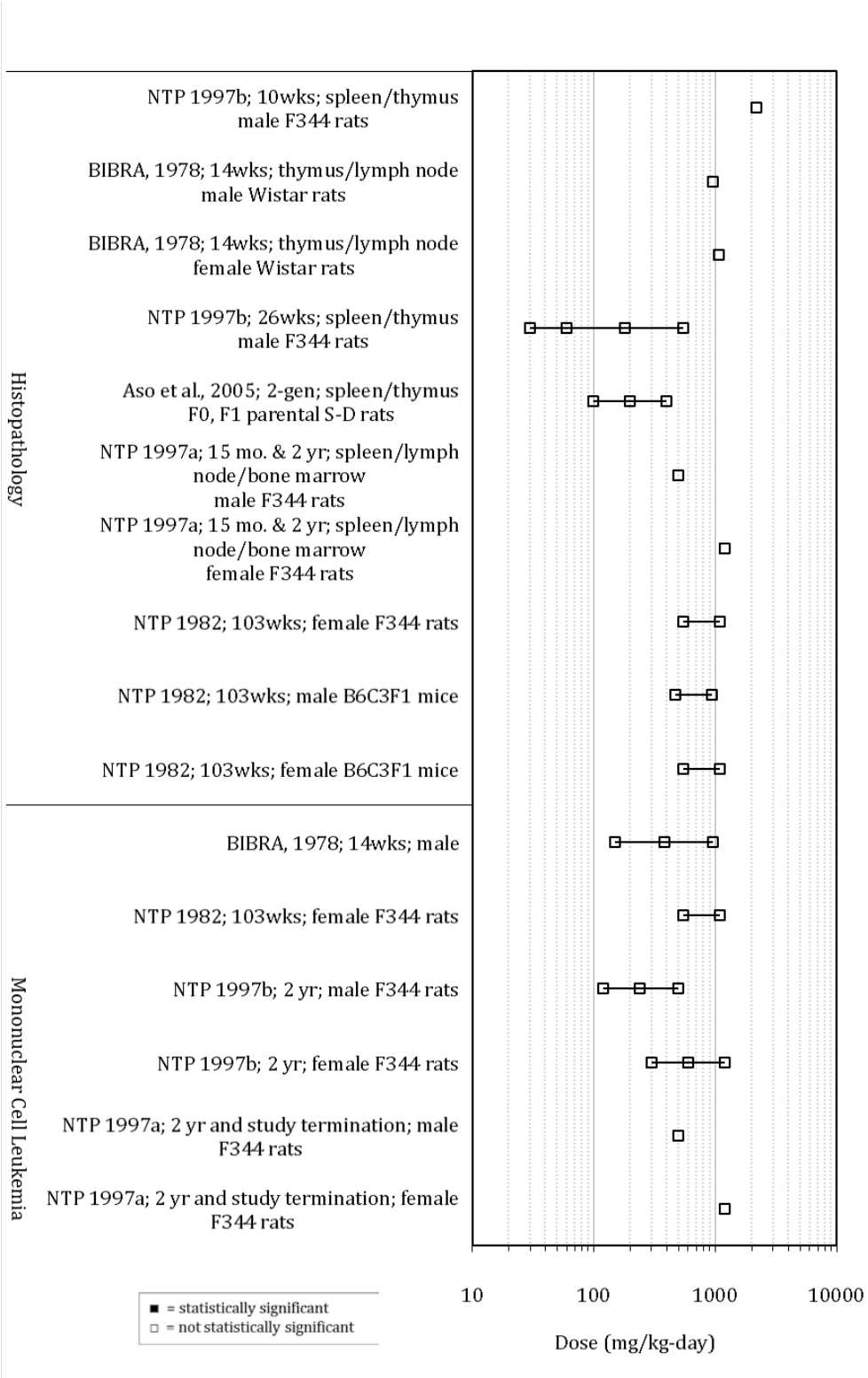

Figure 3-19. Exposure-response array of hematopoietic histopathological effects following oral exposure to BBP.

3.3.8. Thyroid Effects

Table 3-30. Evidence pertaining to thyroid effects in animals following oral exposure to BBP

Reference and study design	Results[a]				
Thyroid weight					
Aso et al. (2005) Rat (Crj:CD(SD)IGS); 24 rats/sex/generation/group 0, 100, 200, 400 mg/kg-day Gavage Multigenerational study F0 and F1 exposed for 4 weeks prior to mating, through mating for 10 weeks, and until weaning of offspring (females) or necropsy (males)	**Thyroid weight** *(percent change compared to control)*				
	mg/kg-day	0	100	200	400
	Absolute weight				
	F0 males	0	−6	5	9
	F1 males	0	0	3	21
	F0 females	0	−4	−6	10
	F1 females	0	5	−2	−1
	Relative weight				
	F0 males	0	−10	0	10
	F1 males	0	0	2	24*
	F0 females	0	−4	−12	9
	F1 females	0	0	−8	−3
Nagao et al. (2000) Rat (Sprague-Dawley); 20–25 rats/sex/generation/group 0, 20, 100, 500 mg/kg-day Diet Multigenerational study F0 males and females: Exposure for 12 weeks prior to mating, 2 weeks cohabitation, and until necropsy at 23 weeks of age (males) or PND 22 (females); F1 animals: Exposure from weaning until necropsy at PND 22	**Thyroid weight** *(percent change compared to control)*				
	mg/kg-day	0	20	100	500
	Absolute weight				
	F0 males	0	2	7	0
	F1 males	0	3	5	7
	F0 females	0	12	1	8
	F1 females	0	−9	−2	4
	Relative weight				
	F0 males	0	3	6	9
	F1 males	0	−3	3	11*
	F0 females	0	14	0	7
	F1 females	0	−10	−2	4

Reference and study design	Results[a]				
BIBRA (1978) Rat (Wistar); 27/sex/group or 45/sex/group (control); interim sacrifices of 9 controls/sex/group and 6 treated rats/sex/group at 2 and 6 weeks 0, 2,000, 5,000, 12,000 ppm 0, 151, 381, 960 mg/kg-day (males)[b] 0, 171, 422, 1,069 mg/kg-day (females)[b] Diet 14 weeks	**Thyroid weight** *(percent change compared to control)*				
	mg/kg-day (M)	0	151	381	960
	Absolute weight				
	2 weeks	0	6	8	4
	6 weeks	0	20*	−18	−13
	14 weeks	0	4	3	4
	Relative weight				
	2 weeks	0	10	8	10
	6 weeks	0	26*	−11	−2
	14 weeks	0	14	14	17
	mg/kg-day (F)	0	171	422	1,069
	Absolute weight				
	2 weeks	0	19	29*	35*
	6 weeks	0	−18*	−15	−13
	14 weeks	0	−1	−3	1
	Relative weight				
	2 weeks	0	10	28*	43*
	6 weeks	0	−19*	−17	−8
	14 weeks	0	−2	−2	5
Tyl et al. (2004) Rat (CD); 30 F0 and F1 parental rats/sex/group 0, 750, 3,750, 11,250 ppm 0, 50, 250, 750 mg/kg-day[b] Diet Multigenerational study Exposure 10 weeks prior to mating and through mating, gestation, and lactation (females) or through 21 days after end of mating (males)	No significant treatment-related effects on absolute or relative thyroid weight were reported in F0 or F1 parental males or females (data not provided).				

Reference and study design	Results[a]				
Thyroid hormones					
Nagao et al. (2000) Rat (Sprague-Dawley); 20–25 parental rats/sex/generation/group; 37–48 F1 offspring/group (from 18–24 litters/group) 0, 20, 100, 500 mg/kg-day Gavage Multigenerational study F0 males and females: Exposure for 12 weeks prior to mating, 2 weeks cohabitation, and until necropsy at 23 weeks of age (males) or PND 22 (females) F1 animals: Exposure from weaning until necropsy at PND 22	**Percent change compared to control at study termination (F0 and F1 parental animals) or PND 22 (F1 weanling rats)**				
	mg/kg-day (M)	0	20	100	500
	TSH F0, parental	0	−9	−12*	−10
	T3 F0, parental	0	0	0	−11*
	T4 F0, parental	0	0	−4	−21*
	TSH F1, parental	0	12	1	5
	T3 F1, parental	0	14	14	14
	T4 F1, parental	0	10	−1	−21*
	TSH F1, weanling	0	−1	−15*	−19*
	T3 F1, weanling	0	23*	8	−8
	T4 F1, weanling	0	4	2	2
	mg/kg-day (F)	0	20	100	500
	TSH F0, parental	0	12*	1	6
	T3 F0, parental	0	13	13	13
	T4 F0, parental	0	−5	−16	−21*
	TSH F1, parental	0	−5	−7	−10
	T3 F1, parental	0	0	0	0
	T4 f1, parental	0	12	8	10
	TSH F1, weanling	0	3	0	9
	T3 F1, weanling	0	0	−17*	−33*
	T4 F1, weanling	0	4	4	9
	Note: TSH, T4, and T3 for all other lifestages examined were not affected.				
NTP (1997b) Rat (F344); 60/sex/group; assessed in 10 rats/sex/group at 6, 8, and/or 15 months and at study termination 0, 3,000, 6,000, 12,000 ppm (males); 0, 6,000, 12,000, 24,000 ppm (females) 0, 120, 240, 500 mg/kg-day (males)[b]; 0 300, 600, 1,200 mg/kg-day (females)[b] Diet	*Percent change*				
	mg/kg-day (M)	0	120	240	500
	TSH				
	6 months	0	167	100	33
	8 months	0	200*	100	100
	15 months	0	0	100*	0
	study termination	0	−50	−50	0
	T3				

Reference and study design	Results[a]				
2 years					
	6 months	0	25	3	−4
	15 months	0	−1	7	1
	study termination	0	−32	3	0
	T4				
	6 months	0	0	0	0
	15 months	0	0	25	−25
	study termination	0	−25	0	0
	mg/kg-day (F)	0	300	600	1,200
	TSH				
	6 months	–	−50	0	−100
	15 months	–	0	100	100
	study termination	–	0	0	0
	T3				
	6 months	–	15	−5	−30*
	15 months	–	−1	−7	−22*
	study termination	–	−22	−25	−36*
	T4				
	6 months	–	0	0	−25
	15 months	–	0	0	−33*
	study termination	–	0	0	0
Thyroid histopathology					
NTP (1997b)	*Percent incidence*				
Rat (F344); 60/sex/group; interim sacrifice of 10 rats/sex/group at 5 months	mg/kg-day (M)	0	120	240	500
	Ultimobranchial cyst				
0, 3,000, 6,000, 12,000 ppm (males); 0, 6,000, 12,000, 24,000 ppm (females)	*15 months*	0	0	10	20
	2 years	4	4	2	4
0, 120, 240, 500 mg/kg-day (males)[b]; 0 300, 600, 1,200 mg/kg-day (females)[b]	**C-cell, hyperplasia**				
	15 months	0	0	10	0
Diet	*2 years*	8	20	24	14
2 years	**Follicle, cyst**				
	15 months	0	0	10	10
	2 years	4	4	0	8

Reference and study design	Results[a]			
	mg/kg-day (F)	0	300	600	1,200
	Ultimobranchial cyst				
	15 months	10	30	0	0
	2 years	4	2	2	0
	C-cell, hyperplasia				
	15 months	0	10	10	0
	2 years	12	12	14	6
	Follicle, cyst				
	2 years	0	2	2	0
	Follicular cell, hyperplasia				
	2 years	0	0	0	2
NTP (1997b) Rat (F344); 15 males/group 0, 300, 2,800, 25,000 ppm 0, 20, 200, 2,200 mg/kg-day[b] Diet 10 weeks	No significant effects on thyroid histopathology reported in control or high-dose animals (quantitative data not reported).				
NTP (1997b) Rat (F344); 15 males/group 0, 300, 900, 2,800, 8,300, 25,000 ppm 0, 30, 60, 180, 550, "high" mg/kg-day[b] Diet 26 weeks	No significant effects on thyroid histopathology reported in control or high-dose animals (quantitative data not reported).				
Aso et al. (2005) Rat (Crj:CD(SD)IGS); 24 rats/sex/generation/group 0, 100, 200, 400 mg/kg-day Gavage Multigenerational study F0 and F1 exposed for 4 weeks prior to mating, through mating for 10 weeks, and until weaning of offspring (females) or necropsy (males)	No significant treatment-related effects on thyroid histopathology were reported by the study authors in F0 or F1 parental animals.				

Reference and study design	Results[a]
Tyl et al. (2004) Rat (CD); 30 F0 and F1 parental rats/sex/group 0, 750, 3,750, 11,250 ppm 0, 50, 250, 750 mg/kg-day[b] Diet Multigenerational study Exposure 10 weeks prior to mating and through mating, gestation, and lactation (females) or through 21 days after end of mating (males)	No significant treatment-related effects on thyroid histopathology were reported by the study authors in control or high-dose parental males or females (data not provided).
BIBRA (1978) Rat (Wistar); 27/sex/group or 45/sex/group (control); interim sacrifices of 9 controls/sex/group and 6 treated rats/sex/group at 2 and 6 weeks 0, 2,000, 5,000, 12,000 ppm 0, 151, 381, 960 mg/kg-day (males)[b] 0, 171, 422, 1,069 mg/kg-day (females)[b] Diet 14 weeks	No significant treatment-related effects on thyroid histopathology were reported by the study authors for males or females.

*Statistically significant (p <0.05) relative to controls based on statistics performed by the study authors.
[a]Percent change compared to control calculated as 100 × ((treated value − control value) ÷ control value).
[b]Calculated as follows: [% in diet × intake food/water (mg)] ÷ body weight (kg) = mg/kg-day.

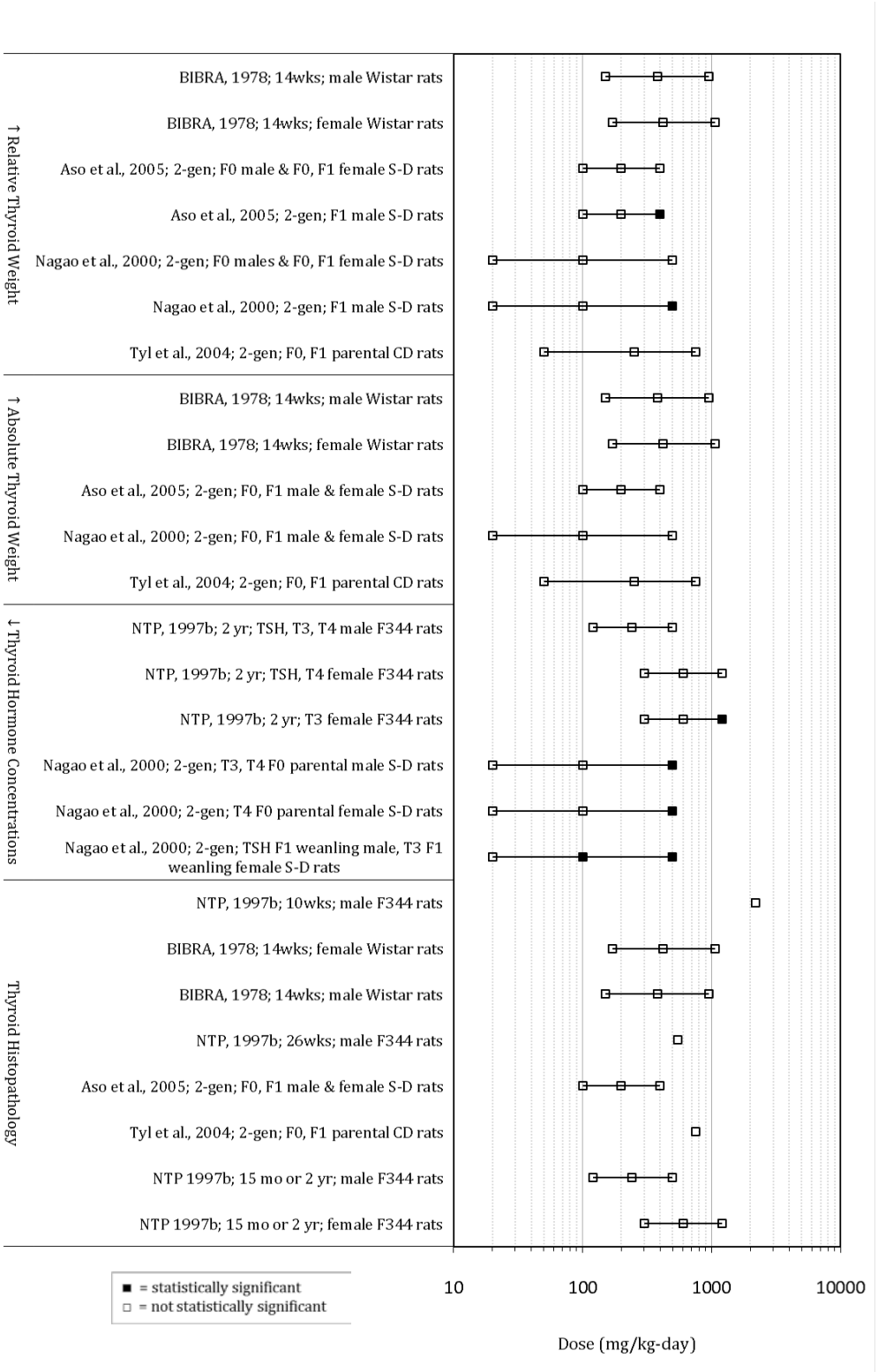

Figure 3-20. Exposure-response array of thyroid effects following oral exposure to BBP.

3.3.9. Immune Effects

Table 3-31. Evidence pertaining to immune effects in animals following oral exposure to BBP

Reference and study design	Results				
BIBRA (1978) Rat (Wistar); 27/sex/group or 45/sex/group (control); interim sacrifices of 9 controls/sex/group and 6 treated rats/sex/group at 2 and 6 weeks 0, 2,000, 5,000, 12,000 ppm 0, 151, 381, 960 mg/kg-day (males) 0, 171, 422, 1,069 mg/kg-day (females) Diet 14 weeks	**Leukocyte count** *(percent change compared to control)*				
	mg/kg-day	0	151	381	960
	male	0	−10	−10	−4
	mg/kg-day	0	171	422	1,069
	female	0	−16	−5	−8
Butala et al. (2004) B6C3F$_1$ mice, 10 female mice/dose 0, 100% BBP 10 applications of 50 µL BBP over 2 weeks then challenged with BBP 7 days later. Animals sacrificed 7 days after challenge.	*Percent change compared to control*				
	Doses (%)	0		100	
	serum IgE	0		6.1	
	IL-4 from Con A-stimulated lymph node cells	0		−52	
	IL-13 from Con A-stimulated lymph node cells	0		36	
	IL-4 m-RNA from stimulated lymph nodes	0		266	
	IL-4 m-RNA from stimulated lymph nodes	Not able to be determined due to vehicle control values being indistinguishable from background			
Dearman et al. (2009) BALB/c mice, 10 mice/dose	*Percent change compared to control*				
	Doses (%)	0	5	10	50	100
	Antibodies *IgE*: No effect (data not reported)					

Reference and study design	Results					
0, 5, 10, 50, or 100% BBP Dermal 15 applications of 100 µL at site of ovalbumin injection (21-day treatment period consisting of 5 consecutive days of treatment followed by 2 days of rest) Ovalbumin s.c. injections: initial injection of 1 µg on study day 0; follow-up injections of 0.1 µg on study day 10 and 15	*IgG*:	0	-9	12	-9	29

Con A = Concanavalin A; IL = interleukin; m-RNA = messenger ribonucleic acid

3.3.10. Neurological Effects

Table 3-32. Evidence pertaining to neurological effects in animals following oral exposure to BBP

Reference and study design	Results
Zhuang et al. (2008) Rat (Wistar); 20 females/dose; neurobehavioral development was assessed in 15–45 pups/sex/dose 0, 0.05, 0.25, 0.75% 0, 50, 250, 750 mg/kg-day (dams) Diet Dams: PNW 4 through mating, gestation, and lactation; F1 pups: GD 0–PNW 6	**Neurobehavioral effects in F1 offspring** In F1 male rats, the following changes were observed: statistically significantly impaired cliff avoidance on PND 7 in high-dose rats (score of 41 vs 61 points in controls) and statistically significantly depressed air righting on PND 14 in all exposure groups (~30–40% lower than controls[a] based on visual inspection of data shown graphically). Other statistically significant neurobehavioral differences were also reported in male offspring, including delayed surface righting on PND 3 (mid-dose group only), increased locomotion in the open field test (low and high doses) and delayed escape latency in the Morris water maze test (low dose only, on 5th day only). No significant neurobehavioral effects were observed in F1 females.
Betz et al. (2013) Rat (Sprague-Dawley); male (NR) 0, 5, 10 ppm (equivalent to 0, 2, 4 mg/kg-day as indicated by study authors) Drinking water Daily for 15 weeks (PND 40–140)	**Fear (freezing) during cue phase of fear conditioning** Significant decreased expression of fear during Cue phase with 10 ppm exposure. **Fear (freezing) during inter-trial interval phase of fear conditioning** Significant decrease in expression of fear during inter-trial interval phase with 10 ppm exposure. **Open field activity in inner portion** No significant change. **Open field activity in outer portion** No significant change. **Open field grooming activity** No significant change. **Open field rearing activity** No significant change. **Social test (contact behavior)** No significant change. **Social test (non-contact behavior)** Increased sniffing and approaching (non-contact behavior) with both treatment. **Social test (self-directed behavior)** No significant change.

3.3.11. Other Toxicity Effects

Table 3-33. Evidence pertaining to other toxicity effects in animals following oral exposure to BBP

Reference and study design	Results				
Body-weight effects[a]					
BIBRA (1978) Rat (Wistar) 27/sex/group or 45/sex/group (control); interim sacrifice of 9 controls/sex/group and 6 treated rats/sex/group at 2 and 6 weeks 0, 2,000, 5,000, 12,000 ppm 0, 151, 381, 960 mg/kg-day (males)[b]; 0, 171, 422, 1,069 mg/kg-day (females)[b] Diet 14 weeks	**Body weight** *(percent change compared to control)*				
	mg/kg-day (M)	0	151	381	960
	day 14	0	−5	−2	−5
	day 39	0	−4	−8*	−11*
	day 98	0	−8*	−8*	−7*
	mg/kg-day (F)	0	171	422	1,069
	day 14	0	2	−1	−8*
	day 39	0	2	2	−3
	day 98	0	0	−3	−5*
Nagao et al. (2000) Rat (Sprague-Dawley); 20–25 parental rats/sex/ generation/group (15–24 litters/generation/group) 0, 20, 100, 500 mg/kg-day Gavage Multigenerational study F0 males and females: exposure for 12 weeks prior to mating, 2 weeks cohabitation, and until necropsy at 23 weeks of age (males) or postpartum day (females); F1 animals: exposure from weaning until necropsy at PND 22 Note: Litters were culled to 8 rats/litter (4/sex, if possible) at PND 4. At PND 22 (F1) or PND 21 (F2), 2 rats/sex/litter were sacrificed	*Percent change compared to control*				
	mg/kg-day (M)	0	20	100	500
	F0, parental	0	−2	0	−7*
	PND 0, F1	0	0	−6*	−7*
	PND 4, F1	0	3	−5	−6
	PND 7, F1	0	2	−3	−6
	PND 14, F1	0	0	−1	−8*
	PND 21, F1	0	1	−1	−7*
	PND 22, F1 (weanling terminal body weight)	0	−2	1	−6*
	Body weight gain, PNDs 22–91, F1	0	−3	−7	−9
	F1, adult (terminal body weight)	0	−4	−7*	−13*
	PND 0, F2	0	0	0	−3
	PND 4, F2	0	3	5	0
	PND 7, F2	0	4	5	−2
	PND 14, F2	0	5	4	−5
	PND 21, F2	0	4	3	−8
	mg/kg-day (F)	0	20	100	500

Reference and study design	Results						
	F0, parental	0	−2	−1	1		
	PND 0, F1	0	2	−6*	−6*		
	PND 4, F1	0	3	−6	−6		
	PND 7, F1	0	1	−5	−6		
	PND 14, F1	0	1	−3	−8*		
	PND 21, F1	0	1	−2	−7*		
	PND 22, F1 (terminal weanling body weight)	0	1	−1	−9*		
	Body weight gain, PNDs 22−91, F1	0	0	3	2		
	F1, adult (terminal body weight)	0	1	1	0		
	PND 0, F2	0	2	0	−3		
	PND 4, F2	0	4	7	0		
	PND 7, F2	0	4	4	−4		
	PND 14, F2	0	9	4	−8		
	PND 21, F2	0	4	2	−12		
NTP (1997b) Rat (F344); 15 males/group 0, 300, 900, 2,800, 8,300, 25,000 ppm 0, 30, 60, 180, 550, "high" mg/kg-day[b] Diet 26 weeks	*Percent change compared to control*						
	mg/kg-day	0	30	60	180	550	ND
	terminal body weight	0	7	10	2	3	−30*
	body weight change	0	11	16	4	5	−44*
NTP (1997b) Rat (F344); 15 males/group 0, 300, 2,800, 25,000 ppm 0, 20, 200, 2,200 mg/kg-day[b] Diet 10 weeks	*Percent change compared to control*						
	mg/kg-day	0	20	200	2,200		
	terminal body weight	0	0	−1	−29*		
	body weight change	0	−1	−3	−45*		
NTP (1997b) Rat (F344); 60 sex/group; interim sacrifice of 10 rats/sex/group at 15 months 0, 3,000, 6,000, 12,000 ppm	**Body weight** *(percent change compared to control)*						
	mg/kg-day (M)	0	120	240	500		
	at interim sacrifice	0	0	−6*	−9*		
	at 69 weeks	0	0	−1	−6		

Reference and study design	Results				
(males); 0, 6,000, 12,000, 24,000 ppm (females) 0, 120, 240, 500 mg/kg-day (males)[b]; 0 300, 600, 1,200 mg/kg-day (females)[b] Diet 2 years	*at study termination*	0	−2	−4	−6
	mg/kg-day (F)	0	300	600	1,200
	at interim sacrifice	0	0	1	−23*
	at 69 weeks	0	−1	−5	−25
	at study termination	0	2	−3	−27
Tyl et al. (2004) Rat (CD); 30 F0 and F1 parental rats/sex/group 0, 750, 3,750, 11,250 ppm 0, 50, 250, 750 mg/kg-day[b] Diet Multigenerational study Exposure 10 weeks prior to mating and through mating, gestation, and lactation (females); or for 21 days after mating (males)	**Body weight** *(percent change compared to control)*				
	mg/kg-day (M)	0	50	250	750
	adult F0 at necropsy	0	−3	4	−2
	adult F1 at necropsy	0	1	4	−9*
	F1 offspring at necropsy	0	0	1	−18*
	F2 offspring at necropsy	0	0	2	−11*
	mg/kg-day (F)	0	50	250	750
	adult F0 at necropsy	0	0	0	−4
	adult, F1 at necropsy	0	1	3	−6*
	F1 offspring at necropsy	0	2	0	−22*
	F2 offspring at necropsy	0	3	3	−11*
	Note: No biologically significant changes were reported by the study authors for F0 parental males or females.				
Hazleton Laboratories (1958) Rat (Sprague-Dawley); 10/sex/group 0, 0.5, 2.0% (0, 5,000, 20,000 ppm) 0, 431, 1,551 mg/kg-day (males)[b]; 0, 490, 1,765 mg/kg-day (females)[b] Diet 90 days	**Body weight** *(percent change compared to control)*				
	mg/kg-day (M)	0	431	1,551	
	males	0	−1	−21*	
	mg/kg-day (F)	0	490	1,765	
	females	0	−1	−11	

Reference and study design	Results				
Aso et al. (2005) Rat (Crj:CD(SD)IGS); 24 rats/sex/generation/group 0, 100, 200, 400 mg/kg-day Gavage Multigenerational study F0 and F1 exposed for 4 weeks prior to mating, through mating for 10 weeks, and until weaning of offspring (females) or necropsy after mating (males)	**Body weight** *(percent change compared to control)*				
	mg/kg-day (M)	0	100	200	400
	F0, parental	0	2	4	−1
	F1, parental	0	0	−2	−4
	F1, offspring at PND 21	0	3	0	−2
	F2, offspring at PND 21	0	−4	0	−7
	mg/kg-day (F)	0	100	200	400
	F0, parental	0	0	6	1
	F1, parental	0	4	6	1
	Note: The study authors indicated that body weights were significantly lowered at PND 0 at 100 mg/kg-day and higher in F1 male offspring and at 100 and 400 mg/kg-day in F2 males and females. No significant effects were observed in F1 female offspring (data presented graphically).				
Betz et al. (2013) Rat (Sprague-Dawley); male (NR) 0, 5, 10 ppm (equivalent to 0, 2, 4 mg/kg-day as indicated by study authors) Drinking water Daily for 15 weeks (began PND 40 and ended PND 140)	No significant change in body weight reported by the study authors.				
Ahmad et al. (2014) Rat (Albino); P0, female (6/group) 0, 4, 20, 100 mg/kg Gavage GD 14 to parturition	**Body weight** *(percent change compared to control)*				
	mg/kg-day	0	4	20	100
	F1 adult male	0	−1	−2*	−4*
Urinary bladder histopathology					
NTP (1997b) Rat (F344); 60 sex/group; 10 rats/sex/group sacrificed at 15 mo 0, 3,000, 6,000, 12,000 ppm (males); 0, 6,000, 12,000, 24,000 ppm (females)	*Percent incidence*				
	mg/kg-day (M)	0	120	240	500
	transitional epithelium; hyperplasia	0	0	0	4
	hemorrhage	0	2	0	0
	inflammation, suppurative	0	4	0	0

Reference and study design	Results				
0, 120, 240, 500 mg/kg-day (males)[b]; 0 300, 600, 1,200 mg/kg-day (females)[b] Diet 2 years	*transitional epithelium; papilloma*	None reported (incidence data not provided)			
	adenocarcinoma, metastatic, intestine large, colon	0	0	2	0
	mg/kg-day (F)	0	300	600	1,200
	transitional epithelium; hyperplasia	8	0	2	20*
	transitional epithelium; papilloma	2	0	0	4
	edema	2	0	2	0
	hemorrhage	0	0	2	0
BIBRA (1978) Rat (Wistar); 27/sex/group or 45/sex/group (control); interim sacrifices of 9 controls/sex/group and 6 treated rats/sex/group at 2 and 6 weeks 0, 2,000, 5,000, 12,000 ppm 0, 151, 381, 960 mg/kg-day (males)[b] 0, 171, 422, 1,069 mg/kg-day (females)[b] Diet 14 weeks	*Percent incidence*				
	mg/kg-day (M)	0	151	381	960
	proteinaceous deposits; 6 weeks	11	NE	NE	0
	proteinaceous deposits; 14 weeks	4	NE	NE	0
	hyperplasia; 14 weeks	0	NE	NE	7
	mg/kg-day (F)	0	171	422	1,069
	proteinaceous deposits; 6 weeks	0	NE	NE	0
	proteinaceous deposits; 14 weeks	0	NE	NE	0
	hyperplasia; 14 weeks	0	NE	NE	0
NTP (1997b) Rat (F344); 15 males/group 0, 300, 2,800, 25,000 ppm 0, 20, 200, 2,200 mg/kg-day[b] Diet 10 weeks	No significant treatment-related effects reported in control or high-dose animals (quantitative data not reported).				
NTP (1997b) Rat (F344); 15 males/group 0, 300, 900, 2,800, 8,300, 25,000 ppm 0, 30, 60, 180, 550, "high" mg/kg-day[b]	No significant treatment- related effects reported in control or high-dose animals (quantitative data not reported).				

Reference and study design	Results			
Diet 26 weeks				
NTP (1997a) Rat (F344); 50–60/sex/group; interim sacrifice of 10 rats/sex/group at 15 months 0, 12,000 ppm (males); 0, 24,000 ppm (females) 0, 500 mg/kg-day (males)[b]; 0, 1,200 mg/kg-day (females)[b] Diet 4 exposure protocols: ad libitum feeding, weight-matched controls, restricted feed (2 years), and restricted feed (lifetime) 2 years to lifetime	**Ad libitum feeding, weight-matched protocol** *(percent incidence)*			
	mg/kg-day (M)	0 (ad libitum)	0 (weight-matched)	500
	transitional epithelium hyperplasia	0	0	4
	mg/kg-day (F)	0 (ad libitum)	0 (weight-matched)	1,200
	transitional epithelium hyperplasia	8	0	20
	Feed-restricted, 2 years or lifetime *(percent incidence)*			
	mg/kg-day (M)	0 (2 years)	500 (2 years)	0 (lifetime)	500 (lifetime)
	transitional epithelium hyperplasia	2	4	0	2
	mg/kg-day (F)	0 (2 years)	1,200 (2 years)	0 (lifetime)	1,200 (lifetime)
	transitional epithelium hyperplasia	0	28	0	32

*Statistically significant (p <0.05) relative to controls based on statistics performed by the study authors.
[a]Percent change compared to control calculated as 100 × ((treated value − control value) ÷ control value).

[b]Calculated as follows: [% in diet × intake food/water (mg)] ÷ body weight (kg) = mg/kg-day.

ND = not determined; NE = not examined

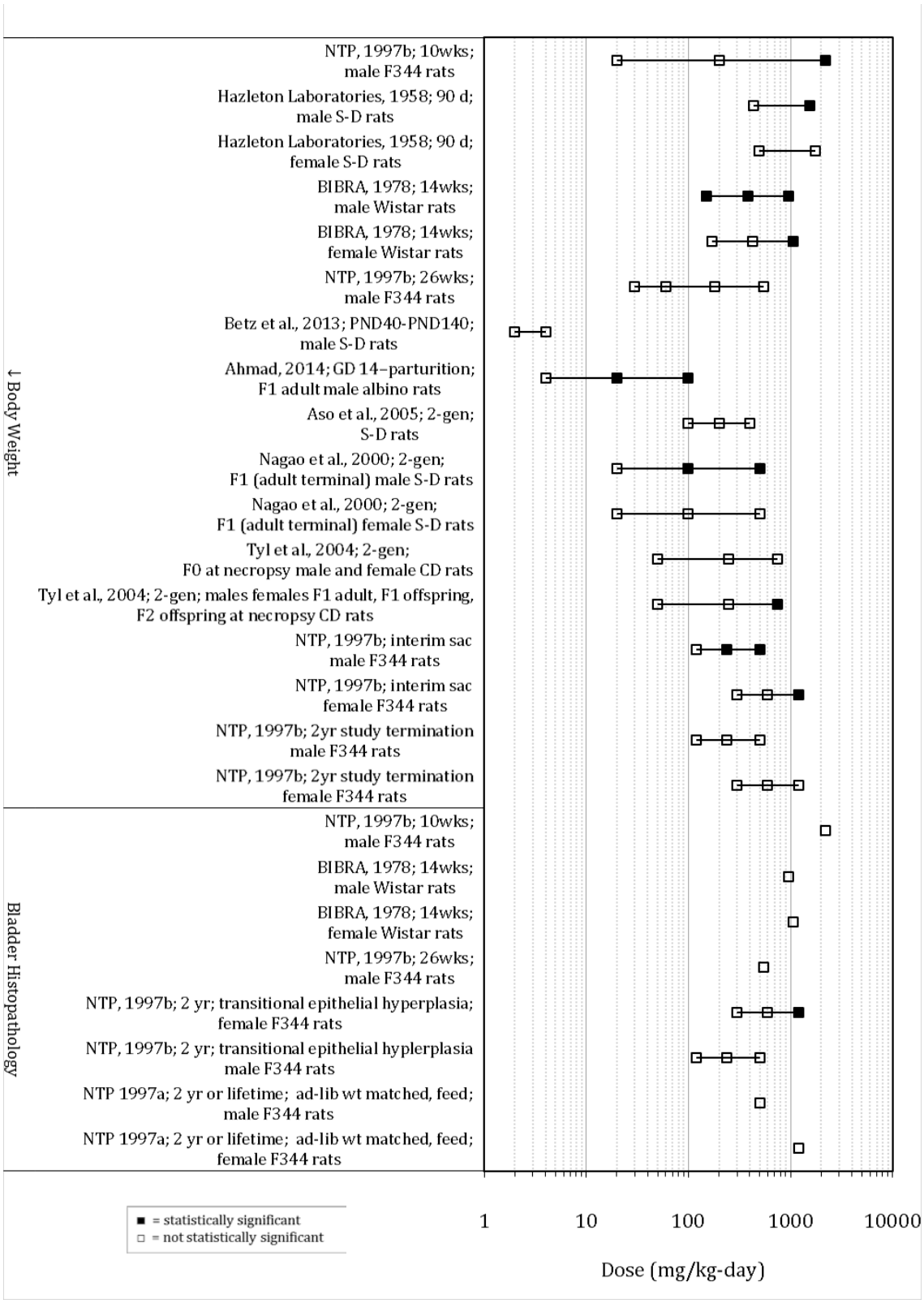

Figure 3-21. Exposure response array of other health effects following oral exposure to BBP.

3.3.12. BBP Metabolite Studies

Table 3-34. Evidence pertaining to toxicity effects in animals following exposure to BBP metabolites

Reference and study design	Results by endpoint[#]					
Developmental body weight						
Ema et al. (1996a) MBzP Rat (Wistar); P0, female (11–15/group) 0, 375, 500, 625 mg/kg-day Gavage GDs 7–9; dams sacrificed on GD 20	**Body weight of live fetuses** *(g, litter mean ± SD)*					
	Dose	0	375	500	625	
	female	3.93 (± 0.13)	3.59 (± 0.18)*	3.43 (± 0.15)*	2.97 (± 0.27)*	
	male	4.2 (± 0.18)	3.91 (± 0.17)	3.67 (± 0.28)*	3.38 (± 0.18)*	
Ema et al. (1996a) MBzP Rat (Wistar); P0, female (10–12/group) 0, 250, 375, 500, 625 mg/kg-day Gavage GDs 10–12; dams sacrificed on GD 20	**Body weight of live fetuses** *(g, litter mean ± SD)*					
	Dose	0	250	375	500	625
	female	3.77 (± 0.1)	3.73 (± 0.22)	3.78 (± 0.21)	3.45 (± 0.43)*	2.8 (± 0.21)*
	male	4.07 (± 0.13)	4.04 (± 0.23)	4.06 (± 0.23)	3.74 (± 0.3)	3.42 (± 0.76)*
Ema et al. (1996a) MBzP Rat (Wistar); P0, female (10–17/group) 0, 250, 375, 500, 625 mg/kg-day Gavage GDs 13–15; dams sacrificed on GD 20	**Body weight of live fetuses** *(g, litter mean ± SD)*					
	Dose	0	250	375	500	625
	female	3.86 (± 0.12)	3.8 (± 0.26)	3.77 (± 0.13)	3.81 (± 0.19)	3.59 (± 0.22)
	male	4.1 (± 0.12)	4.03 (± 0.22)	3.97 (± 0.22)	4 (± 0.13)	4.17
Ema et al. (1996b) MBzP Rat (Wistar); P0, female (10–14/group) 0, 250, 313, 375, 438, 500 mg/kg-day Gavage GDs 7–15; dams sacrificed on GD 20	**Body weight of live fetuses** *(g, litter mean ± SD)*						
	Dose	0	250	313	375	438	500
	female	3.84 (± 0.12)	3.64 (± 0.28)	3.65 (± 0.19)	3.52 (± 0.24)*	3.57 (± 0.21)*	3.35 (± 0.2)*
	male	4.08 (± 0.21)	3.97 (± 0.26)	3.93 (± 0.25)	3.84 (± 0.15)	3.78 (± 0.3)*	3.59 (± 0.12)*

Reference and study design	Results by endpoint[#]				
Ema et al. (1996c)	**Body weight of live fetuses** *(g, litter mean ± SD)*				
MBP	Dose	0	500	625	750
Rat (Wistar); P0, female (10–11/group)	*female*	3.77 (± 0.16)	3.46 (± 0.09)*	3.26 (± 0.17)*	3.15 (± 0.26)*
0, 500, 625, 750 mg/kg-day					
Gavage	*male*	4.05 (± 0.16)	3.74 (± 0.13)*	3.58 (± 0.17)*	3.52 (± 0.17)*
GDs 7–9; dams sacrificed on GD 20					
Ema et al. (1996c)	**Body weight of live fetuses** *(g, litter mean ± SD)*				
MBP	Dose	0	500	625	750
Rat (Wistar); P0, female (10–14/group)	*female*	3.77 (± 0.16)	3.53 (± 0.35)	3.53 (± 0.26)	2.95 (± 0.53)*
0, 500, 625, 750 mg/kg-day	*male*	4.05 (± 0.16)	3.78 (± 0.3)*	3.81 (± 0.19)	3.1 (± 0.4)*
Gavage					
GDs 10–12; dams sacrificed on GD 20					
Ema et al. (1996c)	**Body weight of live fetuses** *(g, litter mean ± SD)*				
MBP	Dose	0	500	625	750
Rat (Wistar); P0, female (10–15/group)	*female*	3.77 (± 0.16)	3.77 (± 0.17)	3.68 (± 0.17)	3.5 (± 0.12)
0, 500, 625, 750 mg/kg-day	*male*	4.05 (± 0.16)	3.97 (± 0.18)	3.9 (± 0.26)	3.81 (± 0.04)
Gavage					
GDs 13–15; dams sacrificed on GD 20					
Ema and Miyawaki (2001)	**Body weight of live fetuses** *(g, litter mean ± SD)*				
MBP	Dose	0	250	500	750	1,000
Rat (Wistar); P0, female (16/group)	*female*	3.17 (± 0.22)	3.15 (± 0.15)	2.8 (± 0.3)*	2.58 (± 0.23)*	2.32 (± 0.29)*
0, 250, 500, 750, 1,000 mg/kg-day						
Gavage	*male*	3.35 (± 0.25)	3.42 (± 0.1)	3.01 (± 0.36)*	2.71 (± 0.3)*	2.47 (± 0.29)*
GDs 0–8, with outcomes determined on GD 20						
Ema et al. (2003)	**Body weight of live fetuses** *(g, litter mean ± SD)*				
MBzP	Dose	0	167	250	375
Rat (Wistar); P0, female (16/group)	*female*	4.63 (± 0.2)	4.58 (± 0.2)	4.39 (± 0.24)	3.67 (± 0.56)*
0, 167, 250, 375 mg/kg-day	*male*	4.95 (± 0.25)	4.95 (± 0.24)	4.7 (± 0.3)	3.82 (± 0.65)*
Gavage					
GDs 15–17; dams sacrificed on GD 21					

Reference and study design	Results by endpoint[#]				
Saillenfait et al. (2003)	**Body weight of live fetuses** *(g, litter mean ± SE)*				
MBP	Dose	0	560	1,120	1,690
Rat (Sprague-Dawley); P0, female (14–15/group)	*male and female*	5.28 (± 0.07)	5.15 (± 0.16)	5.19 (± 0.15)	5.25 (± 0.16)
0, 1.8, 3.6, 5.4 mmol/kg (equivalent to 0, 560, 1,120, 1,690 mg/kg as calculated by study authors)					
Gavage					
GD 10; dams sacrificed on GD 21					
Saillenfait et al. (2003)	**Body weight of live fetuses** *(g, litter mean ± SE)*				
MBzP	Dose	0	280	560	1,120	1,690
Rat (Sprague-Dawley); P0, female (12–14/group)	*male and female*	5.04 (± 0.18)	5.25 (± 0.2)	5.14 (± 0.18)	4.82 (± 0.1)	4.93 (± 0.06)
0, 0.9, 1.8, 3.6, 5.4 mmol/kg (equivalent to 0, 280, 560, 1,120, 1,690 mg/kg as calculated by study authors)						
Gavage						
GD 10; dams sacrificed on GD 21						
Saillenfait et al. (2003)	**Body weight of live fetuses** *(g, litter mean ± SE)*				
MBP	Dose	0	280	560	1,120	1,690
Mouse (OF-1); P0, female (24–25/group)	*male and female*	1.19 (± 0.02)	1.16 (± 0.03)	1.23 (± 0.05)	1.14 (± 0.03)	1.04 (± 0.04)*
0, 0.9, 1.8, 3.6, 5.4 mmol/kg (equivalent to 0, 280, 560, 1,120, and 1,690 mg/kg as calculated by study authors)						
Gavage						
GD 8; dams sacrificed on GD 18						
Saillenfait **et al. (2003)**	**Body weight of live fetuses** *(g, litter mean ± SE)*				
MBzP	Dose	0	280	560	1,120	1,690
Mouse (OF-1); P0, female (20–23/group)	*male and female*	1.21 (± 0.03)	1.24 (± 0.05)	1.21 (± 0.02)	1.13 (± 0.02)	1.11 (± 0.07)
0, 0.9, 1.8, 3.6, 5.4 mmol/kg (equivalent to 0, 280, 560, 1,120, 1,690 mg/kg as calculated by study authors)						
Gavage						
GD 8; dams sacrificed on GD 18						

Reference and study design	Results by endpoint[#]				
Developmental embryotoxic effects					
Ema et al. (1996a) MBzP Rat (Wistar); P0, female (11–15/group) 0, 375, 500, 625 mg/kg-day Gavage GDs 7–9; dams sacrificed on GD 20	**Percent postimplantation loss per litter** *(mean)*				
	Dose	0	375	500	625
		10.2	18.9	25.7*	90.6*
	Maternal adjusted weight gain *(g, mean ± SD)*				
	Dose	0	375	500	625
		53 (± 12)	37 (± 11)*	42 (± 9)	23 (± 13)*
	Maternal food consumption				
	Significant decrease in all treatment groups during treatment, but only remained significantly lower after treatment in the 625 mg/kg group				
	Number of litters totally resorbed				
	Dose	0	375	500	625
		0	0	0	9*
	Number of live fetuses per litter *(mean ± SD)*				
	Dose	0	375	500	625
		12.7 (± 1)	11.6 (± 2.2)	10.6 (± 2.8)	1.4 (± 2.6)*
	Number of resorptions and dead fetuses per litter *(mean ± SD)*				
	Dose	0	375	500	625
		1.5 (± 0.8)	2.7 (± 2)	3.6 (± 2.7)	12.8 (± 2.5)*
	Sex ratio of live fetuses (male/female)				
	No significant change in sex ratio (male/female): 67/73 (control), 63/65 (375 mg/kg), 56/61 (500 mg/kg), 9/8 (625 mg/kg)				
Ema et al. (1996a) MBzP Rat (Wistar); P0, female (10–12/group) 0, 250, 375, 500, 625 mg/kg-day Gavage GDs 10–12; dams sacrificed on GD 20	**Percent postimplantation loss per litter** *(mean)*				
	Dose	0	250	375	500	625
		15.5	16.9	15.3	54.8*	90.4*
	Maternal adjusted weight gain *(g, mean ± SD)*				
	Dose	0	250	375	500	625
		47 (± 10)	25 (± 7)*	41 (± 6)	29 (± 12)*	31 (± 9)*
	Maternal food consumption				
	Significant decrease in food consumption during treatment as well as the remainder of gestation for all dose groups				
	Number of litters totally resorbed				

Reference and study design	Results by endpoint[#]					
	Dose	0	250	375	500	625
		0	0	0	3	7*0
	Number of live fetuses per litter *(mean ± SD)*					
	Dose	0	250	375	500	625
		11.8 (± 1.8)	11.5 (± 2.1)	11.5 (± 1.6)	6.6 (± 5.8)*	1.4 (± 2.5)*
	Number of resorptions and dead fetuses per litter *(mean ± SD)*					
	Dose	0	250	375	500	625
		2 (± 1.9)	2.4 (± 1.6)	2.2 (± 1.9)	8.2 (± 5.7)*	13.5 (± 2.4)*
	Sex ratio of live fetuses (male/female)					
	No significant change in sex ratio (male/female): 62/68 (control), 51/64 (250 mg/kg), 54/61 (375 mg/kg), 44/29 (500 mg/kg), 7/7 (625 mg/kg)					
Ema et al. (1996a)	**Percent postimplantation loss per litter** *(mean)*					
MBzP	Dose	0	250	375	500	625
Rat (Wistar); P0, female (10−17/group)		18.8	12.8	28.3	61.4*	94.2*
0, 250, 375, 500, 625 mg/kg-day	**Maternal adjusted weight gain** *(g, mean ± SD)*					
Gavage	Dose	0	250	375	500	625
GDs 13−15; dams sacrificed on GD 20		47 (± 7)	29 (± 16)*	23 (± 7)*	29 (± 14)*	25 (± 11)*
	Maternal food consumption					
	Significant decrease in food consumption in all dose groups during treatment, but only continued to be low throughout gestation in the 625 mg/kg group					
	Number of litters totally resorbed					
	Dose	0	250	375	500	625
		0	0	0	5*	11*
	Number of live fetuses per litter *(mean ±SD)*					
	Dose	0	250	375	500	625
		11.4 (± 2.2)	13.3 (± 1.2)	10 (± 3.7)	5.6 (± 5.6)*	0.8 (± 2.5)*
	Number of resorptions and dead fetuses per litter *(mean ±SD)*					
	Dose	0	250	375	500	625
		2.5 (± 1.5)	2 (± 1.2)	3.8 (± 3.2)	8.9 (± 5.6)*	13.5 (± 3.2)*
	Sex ratio of live fetuses (male/female)					

Reference and study design	Results by endpoint[#]					
	No significant change in sex ratio (male/female): 64/61 (control), 71/75 (250 mg/kg), 60/40 (375 mg/kg), 38/41 (500 mg/kg), 5/5 (625 mg/kg)					
Ema et al. (1996b)	**Percent postimplantation loss per litter** *(mean)*					
MBzP	Dose	0	250	313	375	438	500
Rat (Wistar); P0, female (10–14/group)		15.8	8.3	18.7	23.8	36.6*	82.3*
0, 250, 313, 375, 438, 500 mg/kg-day	**Food consumption during pregnancy**						
Gavage							
GDs 7–15; dams sacrificed on GD 20	Significantly lower that control on GDs 7–15 at ≥250 mg/kg and on GDs 15–20 at 500 mg/kg						
	Live fetuses per litter *(mean ±SD)*						
	Dose	0	250	313	375	438	500
		11.8 (± 2.1)	12.9 (± 2.3)	11.6 (± 1.5)	10.8 (± 2.9)	9.2 (± 5.2)	2.4 (± 3.3)*
	Number of resorptions and dead fetuses per litter *(mean ±SD)*						
	Dose	0	250	313	375	438	500
		2.2 (± 1.5)	1.2 (± 1.5)	2.8 (± 1.7)	3.4 (± 3)	5 (± 4.4)	12.2 (± 4.2)*
	Number of litters totally resorbed						
	Dose	0	250	313	375	438	500
		0	0	0	0	2	6*
	Sex ratio of live fetuses						
	Sex ratios (male/female): 54/76 (control), 65/64 (250 mg/kg), 74/65 (313 mg/kg), 55/53 (375 mg/kg), 55/65 (438 mg/kg), 13/11 (500 mg/kg)						
	Weight gain during pregnancy						
	Significantly lower than control on GDs 7–15 at ≥313 mg/kg, and on GDs 15–20 at 500 mg/kg; adjusted weight gain significantly lower that control at 500 mg/kg						
Ema et al. (1996c)	**Adjusted maternal body weight gain**						
MBP	No significant change						
Rat (Wistar); P0, female (10–11/group)	**Maternal food intake during pregnancy** *(g, mean ± SD)*						
0, 500, 625, 750 mg/kg-day	Dose	0	500	625	750		
Gavage		384 (± 22)	366 (± 27)	355 (± 20)*	336 (± 30)*		
GDs 7–9; dams sacrificed on GD 20	**Number of litters totally resorbed**						
	Dose	0	500	625	750		
		0	0	1	3		

Reference and study design	Results by endpoint[#]			
	Number of live fetuses per litter *(mean ± SD)*			
	Dose	0	500	625	750
		12.3 (± 2.4)	12.1 (± 1.9)	10.3 (± 4.1)	5.9 (± 4.5)*
	Percent postimplantation loss per litter *(mean)*			
	Dose	0	500	625	750
		13.3	18.4	27.8*	57.7*
	Sex ratio of live fetuses			
	No significant change in sex ratio of live fetuses (male/female): 59/64 (control), 53/68 (500 mg/kg), 46/66 (625 mg/kg), 30/35 (750 mg/kg)			
Ema et al. (1996c) MBP Rat (Wistar); P0, female (10–14/group) 0, 500, 625, 750 mg/kg-day Gavage GDs 10–12; dams sacrificed on GD 20	**Adjusted maternal body weight gain**			
	No significant change			
	Maternal food intake during pregnancy *(g, mean ± SD)*			
	Dose	0	500	625	750
		384 (± 22)	387 (± 16)	370 (± 27)	349 (± 28)*
	Number of litters totally resorbed			
	Dose	0	500	625	750
		0	0	0	9*
	Number of live fetuses per litter *(mean ±SD)*			
	Dose	0	500	625	750
		12.3 (± 2.4)	11.2 (± 2.8)	7.5 (± 3.8)*	1.8 (± 3.3)*
	Percent postimplantation loss per litter *(mean)*			
	Dose	0	500	625	750
		13.3	24.6	46.4*	86.9*
	Sex ratio of live fetuses			
	No significant change in sex ratio of live fetuses (male/female): 59/64 (control), 58/54 (500 mg/kg), 40/42 (625 mg/kg), 15/10 (750 mg/kg)			
Ema et al. (1996c) MBP Rat (Wistar); P0, female (10–15/group) 0, 500, 625, 750 mg/kg-day Gavage GDs 13–15; dams sacrificed on GD 20	**Adjusted maternal body weight gain**			
	No significant change			
	Maternal food intake during pregnancy *(g, mean ± SD)*			
	Dose	0	500	625	750
		384 (± 22)	372 (± 22)	370 (± 18)	350 (± 21)*
	Number of litters totally resorbed			
	Dose	0	500	625	750

Reference and study design	Results by endpoint[#]				
	P0, female	0	0	2	12*
	Number of live fetuses per litter *(mean ±SD)*				
	Dose	0	500	625	750
		12.3 (± 2.4)	8.6 (± 3.5)	4.6 (± 3.4)*	0.6 (± 1.5)*
	Percent postimplantation loss per litter *(mean)*				
	Dose	0	500	625	750
		13.3	34.7*	66.8*	95.5*
	Sex ratio of live fetuses				
	No significant change in sex ratio of live fetuses (male/female): 59/64 (control), 55/40 (500 mg/kg), 25/26 (625 mg/kg), 3/6 (750 mg/kg)				
Ema and Miyawaki (2001) MBP Rat (Wistar); P0, female (16/group) 0, 250, 500, 750, 1,000 mg/kg-day Gavage GDs 0−8 with outcomes determined on GD 20	**Adjusted maternal weight gain** *(g, mean ± SD)*				
	Dose	0	250	500	750	1,000
		33 (± 13)	38 (± 9)	31 (± 10)	37 (± 13)	25 (± 12)
	Maternal adjusted weight gain (body weight gain excluding uterus) was not statistically significantly different among treated and controls					
	Number of live fetuses per litter *(mean ±SD)*					
	Dose	0	250	500	750	1,000
		14.1 (± 1.6)	13.7 (± 2.7)	13.9 (± 2.4)	12.7 (± 2.7)	10.8 (± 3.7)*
	Number of resorptions and dead fetuses per litter *(mean ±SD)*					
	Dose	0	250	500	750	1,000
		1.4 (± 1.5)	1 (± 1)	1.7 (± 1.7)	2.4 (± 2)	3.7 (± 3.1)*
	Percent postimplantation loss per litter *(mean)*					
	Dose	0	250	500	750	1,000
		9.1	6.4	11.3	15.9	26.3*
	Postimplantation loss = (number of resorptions and dead fetuses/ number of implantations) × 100					
	Percent preimplantation loss per female *(mean)*					
	Dose	0	250	500	750	1,000
		5.9	8.7	9.8	19.2	20.2*
	n = number of pregnant females; preimplantation loss = ((number of corpora lutea − number of implantations)/number of corpora lutea) × 100					

Reference and study design	Results by endpoint[#]
	Percent preimplantation loss per litter
	Dose: 0 / 250 / 500 / 750 / 1,000
	5.9 / 8.7 / 3.7 / 7.6 / 8.7
	n = number of litters; preimplantation loss = ((number of corpora lutea − number of implantations)/number of corpora lutea) × 100
	Sex ratio of live fetuses (male/female)
	No significant difference in sex ratio (males/females): 121/104 (controls), 120/99 (250 mg/kg), 108/100 (500 mg/kg), 98/80 (750 mg/kg), 77/74 (1,000 mg/kg)
Ema et al. (2003) MBzP Rat (Wistar); P0, female (16/group) 0, 167, 250, 375 mg/kg-day Gavage GDs 15−17; dams sacrificed on GD 21	**Body weight gain during pregnancy**
	Maternal body weight gain significantly decreased on GDs 15−18 at ≥167 mg/kg and GDs 18−21 at ≥250 mg/kg; adjusted weight gain significantly reduced at ≥250 mg/kg
	Food consumption during pregnancy
	Maternal food consumption significantly decreased on GDs 15−18 at ≥167 mg/kg and GDs 18−21 at ≥250 mg/kg
	Number of litters totally resorbed
	Dose: 0 / 167 / 250 / 375
	0 / 0 / 0 / 0
	Number of live fetuses per litter *(mean ±SD)*
	Dose: 0 / 167 / 250 / 375
	14.1 (± 1.8) / 12.8 (± 1.9) / 13.8 (± 0.8) / 13.2 (± 1.9)
	Number of resorptions and dead fetuses per litter *(mean ±SD)*
	Dose: 0 / 167 / 250 / 375
	1.4 (± 1.1) / 0.7 (± 0.9) / 1.1 (± 0.8) / 1.3 (± 1.9)
	Percent postimplantation loss per litter *(mean)*
	Dose: 0 / 167 / 250 / 375
	9.7 / 5.3 / 8.1 / 10.9
	Sex ratio of live fetuses (male/female)
	No significant change in sex ratio of live fetuses (male/female): 105/101 (control), 109/96 (167 mg/kg), 107/114 (250 mg/kg), 117/94 (375 mg/kg)
Saillenfait et al. (2003) MBP Rat (Sprague-Dawley); P0, female (14−15/group)	**Number of live fetuses per litter** *(mean ±SD)*
	Dose: 0 / 560 / 1,120 / 1,690
	13.46 (± 0.77) / 13.92 (± 0.55) / 13.5 (± 0.69) / 12.77 (± 0.67)
	Percent postimplantation loss per litter *(mean ± SE)*

Reference and study design	Results by endpoint[#]				
0, 1.8, 3.6, 5.4 mmol/kg (equivalent to 0, 560, 1,120, 1,690 mg/kg as calculated by study authors)	Dose	0	560	1,120	1,690
		2.1 (± 1.08)	4.38 (± 1.77)	1.79 (± 1.28)	6.1 (± 1.99)
Gavage	**Percent resorptions per litter** *(mean ± SE)*				
GD 10; sacrificed on GD 21	Dose	0	560	1,120	1,690
		2.1 (± 1.08)	4.38 (± 1.77)	1.79 (± 1.28)	6.1 (± 1.99)
Saillenfait et al. (2003)	**Number of live fetuses per litter** *(mean ±SE)*				
MBzP	Dose	0	280	560	1,120	1,690
Rat (Sprague-Dawley); P0, female (12−14/group)		13.77 (± 1.08)	12.83 (± 1.15)	13.67 (± 1.14)	14.17 (± 0.55)	13.75 (± 1.7)
0, 0.9, 1.8, 3.6, 5.4 mmol/kg (equivalent to 0, 280, 560, 1,120, 1,690 mg/kg as calculated by study authors)	**Percent postimplantation loss per litter** *(mean ± SE)*					
	Dose	0	280	560	1,120	1,690
Gavage		1.61 (± 0.87)	4.1 (± 1.67)	7.44 (± 4.07)	6.2 (± 1.81)	8.93 (± 8.93)
GD 10; sacrificed on GD 21	**Percent resorptions per litter** *(mean ± SE)*					
	Dose	0	280	560	1,120	1,690
		1.61 (± 0.87)	4.1 (± 1.67)	7.44 (± 4.07)	6.2 (± 1.81)	8.93 (± 8.93)
Saillenfait et al. (2003)	**Number of live fetuses per litter** *(mean ±SE)*					
MBP	Dose	0	280	560	1,120	1,690
Mouse (OF-1); P0, female (24−25/group)		12.35 (± 0.88)	12.38 (± 0.71)	6.64 (± 0.91)*	2.32 (± 0.69)*	2.33 (± 0.58)*
0, 0.9, 1.8, 3.6, 5.4 mmol/kg (equivalent to 0, 280, 560, 1,120, 1,690 mg/kg as calculated by study authors)	**Percent postimplantation loss per litter** *(mean ± SE)*					
Gavage	Dose	0	280	560	1,120	1,690
GD 8; sacrificed on GD 18		9.59 (± 2.76)	11.25 (± 2.5)	40.83 (± 6.22)*	83.31 (± 5.03)*	82.42 (± 4.31)*
	Percent resorptions per litter *(mean ± SE)*					
	Dose	0	280	560	1,120	1,690
		9.3 (± 2.76)	10.21 (± 2.48)	40.15 (± 6.17)*	82.21 (± 4.96)*	80.66 (± 4.45)*
Saillenfait et al. (2003)	**Number of live fetuses per litter** *(mean ±SE)*					
MBzP	Dose	0	280	560	1,120	1,690
Mouse (OF-1); P0, female (20−23/group)		11.07 (± 1.4)	11.25 (± 1.1)	12.11 (± 0.88)	12.82 (± 0.54)	7.5 (± 1.58)
0, 0.9, 1.8, 3.6, 5.4 mmol/kg (equivalent to 0, 280, 560, 1,120, 1,690 mg/kg as calculated by study authors)	**Percent postimplantation loss per litter** *(mean ± SE)*					

Reference and study design	Results by endpoint[#]					
Gavage	Dose	0	280	560	1,120	1,690
GD 8; sacrificed on GD 18		14.17 (± 7.15)	14.69 (± 3.16)	7.8 (± 2.51)	12.24 (± 2.57)	47.38 (± 10.45)*
	Resorptions per litter *(mean ± SE)*					
	Dose	0	280	560	1,120	1,690
		14.17 (± 7.15)	14.69 (± 3.16)	7.8 (± 2.51)	10.99 (± 2.39)	45.95 (± 10.35)*
Developmental teratological effects						
Ema et al. (1996a)	**Number of fetuses with external malformations**					
MBzP	Dose	0	375	500	625	
Rat (Wistar); P0, female (11–15/group)		0	0	1	0	
0, 375, 500, 625 mg/kg-day	**Number of fetuses with internal malformations**					
Gavage	Dose	0	375	500	625	
GDs 7–9; dams sacrificed on GD 20		0	2	6	10	
	Dilation of renal pelvis					
	Number of fetuses with skeletal malformations					
	Dose	0	375	500	625	
		2	6	7	10	
	Mainly fusion or absence of ribs, fusion or absent cervical/thoracic/ lumbar vertebral arches or bodies					
Ema et al. (1996a)	**Number of fetuses with external malformations**					
MBzP	Dose	0	250	375	500	625
Rat (Wistar); P0, female (10–12/group)		0	0	0	0	0
0, 250, 375, 500, 625 mg/kg-day	**Number of fetuses with internal malformations**					
Gavage	Dose	0	250	375	500	625
GDs 10–12; dams sacrificed on GD 20		1	0	0	0	0
	Number of fetuses with skeletal malformations					
	Dose	0	250	375	500	625
		1	1	0	1	0

Reference and study design	Results by endpoint[#]					
Ema et al. (1996a)	**Number of fetuses with external malformations**					
MBzP	Dose	0	250	375	500	625
Rat (Wistar); P0, female (10–17/group)		1	0	3	11	1
0, 250, 375, 500, 625 mg/kg	Mainly cleft palate					
Gavage	**Number of fetuses with internal malformations**					
GDs 13–15; dams sacrificed on GD 20	Dose	0	250	375	500	625
		0	0	0	0	0
	Number of fetuses with skeletal malformations					
	Dose	0	250	375	500	625
		0	3	6	13	3
	Mainly fusion of the sternebrae					
Ema et al. (1996b)	**Number of fetuses with external malformations**					
MBzP	Dose	0	250	313	375	438	500
Rat (Wistar); P0, female (10–14/group)		0	1	1	0	13	1
0, 250, 313, 375, 438, 500 mg/kg-day	Mainly cleft palate						
Gavage	**Number of fetuses with internal malformations**						
GDs 7–15; dams sacrificed on GD 20	Dose	0	250	313	375	438	500
		0	0	7	6	10	5
	Included mainly dilatation of renal pelvis and hypoplasia of the kidney						
	Number of fetuses with skeletal malformations						
	Dose	0	250	313	375	438	500
		0	1	8	12	13	6
	Included mainly fusion or absence of cervical vertebral arches, fusion or absence of ribs or sternebrae						
Ema et al. (1996c)	**Number of fetuses with external malformations**					
MBP	Dose	0	500	625	750	
Rat (Wistar); P0, female (10–11/group)		0	0	5	4	
0, 500, 625, 750 mg/kg-day	Mainly cleft palate and agenesis of the lower body					
Gavage	**Number of fetuses with internal malformations**					
GDs 7–9; dams sacrificed on GD 20	Dose	0	500	625	750	
		0	0	3	0	
	Dilation of renal pelvis and hypoplasia of kidney					
	Number of fetuses with skeletal malformations					
	Dose	0	500	625	750	

Reference and study design	Results by endpoint[#]			
	1	10	10	14
	Mainly fusion and/or absence of cervical vertebral arches			
Ema et al. (1996c)	**Number of fetuses with external malformations**			
MBP	Dose	0	500	625	750
Rat (Wistar); P0, female (10–14/group)		0	0	0	1
0, 500, 625, 750 mg/kg-day	**Number of fetuses with internal malformations**			
Gavage	Dose	0	500	625	750
GDs 10–12; dams sacrificed on GD 20		0	3	1	0
	Dilation of the renal pelvis			
	Number of fetuses with skeletal malformations			
	Dose	0	500	625	750
		1	0	0	0
Ema et al. (1996c)	**Number of fetuses with external malformations**			
MBP	Dose	0	500	625	750
Rat (Wistar); P0, female (10–15/group)		0	1	16	9
0, 500, 625, 750 mg/kg-day	Mainly cleft palate			
Gavage	**Number of fetuses with internal malformations**			
GDs 13–15; dams sacrificed on GD 20	Dose	0	500	625	750
		0	0	0	0
	Number of fetuses with skeletal malformations			
	Dose	0	500	625	750
		1	6	10	5
	Mainly fusion of the sternebrae			
Saillenfait et al. (2003)	**Percent of malformed fetuses** *(%)*			
MBP	Dose	0	560	1,120	1,690
Rat (Sprague-Dawley); P0, female (14–15/group)		0	0	0	0
0, 1.8, 3.6, 5.4 mmol/kg (equivalent to 0, 560, 1,120, 1,690 mg/kg as calculated by study authors)	Statistical significance not evaluated			
Gavage				
GD 10; sacrificed on GD 21				

Reference and study design	Results by endpoint[#]				
Saillenfait et al. (2003)	**Percent of malformed fetuses**				
MBzP	Dose	280	560	1,120	1,690
Rat (Sprague-Dawley); P0, female (12–14/group)		0[a]	0.6	0	0
0, 0.9, 1.8, 3.6, 5.4 mmol/kg (equivalent to 0, 280, 560, 1,120, 1,690 mg/kg as calculated by study authors)	Statistical significance not evaluated				
Gavage					
GD 10; sacrificed on GD 21					
Saillenfait et al. (2003)	**Percent of malformed fetuses**				
MBP	Dose	0	280	560	1,120	1,690
Mouse (OF-1); P0, female (24–25/group)		0	0.4	2	9.8	34.7
0, 0.9, 1.8, 3.6, 5.4 mmol/kg (equivalent to 0, 280, 560, 1,120, and 1,690 mg/kg as calculated by study authors)	Statistical significance not evaluated					
Gavage						
GD 8; sacrificed on GD 18						
Saillenfait et al. (2003)	**Percent of malformed fetuses**					
MBzP	Dose	0	280	560	1,120	1,690
Mouse (OF-1); P0, female (20–23/group)		0	0	0	3.2	22.9
0, 0.9, 1.8, 3.6, 5.4 mmol/kg (equivalent to 0, 280, 560, 1,120, and 1,690 mg/kg as calculated by study authors)	Statistical significance not evaluated					
Gavage						
GD 8; sacrificed on GD 18						
Female reproductive effects						
Ema et al. (1996a)	**Number of implantations per litter** *(mean ± SD)*					
MBzP	Dose	0	375	500	625	
Rat (Wistar); P0, female (11–15/group)		14.2 (± 1)	14.4 (± 1.5)	14.3 (± 1.1)	14.2 (± 1.6)	
0, 375, 500, 625 mg/kg-day						
Gavage						
GDs 7–9; dams sacrificed on GD 20						
Ema et al. (1996a)	**Number of implantations per litter** *(mean ± SD)*					
MBzP	Dose	0	250	375	500	625
Rat (Wistar); P0, female (10–12/group)		14 (± 0.6)	13.9 (± 1.4)	13.7 (± 1.8)	14.8 (± 1.7)	14.9 (± 1.4)
0, 250, 375, 500, 625 mg/kg						

Reference and study design	Results by endpoint[#]					
Gavage Dams dosed on GD 10–12 and sacrificed on GD 20						
Ema et al. (1996a) MBzP Rat (Wistar); P0, female (10–17/group) 0, 250, 375, 500, 625 mg/kg-day Gavage GDs 13–15; dams sacrificed on GD 20	**Number of implantations per litter** *(mean ± SD)*					
	Dose	0	250	375	500	625
		13.9 (± 1)	15.2 (± 1.5)	13.8 (± 1)	14.6 (± 0.8)	14.2 (± 1.5)
Ema et al. (1996b) MBzP Rat (Wistar); P0, female (10–14/group) 0, 250, 313, 375, 438, 500 mg/kg-day Gavage GDs 7–15; dams sacrificed on GD 20	**Number of implantations per litter** *(mean ± SD)*					
	Dose	0	250	313	375	438	500
		14 (± 1.3)	14.1 (± 2.1)	14.3 (± 1.7)	14.2 (± 0.9)	14.2 (± 1.5)	14.6 (± 1.1)
Ema et al. (1996c) MBuP Rat (Wistar); P0, female (10–11/group) 0, 500, 625, 750 mg/kg-day Gavage GDs 7–9; dams sacrificed on GD 20	**Number of implantations per litter** *(mean ± SD)*				
	Dose	0	500	625	750
		14.2 (± 1.1)	15 (± 1.3)	14.2 (± 1.3)	14.5 (± 1.9)
Ema et al. (1996c) MBP Rat (Wistar); P0, female (10–14/group) 0, 500, 625, 750 mg/kg Gavage GDs 10–12; dams sacrificed on GD 20	**Number of implantations per litter** *(mean ± SD)*				
	Dose	0	500	625	750
		14.2 (± 1.1)	14.8 (± 0.8)	14.5 (± 1.3)	13.6 (± 2.2)
Ema et al. (1996c) MBP Rat (Wistar); P0, female (10–15/group) 0, 500, 625, 750 mg/kg-day Gavage GDs 13–15; dams sacrificed on GD 20	**Number of implantations per litter** *(mean ± SD)*				
	Dose	0	500	625	750
		14.2 (± 1.1)	14.4 (± 2.4)	14.5 (± 2.3)	14.2 (± 1.7)

Reference and study design	Results by endpoint[#]				
Ema and Miyawaki (2001)	**Number of corpora lutea per litter** *(mean ± SD)*				
MBP	Dose	0	250	500	750	1,000
Rat (Wistar); P0, female (16/group)		16.5 (± 1.2)	16 (± 1.2)	16.2 (± 1)	16.4 (± 1.8)	15.9 (± 0.9)
0, 250, 500, 750, 1,000 mg/kg-day	n = number of litters					
Gavage	**Number of implantations per female** *(mean ± SD)*					
GDs 0–8 with outcomes determined on GD 20	Dose	0	250	500	750	1,000
		15.5 (± 1.3)	14.6 (± 2.5)	14.6 (± 4.2)	13.2 (± 5.4)	12.7 (± 5.1)*
	n = number of pregnant females					
	Number of implantations per litter *(mean ± SD)*					
	Dose	0	250	500	750	1,000
		15.5 (± 1.3)	14.6 (± 2.5)	15.6 (± 1.5)	15.1 (± 1.8)	14.5 (± 1.3)
	n = number of litters					
Ema et al. (2003)	**AGD**					
MBzP	Data presented graphically; no significant effect on AGD of female fetuses					
Rat (Wistar); P0, female (16/group)	**AGD per cube root of body weight ratio**					
0, 167, 250, 375 mg/kg-day	Data presented graphically; no significant effect in female fetuses					
Gavage	**Number of corpora lutea per litter** *(mean ± SD)*					
GDs 15–17; dams sacrificed on GD 21	Dose	0	167	250	375	
		15.7 (± 1.1)	15.1 (± 1.3)	15.9 (± 1.2)	16.1 (± 1.1)	
	Number of implantations per litter *(mean ± SD)*					
	Dose	0	167	250	375	
		14.3 (± 2)	13.5 (± 1.5)	15.1 (± 1.2)	14.8 (± 1.2)	
Saillenfait et al. (2003)	**Number of implantations per litter** *(mean ± SE)*					
MBP	Dose	0	560	1,120	1,690	
Rat (Sprague-Dawley); P0, female (14–15/group)		13.73 (± 0.73)	14.62 (± 0.63)	13.75 (± 0.68)	13.62 (± 0.69)	
0, 1.8, 3.6, 5.4 mmol/kg (equivalent to 0, 560, 1,120, 1,690 mg/kg as calculated by study authors)	**Percent pregnant**					
	Dose	0	560	1,120	1,690	
Gavage		79	93	86	87	
GD 10; sacrificed on GD 21	Statistical significance not evaluated					

Reference and study design	Results by endpoint[#]					
Saillenfait et al. (2003)	**Number of implantations per litter** *(mean ± SE)*					
MBzP	Dose	0	280	560	1,120	1,690
Rat (Sprague-Dawley); P0, female (12–14/group)		14 (± 1.09)	13.5 (± 1.26)	14.5 (± 0.94)	15.08 (± 0.45)	15 (± 0.71)
0, 0.9, 1.8, 3.6, 5.4 mmol/kg (equivalent to 0, 280, 560, 1,120, 1,690 mg/kg as calculated by study authors)	**Percent pregnant**					
	Dose	0	280	560	1,120	1,690
Gavage		93	92	86	93	75
GD 10; sacrificed on GD 21	Statistical significance not evaluated					
Saillenfait et al. (2003)	**Number of implantations per litter** *(mean ± SE)*					
MBP	Dose	0	280	560	1,120	1,690
Mouse (OF-1); P0, female (24–25/group)		13.45 (± 0.89)	13.71 (± 0.65)	11.27 (± 1.04)	12.73 (± 0.72)	13.24 (± 0.75)
0, 0.9, 1.8, 3.6, 5.4 mmol/kg (equivalent to 0, 280, 560, 1,120, 1,690 mg/kg as calculated by study authors)	**Percent pregnant**					
	Dose	0	280	560	1,120	1,690
Gavage						
GD 8; sacrificed on GD 18		83	88	88	96	88
	Statistical significance not evaluated					
Saillenfait et al. (2003)	**Number of implantations per litter** *(mean ± SE)*					
MBzP	Dose	0	280	560	1,120	1,690
Mouse (OF-1); P0, female (20–23/group)		11.93 (± 1.34)	13.06 (± 1.27)	13.05 (± 0.83)	14.59 (± 0.41)	14.5 (± 0.66)
0, 0.9, 1.8, 3.6, 5.4 mmol/kg (equivalent to 0, 280, 560, 1,120, 1,690 mg/kg as calculated by study authors)	**Percent pregnant**					
Gavage	Dose	0	280	560	1,120	1,690
GD 8; sacrificed on GD 18		71	80	83	86	86
	Statistical significance not evaluated					
Male hormones						
Shono et al. (2000)	**Testosterone content of the testes** *(pg/testis,testis mean ± SE)*					
MBP	Dose	0		300		
Rat (Wistar-King A)		852 (± 80.3)		50.9 (± 3.8)*		
Equivalent to 0 and 300 mg/kg-day						
Gavage						
GDs 15–18						

Reference and study design	Results by endpoint[#]			
Male malformations				
Shono et al. (2000) MBP Rat (Wistar-King A) Equivalent to 0 and 300 mg/kg-day Gavage GDs 15−18	**Degree of transabdominal testicular migration** *(number of units from bladder neck where 100 U = distance from bladder neck to lower pole of kidney; mean ± SE)*			
	Dose	0	300	
		9.3 (± 1.9)	57.9 (± 2.6)*	
	Epididymis: nonneoplastic lesions			
	Poorly developed epididymis			
	Testis: nonneoplastic lesions			
	No remarkable changes in the morphological features of Sertoli and Leydig cells			
Shono et al. (2000) MBP Rat (Wistar-King A) Equivalent to 0 and 300 mg/kg-day Gavage GDs 11−14	**Degree of transabdominal testicular migration** *(number of units from bladder neck where 100 U = distance from bladder neck to lower pole of kidney; mean ± SE)*			
	Dose	0	300	
		9.3 (± 1.9)	24.5 (± 5.2)*	
Shono et al. (2000) MBP Rat (Wistar-King A) Equivalent to 0 and 300 mg/kg-day Gavage GDs 7−10	**Degree of transabdominal testicular migration** *(number of units from bladder neck where 100 U = distance from bladder neck to lower pole of kidney; mean ± SE)*			
	Dose	0	300	
		9.3 (± 1.9)	12.3 (± 5.9)	
Male puberty, reproductive development				
Ema et al. (2003) MBzP Rat (Wistar); P0, female (16/group) 0, 167, 250, 375 mg/kg-day Gavage GDs 15−17; dams sacrificed on GD 21	**AGD**			
	Data presented graphically; AGD significantly reduced at 250 and 375 mg/kg in male fetuses			
	AGD per cube root of body weight ratio			
	Data presented graphically; significantly lower in 250 and 375 mg/kg groups than in control group			
	Degree of transabdominal testicular ascent *(number of units from bladder neck where 100 U = distance from bladder neck to lower pole of kidney; mean ± SD)*			
	Dose	0	167	250	375
		18.9 (± 0.3)	18.4 (± 2.3)	23.8 (± 7.1)*	40.1 (± 8.2)*

Reference and study design	Results by endpoint[#]				
	Number of fetuses with undescended testes				
	Dose	0	167	250	375
		2	1	21	79
Shono and Suita (2003) MBP Rat (Wistar-King A); P0, female (6/group) 0, 125, 250, 500, 1,000 mg/kg-day Gavage	**Degree of transabdominal testicular ascent** *(number of units from bladder neck where 100 U = distance from bladder neck to lower pole of kidney; mean ± SD)*				
	Dose	0	125	250	500	1,000
		8.5 (± 1.3)	9.5 (± 1.4)	18.5 (± 1.9)*	33.7 (± 2.8)*	58.6 (± 2.1)*
GDs 15−17; half of sacrificed on GD 20 for fetal examination; remaining offspring examined PNDs 60−70	**Percent of fetuses with undescended testis**				
	Dose	0	125	250	500	1,000
		0	0	25*	61.1*	76.9*

*Result is statistically significant (p <0.05) based on analysis of data by study authors. [#] Results are presented as the raw data as reported by the study authors.

− = for controls, no response relevant; for other doses, no quantitative response reported; (n) = number evaluated from group; NR = not reported

3.4. PRELIMINARY MECHANISTIC INFORMATION FOR BBP

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

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

The information extracted from each study and included in the database, corresponds to the column headings in the spreadsheet, and is as follows: link to HERO record (contained within a URL that links to the study abstract in the HERO database), HERO ID, author(s), year, molecular formulation, in vitro/in vivo, species, cell type, endpoint(s) (i.e., mechanistic outcomes), assay, and mechanistic category. The database supports sorting capabilities, e.g., data can be organized by assay. The database is available through HERO at [http://hero.epa.gov/index.cfm?action=reference.details&reference_id=2451132]. 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 BBP mechanistic studies consists of 31 mechanistic outcomes from 18 in vivo studies, as well as 266 mechanistic outcomes from 84 in vitro assays. Table 3-35 presents a summary of the mechanistic outcomes recorded in the database from each study identified.

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

(11) cellular differentiation and transformation; (12) cellular energetics; and (13) "other," to capture those mechanistic outcomes not easily assigned to a defined category. Mechanistic outcomes in the "other" category include gene expression, proteomics and metabolomics arrays, hormone production, and markers of angiogenesis. The ADME category above includes studies reporting the cellular metabolism of BBP, thermodynamics of protein binding, and cellular transport.

Table 3-35. Summary of mechanistic outcomes evaluated following BBP administration

Mechanistic category	Total # outcomes/ # studies	In vivo (# outcomes/# studies)			In vitro (# outcomes/# studies)				
		Total	Rat	Mouse	Total	Human	Primate	Rat	Mouse
Mutation[a]	9/9	0	0	0	9/9	0	0	0	5/5
DNA damage	6/4	1/1	0	1/1	5/3	1/1	0	0	4/2
DNA repair									
Oxidative stress[b]	8/5	3/2	0	2/1	5/3	0	0	0	5/3
Cell death and division[c]	86/43	1/1	1/1	0	86/43	58/28	0	10/7	12/9
Pathology[d]	12/9	3/3	2/2	1/1	9/7	1/1	0	6/4	0
Epigenetics	3/2	1/1	1/1	0	2/1	2/1	0	0	0
Receptor-mediated and cell signaling[e]	81/38	5/5	3/3	0	76/34	34/18	6/1	5/3	3/2
Immune system[f]	8/5	0	0	0	8/5	3/1	0	0	3/2
Cellular & molecular ADME	4/4	1/1	0	1/1	3/3	3/3	0	0	0
Cellular differentiation and transformation	26/11	2/2	0	2/2	24/11	14/4	0	2/1	8/6
Cellular energetics	1/1	0	0	0	1/1	1/1	0	0	0
Other[g]	53/25	14/8	11/5	1/1	38/19	26/10	0	8/5	1/1
Total	297/94	31/18			266/84				

[a]Database included four outcomes in four studies utilizing *Salmonella typhimurium.*
[b]Database included one outcome in one study utilizing fish in vivo.
[c]Database included one outcome in one study/each utilizing porcine or avian cells, and four endpoints from one study of cultured bovine cells.
[d]Database included one outcome in one study/each utilizing porcine or hamster cells.
[e]Database included one outcome in one study/each utilizing fish or frogs in vivo; one endpoint from one study using fish cells, two outcomes from one study/each using hamster or avian cells, five endpoints from two studies using frog cells, and nine outcomes from five studies using bovine cells in vitro.
[f]Database included two outcomes in one study using rabbit cells in vitro.

[g]Database included two outcomes in one study/each using fish in vivo, as well as porcine, bovine or frog cells in vitro; endpoints primarily consisted of gene expression, proteomics and metabolomics arrays, hormone production, and markers of angiogenesis.

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 BBP-specific information available.

Information summarized in Table 3-35 and Figure 3-14 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.

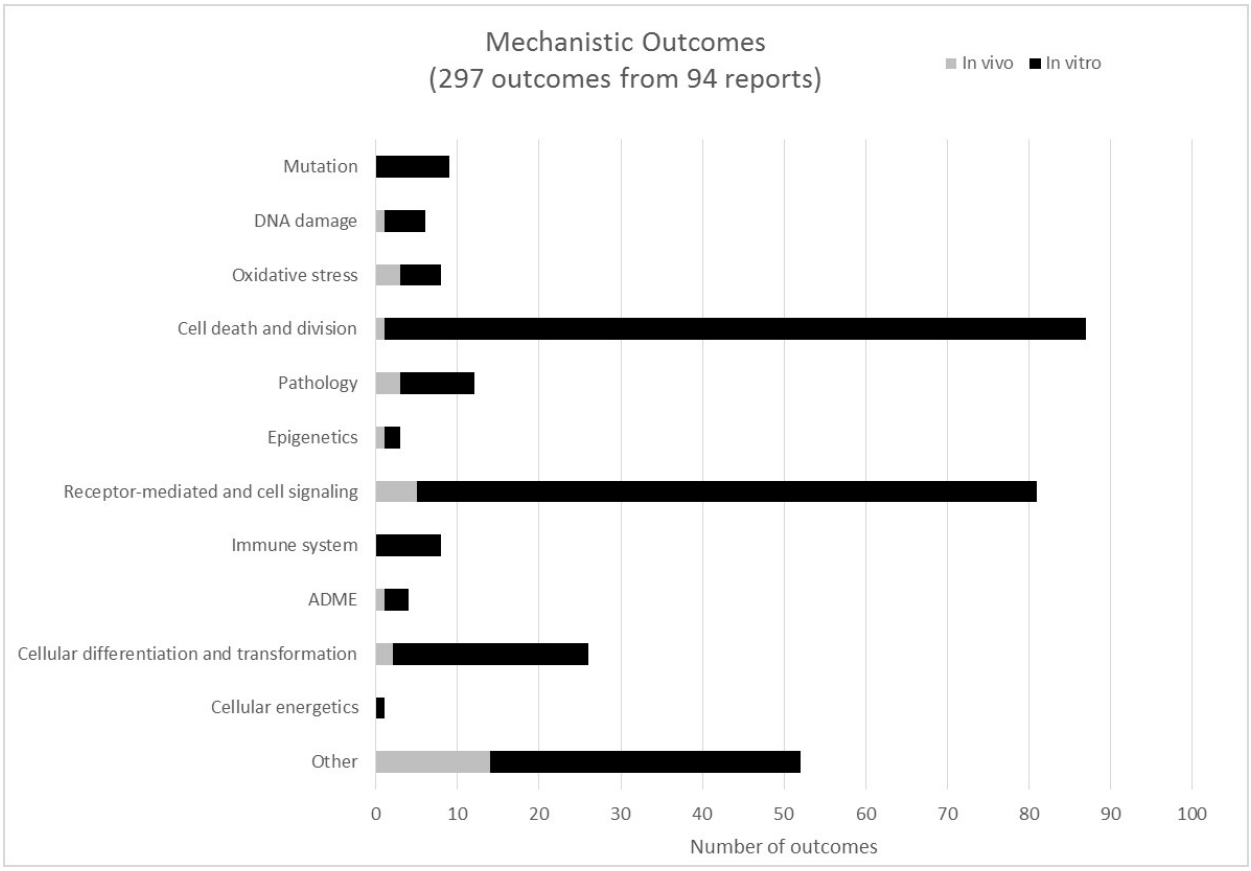

Figure 3-22. Summary of in vivo or in vitro mechanistic data by mechanistic category following oral exposure to BBP.

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