OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

Proposition 65

Evidence on the Developmental Toxicity of

Bisphenol S

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Reproductive and Cancer Hazard Assessment Branch
Office of Environmental Health Hazard Assessment
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PREFACE

This document presents evidence relevant to the evaluation of the developmental toxicity of bisphenol S. On October 9, 2025, the Developmental and Reproductive Toxicant Identification Committee (DARTIC) is scheduled to deliberate on whether bisphenol S has been clearly shown to cause developmental toxicity.

Proposition 65[1] requires the publication of a list of chemicals known to the State to cause cancer or reproductive toxicity within the meaning of the Act (Health and Safety Code section 25249.8). The Office of Environmental Health Hazard Assessment (OEHHA) of the California Environmental Protection Agency maintains this list in its role as lead agency for implementing Proposition 65. The DARTIC advises and assists OEHHA in adding chemicals to the Proposition 65 list of chemicals that cause reproductive toxicity, as required by Health and Safety Code section 25249.8. The DARTIC serves as the state's qualified experts for determining whether a chemical has been clearly shown to cause reproductive toxicity.

The Committee also provides advice and consultation regarding which chemicals should receive their review. At their meeting in December 2020, the DARTIC recommended that bisphenol S be placed in a 'high' priority group for future listing consideration. OEHHA selected bisphenol S for consideration for listing by the DARTIC, and in March 2022, OEHHA solicited from the public information relevant to the assessment of the evidence on the reproductive toxicity of this chemical. In response to this solicitation, several studies were submitted by the BASF Corporation. The submitted information was considered in the development of this document. On December 12, 2023, and December 12, 2024, the DARTIC considered the female and male reproductive toxicity, respectively, of this chemical and determined that bisphenol S has been clearly shown through scientifically valid testing according to generally accepted principles to cause female and male reproductive toxicity. Consequently, bisphenol S was added to the Proposition 65 list based on female reproductive toxicity on December 29, 2023, and the male reproductive toxicity endpoint was added to the list on January 3, 2025.

OEHHA is providing this document to the DARTIC to assist the Committee in its deliberations on whether or not bisphenol S should be listed under Proposition 65 for the developmental toxicity endpoint. The original papers and reports discussed in this document are provided to the DARTIC.

[1] The Safe Drinking Water and Toxic Enforcement Act of 1986 (California Health and Safety Code section 25249.5 *et seq*.).

OEHHA is holding a public comment period on this hazard identification document. For information on how to comment go to https://oehha.ca.gov/comments. Comments on this document will be included in the hazard identification materials that are provided to the DARTIC members prior to the meeting.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

Abbreviation	Definition
µg	microgram
µM	micromolar
8-OHdG	8-Hydroxy-2'-deoxyguanosine
ADME	absorption, distribution, metabolism, and excretion
AGD	anogenital distance
AGI	anogenital index
AMH	Anti-Mullerian hormone
ATP	adenosine triphosphate
atRA	all-*trans* retinoic acid
BKMR	Bayesian kernel machine regression
BMI	body mass index
BPA	bisphenol A
BPAF	bisphenol AF
BPAP	bisphenol AP
BPB	bisphenol B
BPF	bisphenol F
BPP	bisphenol P
BPS	bisphenol S
BPZ	bisphenol Z
CARE	California Regional Exposure Study
CI	confidence interval
COC	cumulus-oocyte complex
CpG	cytosine-guanine dinucleotides
CTB	cytotrophoblasts
DART	developmental and reproductive toxicant
DARTIC	Developmental and Reproductive Toxicant Identification
DEG	differentially expressed gene
DHEA	dehydroepiandrosterone
DNA	deoxyribonucleic acid
dpf	days post fertilization
E [#]	embryonic day [#]
E2	estradiol
EAS	estrogenic, androgenic and steroidogenic
EC50	effective concentration, half-maximal
ECHA	European Chemicals Agency
ECHO	Environmental Influences on Child Health Outcomes
EPA	Environmental Protection Agency
ER	estrogen receptor
EU	European Union
F0-3	filial generation 0, 1, 2, 3
FDA	Food and Drug Administration
FEV1	forced expiratory volume in 1 second

Abbreviation	Definition
FSH	follicle-stimulating hormone
FT3	free triiodothyronine
FT4	free thyroxine
FVC	forced vital capacity
g	grams
GD [#]	gestational day [#]
GFP	green fluorescent protein
GM	geometric mean
GSD	geometric standard deviation
GSI	gonadosomatic index
GSK	glycogen synthase kinase
HAWC	Health Assessment Workspace Collaborative
hCG	human chorionic gonadotropin
HDL	high density lipoprotein cholesterol
HFD	high fat diet
hpf	hours post fertilization
HSI	hepatosomatic index
HUVECs	human umbilical vein epithelial cells
ICC	intraclass correlation coefficient
ICI	ICI 182,780 (estrogen receptor antagonist)
IP	intraperitoneal
IQ	intelligence quotient
IQR	interquartile range
IVF	*in vitro* fertilization
KEGG	Kyoto Encyclopedia of Genes and Genomes
kg	kilogram
L	liter
LC50	lethal concentration, half maximal
LD	lactation day
LDL	low density lipoprotein cholesterol
LGA	large-for-gestational-age
LH	luteinizing hormone
LOD	limit of detection
LOQ	limit of quantification
MARBLES	Markers of Autism Risk in Babies – Learning Early Signs
MDI	mental development index
mg	milligram
miRNA	micro RNA
mL	milliliter
mRNA	messenger RNA
NAC	N-acetyl-L-cysteine
NSC	neural stem cells
ng	nanograms

Abbreviation	Definition
NHANES	National Health and Nutrition Examination Survey
NS	nonsignificant
OEHHA	Office of Environmental Health Hazard Assessment
OR	odds ratio
PDI	psychomotor development index
PDTC	pyrrolidine dithiocarbamate
PIP	posterior inclusion probability
PND	postnatal day
PROTECT	Puerto Rico Testsite for Exploring Contamination Threats
Q	quartile
RBC	red blood cells
RNA	ribonucleic acid
RNA-seq	RNA sequencing
ROS	reactive oxygen species
RR	risk ratio
SC	subcutaneous
SD	standard deviation
SDS	standard deviation score
SG	specific gravity
SGA	small-for-gestational-age
SST	scapular skinfold thickness
STB	syncytiotrophoblast-like cells
T1	tertile one
T2	tertile two
T3	tertile three or triiodothyronine
T4	thyroxine
TBBPA	tetrabromobisphenol A
TCBPA	tetrachlorobisphenol A
Tg	transgenic
TM	trimester
TSH	thyroid stimulating hormone
TUNEL	terminal deoxynucleotidyl transferase dUTP nick end labeling
UV	ultraviolet
WC	waist circumference
WT	wildtype

LIST OF PROTEINS

Symbol (Abbreviation)	Full Name
ACOT2	acyl-CoA thioesterase 2
ACOX1	acyl-CoA oxidase 1
AKT	AKT serine/threonine kinase
AMH	anti-Müllerian hormone
AMHR2	anti-Müllerian hormone receptor 2
ATF4	activating transcription factor 4
BAX	BCL2-associated X protein
BCL2	B cell leukemia/lymphoma 2
BECN1	Beclin 1, autophagy related
CALR	calreticulin
CASP	caspase
CAT	catalase
COX	cyclooxygenase
CRP	C-reactive protein, pentraxin-related
CSF2 (GMCSF)	granulocyte macrophage colony-stimulating factor
CYP19A1	cytochrome P450, family 19, subfamily A, member 1
Cyp450	cytochrome P450
DDIT3 (CHOP)	DNA-damage inducible transcript 3
DIO	iodothyronine deiodinase 1
DNMT3B	DNA methyltransferase 3B
EGF	epidermal growth factor
EGFR	epidermal growth factor receptor
EIF2A	eukaryotic translation initiation factor 2A
ESR (ER)	estrogen receptor
FABP4	fatty acid binding protein 4, adipocyte
FGF21	fibroblast growth factor 21
FIS1	fission, mitochondrial 1
Gap43	growth associated protein 43
GPX	glutathione peroxidase
Gst	glutathione S-transferase
H3K4me3	histone 3 lysine 4 trimethylation
H3K9me3	histone 3 lysine 9 trimethylation
HSD11B1	hydroxysteroid 11-beta dehydrogenase 1
IL	interleukin
IMMT	inner membrane mitochondrial protein
LAMP1	lysosomal associated membrane protein 1
MAP1LC3A (LC3A)	microtubule-associated protein 1 light chain 3 alpha
MAP1LC3B (LC3B)	microtubule-associated protein 1 light chain 3 beta
MAP2	microtubule associated protein 2
MAPK	mitogen-activated protein kinase
MTOR	mechanistic target of rapamycin kinase

Symbol (Abbreviation)	Full Name
NFKB	nuclear factor kappa B
Nos2	nitric oxide synthase 2
PAX6	paired box 6
PERK	protein kinase RNA-like endoplasmic reticulum kinase
PLIN2 (ADRP)	perilipin 2
PPAR	peroxisome proliferator activated receptor
RPN1	ribophorin I
SCP2	sterol carrier protein 2
Sod	superoxide dismutase
SQSTM1 (P62)	sequestosome 1
STRA8	stimulated by retinoic acid gene 8
THRB	thyroid hormone receptor beta
TNFA	tumor necrosis factor alpha
TUBB3 (TUJ1)	tubulin beta 3 class III
UBC	ubiquitin C
ULK1	Unc-51 like kinase 1
VDAC1	voltage dependent anion channel 1

LIST OF GENES

Symbol (Abbreviation)	Full Name
Acaca	acetyl-Coenzyme A carboxylase alpha
acsl	acyl-CoA synthetase long chain
Actn2	actinin alpha 2
Adipoq	adiponectin, C1Q and collagen domain containing
adprhl2	ADP-ribosylserine hydrolase like 2
AFP	alpha fetoprotein
AHSP	alpha hemoglobin stabilizing protein
ANO1	anoctamin 1
APO	apolipoprotein
Ar	Androgen receptor
arr3a	arrestin 3a, retinal (X-arrestin)
Bad	BCL2-associated agonist of cell death
Bax	BCL2-associated X protein
Bcl2	B cell leukemia/lymphoma 2
Becn2	Beclin 2
cacna1sa	calcium channel, voltage-dependent, L type, alpha 1S
cacna1sb	calcium channel, voltage-dependent, L type, alpha 1S
cacna2d1a	calcium channel, voltage-dependent, alpha 2/delta subunit
Casp	caspase
Cat	catalase
ccl34a.4 (cc-chemokine)	chemokine (C-C motif) ligand 34a, duplicate 4
Cebpa	CCAAT/enhancer binding protein alpha
chrna	cholinergic receptor, nicotinic, alpha
Crhb (crh)	*corticotropin releasing hormone b*
cyba	cytochrome b-245, alpha polypeptide
Cycs	cytochrome c, somatic
cyp	cytochrome P450
Dio	iodothyronine deiodinase 1
DNMT	DNA methyltransferase
Dot1l	DOT1 like histone lysine methyltransferase
Drd	dopamine receptor D
elavl3	ELAV like neuron-specific RNA binding protein 3
DPPA5 (ESG1)	developmental pluripotency associated 5
Esr (Er)	estrogen receptor
FABP	fatty acid binding protein
Fads2	fatty acid desaturase 2
Fasn	fatty acid synthase
FGA	fibrinogen alpha chain
FGB	fibrinogen beta chain
FGF13	fibroblast growth factor 13
FGG	fibrinogen gamma chain
foxa2	forkhead box A2

Symbol (Abbreviation)	Full Name
fsh	follicle stimulating hormone
gap43	growth associated protein 43
gfap	glial fibrillary acidic protein
gh1	growth hormone 1
Glrx2	glutaredoxin 2
gnrh3	gonadotropin-releasing hormone 3
Gper1	G protein-coupled estroen receptor 1
Gpx	Glutathione peroxidase
grk1b	G protein-coupled receptor kinase 1 b
gsto1	glutathione S-transferase omega 1
hdac	histone deacetylase
hhex	hematopoietically expressed homeobox
HNF4A	hepatocyte nuclear factor 4 alpha
Hsd11b	hydroxysteroid 11-beta dehydrogenase
hsd17b	hydroxysteroid 17-beta dehydrogenase
hsd3b	hydroxysteroid 3-beta dehydrogenase
hsp	heat shock protein
hspa5 (bip)	heat shock protein 5
htr1a	5-hydroxytryptamine (serotonin) receptor 1A
ifng	interferon gamma
IGF1	insulin like growth factor 1
il	interleukin
ins	preproinsulin
isl1	ISL LIM homeobox 1
kdm5ba	lysine demethylase 5Ba
kiss1	KiSS-1 metastasis suppressor
kiss1ra (kiss1r)	KISS1 receptor a
kiss2	kisspeptin 2
KLF4	KLF transcription factor 4
Kmt2e	lysine (K)-specific methyltransferase 2E
KRT14	keratin 14
LBFABP	liver basic fatty acid binding protein
lh	luteinizing hormone
Lpl	lipoprotein lipase
lyz	lysozyme
mao	monoamine oxidase
map1lc3a (lc3a)	microtubule-associated protein 1 light chain 3 alpha
map1lc3b (lc3b)	microtubule-associated protein 1 light chain 3 beta
MAP2	microtubule associated protein 2
mbp	myelin basic protein
MKI67 (KI67)	marker of proliferation Ki-67
mmp13	matrix metallopeptidase 13
Mstnb (mstn1)	myostatin b

Symbol (Abbreviation)	Full Name
MT4	metallothionein 4
Mttp (mtp)	microsomal triglyceride transfer protein
mx	myxovirus (influenza) resistance
myh7	myosin heavy chain 7
Nampt	nicotinamide phosphoribosyltransferase
NANOG	Nanog homeobox
Nd1	NADH dehydrogenase 1
neurog1 (ngn1)	neurogenin 1
nfkb	nuclear factor kappa B
nos	nitric oxide synthase
Nppa (anp)	natriuretic peptide A
OCT4	octamer-binding transcription factor 4
OLFM1	olfactomedin 1
opn1lw	opsin 1 (cone pigments), long-wave-sensitive
opn1mw	opsin 1 (cone pigments), medium-wave-sensitive
opn1sw	opsin 1 (cone pigments), short-wave-sensitive
OTX2	orthodenticle homeobox 2
OVOL1	ovo like transcriptional repressor 1
park7	parkinson protein 7
PCDH8	protocadherin 8
pde6	phosphodiesterase 6
pdx1	pancreatic and duodenal homeobox 1
perk	protein kinase RNA-like endoplasmic reticulum kinase
PGR	Progesterone receptor
Ppar	peroxisome proliferator activated receptor
Prdx	peroxiredoxin
Prkaa2	protein kinase, AMP-activated, alpha 2 catalytic subunit
prl	prolactin
ptfl1a	pancreas associated transcription factor 1a
ptgr1.2 (prost1.2)	prostaglandin reductase 1, tandem duplicate 2
pth1a (pth1)	parathyroid hormone 1a
rag	recombination activating gene
RBMXL2	RNA binding motif protein X-linked like 2
ren	renin
rho	rhodopsin
Setd	SET domain containing
SLCO1A2	solute carrier organic anion transporter family member 1A2
SOD	superoxide dismutase
SOX2	SRY-box transcription factor 2
SPACA1	sperm acrosome associated 1
Spo11	SPO11 initiator of meiotic double stranded breaks
Src2	steroid receptor coactivator 2
Srd5al (5α-R3)	steroid 5 alpha-reductase 3

Symbol (Abbreviation)	Full Name
Srebf1	sterol regulatory element binding transcription factor 1
Star	steroidogenic acute regulatory protein
SULT1B1	sulfotransferase family 1B member 1
Suz12	SUZ12 polycomb repressive complex 2 subunit
syn2a	synapsin IIa
TET	tet methylcytosine deoxygenase
Tex	testis expressed gene
TGFA	transforming growth factor alpha
thr	thyroid hormone receptor
THRSP	thyroid hormone responsive
ticam1 (*trif*)	TIR domain containing adaptor molecule 1
tlr	toll-like receptor
tnfa	tumor necrosis factor alpha
tpo	thyroid peroxidase
tsh	thyroid stimulating hormone
tshr	thyroid stimulating hormone receptor
ttr	transthyretin
Tuba (*a1-tubulin*)	alpha tubulin
TUBB3 (TUJ1)	tubulin beta 3 class III
ugt1	UDP glucuronosyltransferase 1
vegf	vascular endothelial growth factor
VPS53	VPS53 subunit of GARP complex
vtg	vitellogenin
wnt	wingless-type MMTV integration site family

SUMMARY

Introduction

This document presents evidence relevant to the evaluation of the developmental toxicity of bisphenol S (BPS), also identified as 4,4'-sulfonyldiphenol. BPS consists of two hydroxyphenyl groups connected by a sulfonyl group and is an analogue of bisphenol A (BPA).

Uses, Occurrence and Exposure

BPS is part of polyethersulfone plastic, which is used to make hard plastic items and synthetic fibers for clothing and other textiles, and as a color developer in thermal paper. It has been detected in cash register receipts, personal care products, foods, baby bottles, and other products. Data from Biomonitoring California (https://biomonitoring.ca.gov) found BPS was detected in approximately two-thirds of Californians tested. Data from other US-based human biomonitoring studies indicate that as BPA has been removed from many products over the last decade, the levels of BPS detected in human samples have increased.

Systematic Literature Review Approach

Using a systematic approach, the Office of Environmental Health Hazard Assessment (OEHHA) conducted literature searches on the developmental and reproductive toxicity of BPS, including primary searches in major biomedical databases, searches in other data sources such as reports by other health agencies, and additional focused searches. In addition, OEHHA conducted a data call-in from March 4 to April 18, 2022 to solicit relevant information. This document focuses on literature relevant to developmental toxicity (last comprehensive search, October 2024). Additional studies that came to OEHHA's attention after the last comprehensive search are also included in this document.

Pharmacokinetics of BPS

BPS is rapidly absorbed in humans after oral exposure and to a lesser extent by the dermal routes. Once absorbed, BPS is distributed throughout the body and has been detected in human umbilical cord blood, amniotic fluid, and the placenta. BPS undergoes metabolism primarily in the liver, where it can be conjugated, and then

excreted in urine and feces. Estimates of the half-life of BPS in humans exposed by the oral route range between 7 to 9 hours.

Developmental Toxicity

Studies on the developmental toxicity of BPS evaluated potential adverse effects of preconceptional or prenatal exposure on the developing offspring. We present evidence from human epidemiologic studies, evidence from whole animal *in vivo* mammalian and non-mammalian studies, and evidence from studies that help inform consideration of mechanisms of action, most of which used *in vitro* experimental designs.

Studies in Humans

Overview

OEHHA identified 65 epidemiologic studies related to the potential developmental toxicity of BPS in humans. These observational studies used cohort, case-control, or cross-sectional study designs, measured BPS in maternal urine or serum, placenta, or cord blood, and analyzed associations with fetal or offspring outcomes.

BPS was typically not the sole chemical exposure of interest and methodological challenges related to the characterization of BPS exposure in observational studies should be considered. Most studies measured BPS levels in a single urine spot sample, which may be insufficient to assess exposure across pregnancy or in a specific trimester considering BPS' short half-life. Levels of detection (LOD) for BPS varied widely across studies. The percentages of samples with BPS detected for each study were similarly varied, ranging from 14% to 99%. Imprecise exposure assessment resulting in non-differential misclassification of exposure would likely bias the estimate of any association of risk towards the null.

Birth Outcomes

Gestational length. Twelve studies examined associations between BPS exposure and gestational length. Authors analyzed gestational length as either a binary variable for preterm birth defined as birth before 37 weeks or as a continuous variable as the number of gestation days or weeks. BPS was significantly associated with higher odds of preterm birth in three studies. BPS was significantly associated with shorter gestation length in four studies (three of which showed effects in specific population subgroups only) and longer gestation length in one study. In general, associations with both outcomes were stronger when BPS was measured before conception or in the first trimester compared to later in pregnancy.

Fetal Size. Seven studies examined associations between BPS exposure and at least one fetal growth outcome measured by ultrasound between 16 and 35 weeks. BPS exposure was associated with decreased fetal weight in two of four studies (one of which showed effects in male fetuses only) and increased fetal weight in one study. BPS exposure was associated with larger head circumference in two of six studies (one of which showed effects in female fetuses only). BPS exposure was associated with longer femur length in two of five studies (one of which showed effects in female fetuses only) and shorter femur length in one study. There were no significant associations between BPS exposure and fetal abdominal circumference (five studies) or biparietal diameter (three studies).

Birth Size. Eighteen studies examined associations between BPS exposure and offspring size at birth. The specific outcomes were birthweight (14 studies), birthweight z-score (eight studies), weight-for-length measures (four studies), and adiposity (two studies). The directions of associations were mixed for birthweight. Two studies reported statistically significant associations with lower birthweight, one study reported an inverse U-shaped relationship with birthweight, and two studies reported associations with higher birthweight. In an analysis of data from eleven US cohort studies, the direction of associations with birthweight varied by race and ethnic group and by fetal sex. That study also reported significant associations with birthweight z-score with estimates varying by trimester of BPS exposure measurement, race and ethnic group, and fetal sex.

When size at birth was analyzed as a binary variable, BPS exposure was associated with higher odds of small-for-gestational age in two studies and lower odds of small-for-gestational age in one study. BPS was associated with higher odds of large-for-gestational age in two studies (one of which showed effects in Hispanic individuals only). One study reported a significant association between BPS measured in the first trimester and lower ponderal index and one study reported associations between BPS measured in the third trimester and increased abdominal skinfold thickness.

Other birth outcomes. For women over 28 years of age, BPS exposure was associated with decreased cord blood leukocyte telomere length in one study. There was no evidence of an association between BPS exposure and risk of neural tube defects in one case-control study.

Infant growth

Five studies examined associations between prenatal BPS exposure and infant growth trajectories in the first two years of life. In one study, exposure measured in the third trimester was associated with increased risk of rapid growth from birth to 12 months in females and in a second study, BPS exposure measured in the first trimester was

associated with increased odds of having a growth trajectory characterized as ‘low-increasing’ versus ‘moderate-stable.’

Seven studies measured associations between prenatal BPS and infant size at various points after birth. There were statistically significant associations between BPS and larger subscapular skin fold, arm circumference, and abdominal skinfold thickness at six months (one study), smaller subscapular skinfold from birth to 4 years (one study), larger body mass index z-score at 2 years (one study), larger body mass index at three and 36 months (one study), and larger fat mass percent at 36 months (one study).

Neurodevelopment

Thirteen studies evaluated the effects of prenatal BPS exposure and offspring neurodevelopment with a wide range of studied outcomes. Two studies examined associations between BPS and markers of early cognitive development – non-nutritive sucking measured before 8 weeks (one study) and infant eye tracking at 24 months (one study). Prenatal BPS detected in trimester two was associated with reduced reaction time on the infant eye tracking task.

Four studies evaluated neurodevelopmental outcomes between 2 and 4 years of age. One of the studies reported an association between prenatal BPS exposure and lower psychomotor development index scores, and both higher and lower mental development index scores depending on timing of exposure measurement. One of the studies reported an association between prenatal BPS exposure and worse cognitive scores for high socioeconomic status participants only. Two other studies reported no evidence of associations with cognitive outcomes.

Three studies assessed associations between prenatal BPS exposure and socioemotional behavioral development. In one study, BPS was associated with worse emotional reactive behavior and internalizing behavioral problems among female children ages 2 to 3. In the second study, BPS was associated with worse child social behavior and autistic traits at age 3, and in the third study, higher BPS levels were similarly associated with increased odds of offspring emotional problems at age 4.

Lastly, three studies reported no associations between prenatal BPS exposure and intelligence quotient or its subscales among offspring ages 6 to 7, and one study reported no associations between BPS and offspring vision.

Immune function

Six studies and one meta-analysis (of four birth cohorts) examined associations between prenatal BPS exposure and offspring immune function and related outcomes.

Across studies, BPS exposure was associated with higher odds of asthma in three studies (with some variability by offspring sex), higher odds of bronchiolitis (one study), lower odds of atopic dermatitis (one study, girls only) and both higher (one study) and lower (one study) lung function scores. The meta-analysis reported associations between detectable prenatal BPS and lower odds of late and persistent wheeze, and no associations with asthma or measures of lung function.

Endocrine and metabolic effects

Nine studies examined associations between gestational BPS exposure and various endocrine and metabolic effects in offspring. Some offspring outcomes were measured at birth. In these studies, gestational BPS exposure was associated with lower cord blood follicle-stimulating hormone in pregnancies with normal body mass index (one study), lower cord blood thyroid-stimulating hormone in males (one study), and higher thyroid-stimulating hormone levels measured via heel prick at birth (one study).

Other outcomes were measured later in childhood. In those studies, gestational BPS exposure was associated with lower insulin and glucose levels in 9 to 10-year-old boys (one study), higher urinary kisspeptin levels at age 6, where again, stronger effects were observed in boys (one study), and marginally higher digit ratios – an indicator of disrupted prenatal sex hormones – in 4-year-old girls (one study). Other studies reported no associations with offspring artery health (one study), offspring body mass index at 5 years (one study), and child thyroid function (one study).

Bone mass and mineral density

Two studies examined associations between gestational BPS exposure and offspring bone mass and mineral density. In these studies, trimester one BPS exposure was associated with lower bone mineral density in offspring ages 3−6 (one study, boys only) and 6−10 (one study).

Offspring reproductive development

One study evaluated prenatal exposure to BPS and offspring reproductive development and reported that higher BPS levels were associated with delays in onset of menstruation in female offspring. A second study reported associations between prenatal BPS and longer anus-clitoris and anus-fourchette distance at 48 months in girls and higher odds of rapid anus-genital distance growth in girls.

Studies in Animals

Overview

BPS-mediated effects on development were evaluated in more than 80 *in vivo* studies in mammalian and non-mammalian animal models, including studies in mice, rats, sheep, zebrafish, Chinese medaka fish, nematodes (*C. elegans*), chick embryos, and fruit flies (*D. melanogaster*).

BPS-related outcomes reported in the reviewed studies included effects on early embryo development; implantation; the placenta; birth and growth outcomes; structural malformations and variations; sex ratio; neurodevelopment and behavior; the visual, circulatory, and immune systems; metabolism; and the reproductive system. The outcomes may result from direct effects on the embryo or extraembryonic structures (e.g., the placenta), direct effects on the reproductive system of either parent, or some combination of these. *In vivo* exposures were all developmentally relevant, and included gestational, perinatal, and early postnatal exposures.

Early embryo development and implantation

In two mouse studies and one sheep study of BPS, embryo development was inhibited with developmental arrest of pre-implantation embryos. One study in chick embryos reported reduced growth and developmental delays.

In four rat studies of BPS, there were effects on implantation, including decreased number of implantation sites and implantation index, and increased resorptions and post-implantation loss. One of the studies found no effect on the number of implantation sites.

Placental effects

In one mouse study of BPS, placenta histopathology findings included decreased ratio of spongiotrophoblast zone to giant cell area with altered placental neurotransmitter concentrations. In one rat study of BPS, placental weight was increased. In sheep treated with BPS, placental weight was increased with a decrease in trophoblast-derived binucleate cells.

Birth and growth outcomes

Four mouse studies reported effects of BPS on birth outcomes, including increased parturition distress, total litter loss, and early postnatal pup mortality with a higher occurrence in males, and decreased body length. Two of these studies and two additional mouse studies found no effect on litter size and/or birthweight. One rat study

reported altered fetal weights and no effect on litter size. In three rat studies of BPS, there was decreased litter size and number of liveborn pups, and increased number of stillborn pups and total litter loss. One of these studies reported no effect on viability index or birthweight.

In fish, BPS effects on hatching include decreased hatching rates and/or hatching times in seven zebrafish studies and one Chinese medaka fish study, accelerated hatching rates in two zebrafish studies, and altered hatching rates in two multi-generational zebrafish studies with directionality dependent on generation. Eight zebrafish studies reported no effects on hatching rate.

Body length was decreased by BPS treatment in seven zebrafish studies and one Chinese medaka study and increased in three zebrafish studies. Five zebrafish studies found no effect on body length. Body weight was increased by BPS in two zebrafish studies. One zebrafish study found no effect on body weight. One transgenerational zebrafish study reported that BPS decreased hepatosomatic index (HSI).

One zebrafish study reported BPS effects on swim bladder function while another zebrafish study found no effects.

One chick embryo study of BPS found decreased pipping success. In three chick embryo studies, there was increased mortality, gallbladder size, and/or gallbladder-somatic index, and decreased survival, growth, mass, and tarsus length. One of these studies found no effect on body weight or HSI.

In six *C. elegans* studies of BPS, there was decreased lifespan, survival, hatching, growth, and/or body length or width. One of these studies found no effect on lifespan or larval development. One study reported increased accumulation of lipofuscin, a senescence-related marker.

One *Drosophila* study of BPS found decreased hatching rate, larval body width, and number of pupae formed, and observed melanotic mass formation.

Structural malformations and variations

One rat study of BPS found increased incidences of total visceral variations, including renal dilatation and dilated ureters; several skeletal variations; and total skeletal malformations. One sheep study found an increased incidence of a skeletal variation in males.

Morphological effects of BPS were reported in seven zebrafish studies and one chick embryo study. Craniofacial and/or spinal abnormalities were observed in five zebrafish studies and one Chinese medaka study, and yolk sac effects in two zebrafish studies

and one Chinese medaka study. There were no effects on malformations or abnormalities in four zebrafish studies.

One chick embryo study of BPS found gastrointestinal, heart, eye, craniofacial, limb, and body pigmentation defects.

Sex ratio

Five mouse studies, four rat studies, and one sheep study found no effect of BPS on sex ratio. One mouse study found a decreased male:female sex ratio, which may have been due to a high mortality in male pups compared to females.

Sex ratio was altered in three zebrafish studies of BPS, with results depending on dose timing and duration. Male:female sex ratio was increased in two studies and decreased in one study.

Neurodevelopment and behavior

Four mouse studies of BPS found altered social and maternal behavior, decreased memory, and/or increased depression and anxiety. One of these studies found no effects on some social, locomotion, and cognitive parameters. One rat study reported decreased learning and memory function and effects on hippocampal neurogenesis. In one rat study, there were no effects on neuronal development or function.

Effects of BPS on neurogenesis were reported in five zebrafish studies. Neurobehavioral effects were reported in nine zebrafish studies. There was altered spontaneous movement and/or swim behavior in five studies, altered locomotor behavior in three studies, decreased thigmotaxis or “wall-hugging” behavior in one study, increased social anxiety responses in one study, and altered shoaling behavior in one study. Two zebrafish studies reported no effect on spontaneous movements and five studies found no effects on locomotor activity.

BPS-related effects on visual development and behavior were reported in four zebrafish studies.

In five *C. elegans* studies of BPS, there was altered locomotor activity and/or effects on neural functionality. One *Drosophila* study found increased locomotion exploratory capacity, decreased learning ability, and decreased social interaction, and increased brain size in female offspring.

Circulatory system effects

There were effects of BPS on heart rate, size, edema, and/or related circulatory outcomes in eight zebrafish studies, vessel development in five zebrafish studies. and pericardial edema in the Chinese medaka study. There were no effects of BPS on heartbeat and/or rate in three zebrafish studies, cardiac edema in three zebrafish studies.

Metabolic effects

Two mouse studies, four rat studies, and one sheep study found effects of BPS on body composition and adipose tissue, including increased body weight and/or altered adipocyte size.

One mouse and one rat study each found effects of BPS on liver function. In mice, there was evidence of excessive hepatic lipid accumulation. In rats, there was increased absolute liver weight and microvesicular steatosis.

Three mouse studies and two rat studies of BPS found markers of altered metabolism in plasma, serum, or other tissues. In mice, there were increased levels of serum non-esterified fatty acids and triglycerides, decreased placental fatty acids, and/or decreased blood glucose levels. In rats, there were increased plasma fatty acid levels. These studies found no effects on fasting glucose, triacylglycerol, cholesterol, and/or testicular fatty acid levels.

Five zebrafish studies found effects of BPS on glucose and lipid metabolism. One of the studies used RNA-seq and identified terms related to cellular energy and glucose metabolism.

Immune effects

Effects of BPS on the developing immune system were observed in two zebrafish studies, including increased lysozyme activity or neutrophil counts.

Developing Reproductive System

Female reproductive effects. Several studies reported effects of developmental BPS exposure on the female reproductive system. Three mouse studies and one rat study found effects of BPS on ovarian development. In mice, BPS treatment altered folliculogenesis, decreased ovarian reserves, and/or damaged oocyte structure. In rats, there was a decreased number of *corpora lutea*. Puberty onset was altered in two mouse and two rat studies of BPS. Two mouse studies found no effect on puberty timing.

Two mouse studies found effects of BPS on developing mammary glands, including accelerated development of terminal end buds and glands, and decreased mammary gland ductal area. One of these studies reported multiple findings of mammary neoplastic lesions.

There were BPS effects on the estrous cycle in two mouse studies, including increased cycle length, altered length of phases, and earlier first estrus. One mouse study found no effect of BPS on the timing of first estrus or estrous cycle length. One rat study found no effect on F1 female fertility index.

One mouse and one rat study found no effects of BPS on uterine weight.

Two mouse studies found effects of BPS on reproductive performance, including decreased litter size and increased spontaneous abortions, infertility, and time to successful mating.

Female reproductive effects of BPS were reported in one zebrafish study and one chick embryo study. A transgenerational zebrafish study reported an altered gonadosomatic index, with directionality depending on dose. In one chick embryo study, there were gonadal histopathology findings, including thin and atrophic ovaries.

Male reproductive effects. Several studies reported effects of developmental BPS exposure on the male reproductive system. Two mouse and two rat studies found effects of BPS on male offspring reproductive organ weights and histopathology. In mice, relative testes weight was increased and there was abnormal spermatogenesis staging distribution. One of these studies found no effect on testis weight. In rats, there was increased absolute testes weight, decreased absolute seminal vesicle weight, and/or histopathological findings in the seminiferous tubules. Two rat studies found no effects on male reproductive organ weights.

Sperm parameters were altered in two mouse studies and one rat study. In mice, there was decreased sperm concentration and motility. In rats, there was decreased sperm number, motility, and daily sperm production, and fewer spermatogonia, spermatocytes, and spermatids.

Anogenital distance, a marker of developmental endocrine disruption, was decreased in one rat study. However, four other rat studies found no effect of BPS.

One mouse study found effects of BPS on male mammary gland development, including increased size of epithelial anlagen. In two rat studies, there were no effects on mammary gland development.

The onset of puberty was not affected in three male rat studies.

One transgenerational zebrafish study of BPS found male reproductive effects, including decreased gonadosomatic index and fecundity, and increased fertility that was dependent on generation.

Reproductive effects in C. elegans. Effects of BPS on reproduction were observed in *C. elegans,* an organism with a hermaphroditic life cycle. Five studies reported a decrease in number of egg-laying days, number of eggs laid, fertility, and brood size, and/or an increased protrusion of the vulval structure.

Mechanistic Considerations

There is mechanistic evidence for BPS relevant to developmental toxicity from molecular human epidemiology studies, *in vivo* and *in vitro* studies in mammalian and non-mammalian models, and acellular systems.

BPS affected outcomes related to early embryonic and extraembryonic development; oxidative stress; genetic damage; epigenetic alterations; cell proliferation, apoptosis, and autophagy; endocrine effects; organ system effects; nitric oxide (NO) signaling effects; and organelle effects.

Early embryonic and extraembryonic effects

BPS effects included decreased blastocyst attachment and altered pluripotency and gastrulation markers in human cell models. In bovine blastocysts, BPS exposure accelerated embryo development. In human and mouse placental cell models, BPS affected trophoblast signaling and function.

Oxidative stress

In a study of pregnant humans, higher urinary BPS levels were associated with higher urinary levels of a biomarker of lipid peroxidation. There were increases in reactive oxygen species and/or lipid peroxidation in rodent gonadal tissue, mouse embryos, zebrafish, *Drosophila*, *C. elegans,* a rat embryonic cardiac cell line, a human choriocarcinoma cell line, and in human umbilical vein endothelial cells (HUVECs).

Key antioxidant system components were altered in rodent gonadal tissue, zebrafish, *Drosophila*, *C. elegans*, and/or a human choriocarcinoma cell line, with directionality that demonstrated an acute oxidative challenge during shorter exposures and an overwhelmed antioxidant system with longer exposures. BPS altered oxidative stress-related gene expression, protein levels, and/or protein phosphorylation in mouse embryos and gonadal tissue, zebrafish whole body and eyes, HUVECs, primary chicken embryonic hepatocytes, and a rat embryonic cardiac cell line.

Genetic damage

In a study of pregnant humans, higher urinary BPS levels were associated with higher urinary levels of a biomarker of oxidative damage to DNA. In a *C. elegans* study, BPS decreased expression of DNA damage response- and checkpoint activation-related genes.

Epigenetic alterations

BPS altered DNA and histone methylation and expression of genes and proteins involved in epigenetic processes in rodents, zebrafish, zebrafish gonadal tissue, and human amniotic and fetal stem cells. One epigenomic study in pregnant humans identified an association between urinary BPS levels and a differentially methylated CpG site in umbilical cord blood DNA. In rats, BPS altered post-translational modification of proteins involved in sperm development and maturation.

Cell Proliferation, Apoptosis, and Autophagy

BPS altered cell proliferation, impaired autophagy, and induced apoptosis in mouse gonadal tissue, rat adipose tissue, zebrafish whole body and brain, bovine blastocysts, human cerebral organoid and placenta-on-a-chip models, human amniotic and fetal stem cells, HUVECs, primary embryonic chicken hepatocytes, and a rat embryonic cardiac cell line.

Endocrine effects

BPS studies reported various endocrine effects across *in vivo* and *in vitro* models.

Gonadotropin levels were altered in rat plasma, zebrafish, and a human placenta-on-a-chip model, and Anti-Müllerian hormone levels were increased in bovine blastocysts.

Testosterone levels were altered in rodent and zebrafish plasma/serum with consistent decreases in males. Estradiol (E2) levels were increased in rodent and zebrafish serum/plasma and decreased in a human choriocarcinoma cell line. The E2/testosterone ratio was increased in zebrafish plasma. Dehydroepiandrosterone, a sex hormone precursor, was decreased in mouse serum. Aromatase levels and activity were increased in zebrafish brain tissue. BPS increased estrogen receptor activity and signaling pathways in zebrafish liver and tail somites and human endometrial cells. BPS was predicted to bind to zebrafish estrogen receptor in docking models.

Progesterone levels were altered in mouse serum and a human placenta-on-a-chip model, and corticosterone levels were increased in rat plasma.

Thyroid hormone levels and signaling were altered in zebrafish. Studies found that BPS likely binds to thyroid hormone receptors and decreases the binding of endogenous thyroid hormones in zebrafish, potentially leading to dysregulation of thyroid hormone signaling.

BPS also altered the expression of several endocrine-related genes and proteins in rodent gonadal, mammary gland, and brain tissues; zebrafish whole body and gonadal, brain, liver, and retinal tissues; bovine blastocysts; sheep preadipocytes; chicken embryo liver tissue; a cellular model of human implantation; primary chicken embryonic hepatocytes; a human choriocarcinoma cell line; and/or a human endometrial cell line.

Organ system effects

Studies reported effects of BPS on placenta and organ system development, including the central nervous, visual, immune, and metabolic systems in humans, rats, zebrafish, and human model systems (e.g., organoids, placenta-on-a-chip models).

The expression of several genes and/or proteins related to neurodevelopment were altered in rat brain tissue, zebrafish whole body and brain tissue, and/or a human cerebral organoid model. Proteomics studies indicated altered neuronal differentiation and nervous system development in human cerebral organoids.

Ocular retinoid metabolism and the expression of several genes and/or proteins related to the visual system were altered in zebrafish eyes.

Expression of immune-related genes and/or proteins were altered in rat liver tissues and in zebrafish. One study of BPS reported immunotoxic effects in a human placenta-on-a-chip model.

There were several metabolism-related effects reported *in vivo* in humans, rodents, sheep, zebrafish, and *Drosophila*, and *in vitro* in mouse, sheep and chicken cells exposed to BPS. A metabolomics study of pregnant humans reported an association between prenatal urinary BPS levels and newborn fatty acid metabolite profiles. There were effects on glucose, cholesterol, lipid, and/or triglyceride levels in rodent blood, serum, and plasma and zebrafish whole body, brain, and plasma, as well as increased lipid accumulation in pre-adipocyte mouse embryonic fibroblasts. The expression of several metabolism-related genes and proteins were altered in mice, rats, sheep, zebrafish, *Drosophila*, primary fetal sheep adipocytes, and primary chicken embryo hepatocytes. Transcriptomic studies consistently identified biological pathways and gene ontology terms involved in cellular, glucose, and/or lipid metabolism. Proteomics studies indicated altered levels of proteins related to fatty acid metabolism, obesity and insulin resistance, and adipocyte function and differentiation.

Effects of BPS on nitric oxide signaling included increased NO synthase (NOS) activity and/or NO levels, key regulator molecules in the developing organism, in zebrafish and HUVECs. NOS gene expression was upregulated in the same models. Transcriptomic studies consistently identified biological pathways and gene ontology terms involved in cardiac/cardiovascular-related terms including contractility, hypertrophy, and endothelial cell-related processes.

Organelle effects

BPS studies reported effects on mitochondria and the endoplasmic reticulum. One study in humans reported an inverse association between first trimester urinary BPS level and umbilical cord blood mitochondrial DNA copy numbers in male offspring. There was an increased number of active/functional mitochondria in zebrafish brains and decreased mitochondrial membrane potential and increased ATP levels in *C. elegans*. Proteomics studies indicated altered proteins related to mitochondrial function and dynamics. There were markers of endoplasmic reticulum stress observed in zebrafish.

1 INTRODUCTION

1.1 Identity of Bisphenol S (BPS)

BPS consists of two hydroxyphenyl groups connected by a sulfonyl group and has the molecular formula $C_{12}H_{10}O_4S$. It is an analog of bisphenol A (BPA), and its International Union of Pure and Applied Chemistry (IUPAC) name is 4-(4-hydroxyphenyl) sulfonylphenol. Other names for BPS include 4,4'-sulfonyldiphenol, 4-hydroxyphenyl sulfone, and 4,4′-sulfonylbisphenol. The chemical structure of BPS is shown in Figure 1. The Chemical Abstracts Service (CAS) registration number for BPS is 80-09-1.

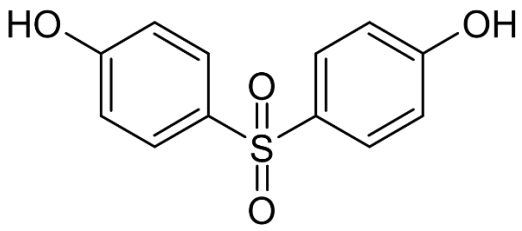


Figure 1 Structure of BPS

1.2 Uses, Occurrence, and Exposure

1.2.1 Use and Production

BPS is a common replacement for BPA in some types of paper receipts. BPS is part of polyethersulfone and used to make hard plastic items and synthetic fibers for clothing and textiles. BPS can be used to make colors last longer in some fabrics. It can be used in coatings of nonstick pans, baby bottles, and parts of electronics (i.e., screens for mobile phones) (Biomonitoring California 2020).

According to the US Environmental Protection Agency (US EPA), the 2019 national aggregated production volume of BPS was 1,000,000 to 10,000,000 pounds. Almost all of the BPS reported to the US EPA was imported (US EPA 2020). The European Chemicals Agency (ECHA) reported that at least 10,000 million metric tons of BPS are manufactured or imported annually into the European Economic Area per year (ECHA 2023). The BPS global market size in 2023 was approximately 185 thousand metric tons and is projected to reach 280 thousand metric tons in 2033 (ChemAnalyst 2024).

Some increases in BPS use are associated with actions taken to reduce the use of BPA. In 2011 Governor Brown signed into law a ban on the use of BPA in baby bottles and spill-proof cups; the US Food and Drug Administration (FDA) similarly banned this

use in 2012, and restricted use of BPA-based epoxy resins in packaging materials for infant formula in 2013 (US FDA 2014). The European Union (EU) instituted greater restrictions on BPA that became effective in 2020, including an EU-wide ban on its use in thermal paper. Since the restrictions on BPA use and public concerns regarding its safety, manufacturers have been gradually replacing BPA with BPS and other analogs such as bisphenol F (BPF). ECHA projected the use of BPS in thermal paper in the EU to be 61% in 2022, and for BPA to be mainly replaced by BPS for this use (ECHA 2022). Between 2024 and 2033, the online market analysis platform Chem Analyst (2024) projects a possible 4.2% increase in market global demand for BPS.

ChemAnalyst (2024) notes that:

> "Bisphenol S finds diverse applications as Heat Sensitive Developers, Polymer Modifiers, Flame Retardants, Water Soluble Resins, and Thermosetting Resins, and in the production of various intermediates. Thermal paper, driven by increased online purchasing and the growing significance of labeling in the food and beverage industry, constitutes the major source of demand for BPS globally. The rising use of epoxy resins for aesthetic purposes further fuels the demand for Bisphenol S. Polyurethane systems, known for providing strength, durability, and resilience in challenging conditions, are contributing significantly to the growth of the BPS market" (ChemAnalyst 2024).

1.2.2 Occurrence

The European Chemicals Agency (ECHA 2023) notes that BPS:

> "can be found in products with material based on: "leather (e.g. gloves, shoes, purses, furniture), paper (e.g. tissues, feminine hygiene products, diapers, books, magazines, wallpaper), paper used for articles with intense direct dermal (skin) contact during normal use such as printed articles (e.g. newspapers, books, magazines, printed photographs) and paper used for articles with intense direct dermal (skin) contact during normal use such as personal hygiene articles (e.g. diapers, feminine hygiene products, adult incontinence products, tissues, towels, and toilet paper)" (ECHA 2023).

BPS has also been detected in personal care products (e.g., hair care products, makeup, lotions, toothpaste), paper products (e.g., currency, tickets, mailing envelopes, airplane boarding passes), and food (dairy products, meat, vegetables, canned foods). BPS has been detected in environmental samples such as dust and sediment and human biological samples (X Fan et al. 2021; Pelch K et al. 2017).

Some examples of BPS detections in environmental samples and consumer products are provided below.

- House dust. BPS was detected in all house dust samples from 38 families in Northern California, collected between May 2015 to August 2016 (Shin et al. 2020). Similarly, BPS was detected in over 75% of house dust samples collected from 2007 to 2010 in 13 cities across Canada under the Canadian House Dust Study. The median concentration was 0.242 micrograms per gram (µg/g), and the range was < 0.017 to 35.1 (X Fan et al. 2021).

- Paper receipts. BPS was detected in 75% of receipts submitted by volunteers from several US locations, with the majority from southeast Michigan (Miller and Olson 2018).

- Food. Fifty adults in North Carolina collected 776 duplicate-diet solid food samples over a six-week monitoring period in 2009–2011. A 32% detection frequency was reported for BPS. The researchers calculated a daily dietary exposure of 13,640 nanograms per day (ng/day) and a dietary intake dose of 238 nanograms per kilogram per day (ng/kg/day) (Morgan and Clifton 2021).

- Fish. Fish packaged with thermal labels on plastic film were found with BPS with a mean concentration of 147 nanograms per gram (ng/g), and a maximum of 1,140 ng/g, exceeding the European Union specific migration limit (50 ng/g wet weight) (Xu et al. 2023).

- Meat. In a study in Albany, NY, BPS was detected in 43% of fresh meat and meat products (n = 51) with a mean concentration of 0.609 ng/g, and a 95th percentile of 0.780 ng/g (Liao and Kannan 2013).

  Cao et al (2022a, b) reported concentrations of BPS in composite samples of meat and meat products in the Canadian Total Diet Study from 2008 to 2020. In 2008, BPS was detected in meat samples with measured concentrations ranging from 0.070 ng/g in canned luncheon meats to 105 ng/g in fresh pork and 140 ng/g in veal cutlets. In 2020, measured concentrations of BPS in meat samples ranged from 0.14 ng/g in cured pork to 26 ng/g in ground beef and 118 ng/g in roast beef. The authors noted that, while levels varied across years, there was no trend, and that:

  > “The lack of trend for BPS over the period of 13 years (2008–2020) does not support the speculation that BPS is being used to replace BPA in food packaging, and sources other than food packaging may be possible and should be investigated for BPS.” (Cao et al. 2022a, b)

1.2.3 Exposure

Human biomonitoring studies indicate that exposure to BPS is widespread. The table and figures below present data on urine BPS concentrations from recent biomonitoring studies. Table 1.1 presents data from the state's Biomonitoring California program.

Table 1.1 BPS urine concentrations (µg/L) in recent studies of California residents

Study Name[1]	Sampled Group	Geometric mean (µg/L)	50th Percentile	90th Percentile	Number of Participants	Detection Frequency
CARE-LA	Women	0.38 (95% CI, 0.27–0.54)	0.342	2.42	60	76.7%
CARE-2	Adults	Not calculated	0.233	2.25	151	64.9%
CARE-3	Adults	Not calculated	0.288	2.85	90	64.4%

[1] CARE-LA: California Regional Exposure Study (CARE), Los Angeles County. Sample collection in 2018; CARE-2: Region 2. Sample collection in 2019; CARE-3: Region 3. Sample collection in 2020.
*Geometric mean not calculated when the chemical was found in <65% of samples; the Limit of Detection was 0.100 µg/L (wet weight)
CI: confidence interval; µg/L: microgram per liter. Data available at **https://biomonitoring.ca.gov/.** (Biomonitoring California 2020)

In another study conducted in California, urine samples were taken from pregnant women and analyzed for several chemicals including BPS. This is the Markers of Autism Risk in Babies – Learning Early Signs (MARBLES) study, a high-familial risk autism spectrum disorder cohort, in which 218 pregnant women in California were sampled between 2007–2014 (K Kim et al. 2021). The researchers reported increasing BPS detection in urine across time (see Table 1.2), from 0% in 2007 to 32% in 2014 [limit of detection (LOD)= 0.5 nanograms per milliliter (ng/ml), equivalent to 0.5 micrograms per liter (µg/L)]. The 95th percentile BPS level was 2.8 ng/mL. Because the LOD for the MARBLES study was higher than for the recent Biomonitoring California studies (LOD= 0.1 µg/L), frequencies of detections cannot be directly compared across these studies.

Table 1.2 BPS exposure in pregnant women in California during 2007-2014 from a high-familial risk autism spectrum disorder cohort
(Adapted from K Kim et al. 2021)

Year	Number of Samples	BPS Detection Frequency (%)	BPA Detection Frequency (%)
2007	51	0	67
2008	121	5	63
2009	181	9	58
2010	112	14	59
2011	67	6	55
2012	65	26	62
2013	106	26	62
2014	57	32	42

At the national level, biomonitoring for BPS has been conducted under the US Centers for Disease Control and Prevention's National Health and Nutrition Examination Survey (NHANES) study. Urinary BPS concentration levels were reported in summary form for 1808 adults and 868 children for the years 2013−2014. Participants were selected using a random selection approach. BPS was detected in 89.4% of urine samples with median levels of 0.37 µg/L for adults and 0.29 µg/L for children (LOD = 0.1 µg/L). Urinary BPS levels in adults varied by race/ethnicity, where non-Hispanic Black and Hispanic adults had significantly higher BPS levels compared to non-Hispanic White adults. Urinary BPS levels in children varied by gender (females had higher BPS levels than males) and race/ethnicity (Hispanic children had higher BPS levels than non-Hispanic White children) (Lehmler et al. 2018).

K Kim et al. (2021) presented data on temporal trends in BPA and BPS urinary levels for pregnant women in the NHANES and MARBLES studies, as well as two additional studies: LIFECODES (pregnant individuals in Massachusetts, 2007–2009), and Puerto Rico Testsite for Exploring Contamination Threats (PROTECT) (pregnant individuals in Puerto Rico, 2011–2016). They also presented NHANES data for non-pregnant women. For NHANES, they selected the ages 20 to 50 stratified by pregnancy status, for the years 2013–2015. Figure 2, adapted from K Kim et al. (2021), indicates decreasing BPA levels with concomitant increases in BPS levels measured in urine samples of pregnant and non-pregnant women during the period covered by these studies, 2007–2015.

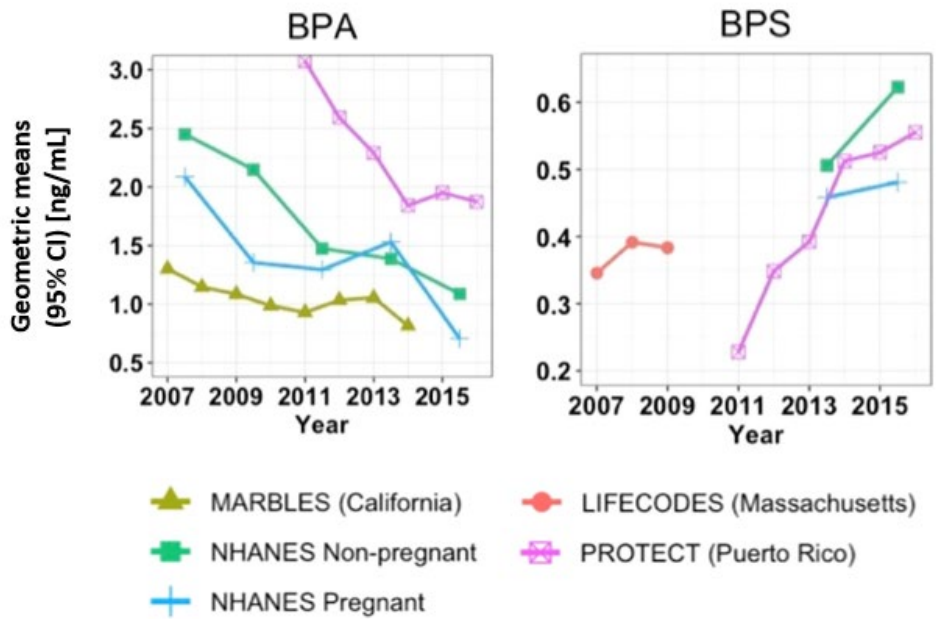


Figure 2 BPS and BPA in pregnant women measured in urine samples collected between 2007 and 2015 in four biomonitoring studies (The published y-axis title indicated that 95% CI were presented, but figures here are shown as they were in the published document. Also note the different y-axis scale for each chemical). (Source: K Kim et al. 2021 [adapted]).

In an online crowdsourced study, BPS was detected in urine above the sample-specific method reporting limit in 81% of 726 US participants with values ranging from 0.084–921 ng/mL, and a median of 0.48 ng/mL. Samples were collected between February 2017 and October 2018 and analyzed by one of two laboratories (Dodson et al. 2020).

BPS levels in humans have been associated with product use and behaviors in some studies:

- In a study of children in Baltimore City, Maryland concentrations of urine BPS were higher with recent use of an air freshener and canned food consumption (Fandiño-Del-Rio et al. 2024).
- In a study of men seeking fertility treatment in Boston, Massachusetts, self-reported use of fabric softener or paints/solvents, and self-reported beef or cheese intake during the 24 hours prior to urine collection were associated with higher urinary concentrations of BPS (Ghayda et al. 2019).
- In a Korean intervention study, mothers were asked to avoid foods in cans and plastic containers, fast foods, and delivery foods for three days. Children were school-aged and were home with their mothers over summer vacation during the study. If children went to day-care centers, mothers were asked to prepare homemade meals and snacks for them during the intervention period. Percent

reductions in urinary BPS levels (during intervention vs. without intervention) were significant for mothers (-63.9%, 95% CI: -79.3 to -37.1) but not for children (-34%, 95% CI: -57.6 to 2.8) (Kim et al. 2020).

- In an intervention study including premenopausal women with obesity in California, there was a 55% decrease in urinary BPS concentrations among 15 participants randomized to a 3-week intervention that encouraged them to avoid canned/plastic packaged food and beverages, cosmetics, and hygiene products. They were provided bisphenol-free glass storage containers as replacements (Hagobian et al. 2021).

1.2.4 Considerations for Exposure Assessment in Epidemiologic Studies

The ability of a study to detect an association if one exists depends on several characteristics related to the assessment and magnitude of exposure. These include the LOD of BPS in the analysis of the samples taken, the percentage of the samples with BPS levels above the LOD, and the median and variability in BPS exposure levels. In the epidemiologic studies presented in this document there was considerable variation in the LODs and, as such, in the ability to detect BPS in the samples. Also, measured BPS levels in the participants across studies differed substantially. Some of the variation in BPS exposure across studies may be explained by study year, as BPS occurrence has changed over time, or by country. Other very important considerations are that (i) BPS is rapidly eliminated in urine, with a short half-life (estimates range between 7 to 9 hours for oral exposures; see Section 3. Pharmacokinetics of BPS), and (ii) although many epidemiological studies measured BPS at multiple points in pregnancy, most studies relied on a single urine sample to classify exposure during a given period (e.g., trimester). There is a general consensus that in many circumstances a single urine sample may be insufficient to adequately assess exposure to non-persistent chemicals, such as BPS (Fays et al. 2020; Verner et al. 2020). Among the studies that measured BPS at multiple time points during pregnancy (e.g., each trimester), some assessed the correlations of BPS exposure levels across time. The reported intraclass correlation coefficients (ICC) were generally low, ranging from 0.01 to 0.45.

1.3 Reviews by Other Health Agencies

The US EPA, the National Institute for Occupational Safety and Health (NIOSH), the FDA, and the National Toxicology Program (NTP) have not reached conclusions or classified BPS as to its potential to cause developmental toxicity.

ECHA has identified BPS as a substance meeting the criteria of a reproductive toxicant (toxic for reproduction category 1B, H360FD"[2]). ECHA's description for category 1B is as follows (ECHA 2022):

> "Reproductive toxicant category 1B adverse effects on sexual function and fertility or on development or reproductive toxicant category 2 with R60 (May impair fertility) or R61 (May cause harm to the unborn child)".

In the summary of classification and labelling, the hazard statement listed is "May damage fertility. May damage the unborn child." (See: https://echa.europa.eu/substance-information/-/substanceinfo/100.239.213).

ECHA (2022, pp 12–13), in identifying BPS as a substance of "very high concern because of its toxic for reproduction", stated:

> "Based on all available scientific evidence, it can be concluded that BPS fulfils the WHO/ International Programme on Chemical Safety (2002) definition of an endocrine disruptor:
>
> - It shows clear reproductive adverse effect in rodents and fish. The reproductive endocrine system is highly conserved not only between mammals, but also between mammals and other vertebrates like fish.
> - It has endocrine modes of action: clear estrogenic mode of action and alteration of steroidogenesis.
> - The adverse effects, including the recognized EAS [estrogenic, androgenic and steroidogenic]-mediated effects (e.g., on estrous cycle and sex ratio) and effects sensitive, but not diagnostic of EAS (e.g. fecundity, fertility, implantation sites and number of pups), are a consequence of the endocrine modes of action."
>
> "The assessment performed demonstrates that there is scientific evidence of probable serious effects of BPS to the environment and human health due to its endocrine disrupting properties, which give rise to an equivalent level of concern to those of other substances listed in points (a) to I of Article 57 of the REACH Regulation" (ECHA 2022).

[2] H360FD is the hazard statement code for "May damage fertility. Suspected of damaging the unborn child"

2 OVERVIEW OF SYSTEMATIC LITERATURE REVIEW APPROACH

Searches of the published scientific literature on the developmental and reproductive toxicity (DART) of BPS were conducted in January 2022 and updates to the original search were conducted in February 2023, July 2023, January 2024, and October 2024. Additional studies that came to OEHHA's attention after the last comprehensive search (e.g., via updated focused searches in PubMed) are also included in this document. The goal of the searches was to identify peer-reviewed journal articles (open source and proprietary), print and digital books, reports, and gray literature that potentially reported toxicological and epidemiological information on the DART of this chemical.

The searches were conducted using the following three approaches:

- Primary searches in major biomedical databases, conducted by OEHHA librarian Nancy Firchow, MLS
- Searches in other data sources, including authoritative reviews and reports, and databases or web resources, conducted by OEHHA scientists
- Additional focused searches, conducted by OEHHA scientists

In addition to information identified from these searches, relevant literature was identified in the following:

- One submission received during the data call-in period (March 4 to April 18, 2022) (https://oehha.ca.gov/proposition-65/comments/comment-submissions-request-relevant-information-reproductive-toxicity)

2.1 Primary Search Process

The US EPA Computational Toxicology (CompTox) Chemicals Dashboard (https://comptox.epa.gov/dashboard) was used to identify synonyms for BPS. The PubMed MeSH database (https://www.ncbi.nlm.nih.gov/mesh/) was used to identify subject headings and other index terms related to the chemical, reproduction and development, and adverse effects on reproduction and development.

Preliminary searches were run, and results evaluated to identify additional relevant search terms. The resulting search strategies were then executed in PubMed where searches were divided as follows:

- Human DART studies (including *in vitro* studies)
- Animal DART studies (including *in vitro* studies)
- Absorption, distribution, metabolism, and excretion (ADME) studies

There were no restrictions in the searches on exposure route or duration of exposure, or on publication language. The full DART search strings used in PubMed are included in Appendix A.

The PubMed search strategies were then tailored for use in the additional databases and data sources (see details in Appendix A), according to the search interface and features unique to each resource. For instance, MeSH terms were replaced with Emtree terms for the Embase search strategies.

2.2 Literature Screening Process

The results of the literature searches were uploaded to EndNote libraries and duplicates were removed. In addition to the studies identified through this process, other relevant studies were identified from citations in individual articles, through alert services (e.g., ScienceDirect, Google Scholar, etc.), and through February and July 2023, and January and October 2024 updates to the searches. A total of 1,683 references were identified in the searches for human and animal DART data and a total of 759 references were identified in the searches for ADME data (see Appendix Table A.7).

The EndNote libraries containing the literature search results (citations) for BPS were uploaded to HAWC (Health Assessment Workspace Collaborative, https://hawcproject.org). HAWC is a tool used for multi-level screening of literature search results.

In Level 1 screening, citations were reviewed independently by OEHHA scientists, based solely on study titles and abstracts, using specific inclusion and exclusion criteria to eliminate studies or articles that did not contain information on DART or other key related topics (e.g., pharmacokinetics, mechanisms of action). This initial screen (Level 1) was intended to identify all studies deemed to have a reasonable possibility of containing information relevant to DART that could be useful for the review process, and to further identify (i.e., tag in HAWC) studies relevant to particular aspects of DART (e.g., male reproductive toxicity, female reproductive toxicity, developmental toxicity).

For purposes of identifying the available evidence on the developmental toxicity of BPS, citations identified as having a reasonable possibility of containing information relevant to developmental toxicity underwent Level 2 screening. In the Level 2 screening of this subset of citations, the full text was obtained. These full papers were screened independently by one OEHHA scientist, using similar inclusion/exclusion criteria as was used in the Level 1 screening. However, Level 2 reviewers could make more accurate judgements about the relevance of the articles because they were reviewing the full text in addition to the title and abstract. Following Level 2 screening, the tagging of articles according to key topics was updated in HAWC. Level 1 and 2 screenings were repeated

as search results were updated, and with additional relevant studies identified from citations in individual articles and alert services (e.g., ScienceDirect, Google Scholar) (See Appendix A for additional details).

A total of 270 references were cited in this document.

3 PHARMACOKINETICS

This section describes the absorption, distribution, metabolism, and excretion of BPS in humans, laboratory animals, and *in vitro* models. Since humans and laboratory animals share many of the reported metabolic pathways and BPS metabolites, data from animal studies are included when human data are unavailable or incomplete. Data from animal studies are useful to complement human data and highlight observed route, species, and sex differences.

3.1 Absorption

The primary route of human exposure to BPS is oral, however, exposure may also occur via the dermal and inhalation routes (Kumar et al. 2018). Following oral exposure, BPS is rapidly absorbed with a high bioavailability in humans (Khmiri et al. 2020; Oh et al. 2018), rats and mice (BASF 2019b; Waidyanatha et al. 2018; Waidyanatha et al. 2020), and pigs (Gayrard et al. 2019), with some of these studies showing evidence of BPS undergoing enterohepatic circulation. It has been demonstrated that BPS is absorbed in humans via the dermal route, though absorption and bioavailability were lower compared to the oral route (Khmiri et al. 2020; Liu and Martin 2019; Oh et al. 2018; Reale et al. 2021).

3.1.1 Oral dosing

BPS was rapidly and well absorbed in humans. In a study of women administered a single oral dose of 0.1 mg/kg radiolabeled BPS, the time to maximum plasma concentration (T_{max}) of free and glucuronidated BPS was 0.7 and 1.1 hours, respectively, and oral bioavailability was approximately 62% (Khmiri et al. 2020). Small plasma concentration peaks occurred between 4 and 10 hours, indicating possible enterohepatic recirculation (Khmiri et al. 2020). Similarly, in a study of men and women administered a single oral dose of 8.75 µg/kg radiolabeled BPS, serum concentrations of free and total BPS increased rapidly, with T_{max} values of 0.6 hours for free BPS and 0.7 hours for total BPS (Oh et al. 2018).

Kinetic parameters derived from rodent studies demonstrated some species and dose dependency, but were generally independent of sex in mice (Waidyanatha et al. 2018; Waidyanatha et al. 2020) and rats (BASF 2019b). Despite the absence of sex differences in T_{max} and plasma half-life of total BPS in mice, there were sex differences in some pharmacokinetic parameters in rats. After a single oral BPS exposure of 110 mg/kg, female rats had a shorter absorption plasma half-life for total BPS compared to males (0.08 and 0.33 hours, respectively), with a relatively longer elimination half-life compared to males (14.3 vs. 11.2 hours, respectively) (Waidyanatha et al. 2020).

In one set of studies of male and female rats exposed to a single gavage dose of 30 or 300 mg/kg BPS, there were two T_{max} peaks in plasma at 1 and 4 hours, indicating possible enterohepatic circulation, in both sexes and doses (BASF 2019b). Internal exposure (maximum concentration [C_{max}] and area under the curve) was sex dependent at one hour and increased with dose. In male rats, oral absorption was independent of dose at 93–95% and somewhat dose dependent in females with 87% and 96% absorption in the low- and high-dose groups, respectively (BASF 2019b). In another set of studies in male and female rats exposed to a single BPS dose of 110 mg/kg by gavage, the T_{max} of total BPS was approximately 0.6 hours in females and 1.75 hours in males (Waidyanatha et al. 2020). In male rats gavaged with 34, 110, or 340 mg/kg BPS, the T_{max} value of total BPS increased from 0.99 to 2.77 hours with increasing dose. In male mice, T_{max} was 3.08 hours after a single gavage exposure of 340 mg/kg. T_{max} data was not reported for female mice (Waidyanatha et al. 2020). After exposure to a single gavage dose of 110 mg/kg, the calculated oral bioavailability for rats and mice in these studies ranged from 11% to 15% in both sexes and species (Waidyanatha et al. 2020) and was lower compared to that calculated for the BASF (2019b) studies in rats. C_{max} and area under the curve were dose dependent in males in both species for free and total BPS except for C_{max} on total BPS in mice (Waidyanatha et al. 2020). The discrepancy in bioavailability ranges between the two studies outlined above may have been due to the method of calculating absorption. In the BASF (2019b) study, oral absorption was calculated by summing the radioactivity in bile, urine, cage wash, and carcass, whereas the study by Waidyanatha et al. (2020) calculated bioavailability using area under the curve and dose data for intravenous and gavage exposures.

As mentioned earlier, in rats administered a single gavage dose of BPS, there were two plasma concentration peaks that occurred between 1 and 4 hours, indicating possible enterohepatic circulation (BASF 2019b). Potential enterohepatic circulation was further supported in bile duct-cannulated male rats administered a single gavage dose of BPS, with 53% of the dose secreted into the bile within 24 hours (Waidyanatha et al. 2018).

The plasma half-life of unconjugated BPS in males following a single gavage dose (34, 110, or 340 mg/kg) was estimated to be 2.86–4.21 hours in mice and 5.77–11.9 hours in

rats. In females treated with a single gavage dose of 110 mg/kg BPS, the plasma half-life of unconjugated BPS was 3.29 hours in mice and 4.11 hours in in rats. For total BPS at 110 mg/kg, the absorption half-life was 0.08 and 0.33 in female and male rats, respectively. In mice, the absorption half-life was 0.18 hours with no sex differences (Waidyanatha et al. 2020).

In 28 days-old female piglets were gavaged with 10 mg/kg (40 µmol/kg) BPS. Plasma C_{max} of BPS was 0.51 µmol/L per µmol/kg, with a T_{max} equal to 0.53 hours. Gastric absorption of BPS was estimated to be 99% compared to 77% for BPA. When BPA and BPS were administered at 47.5 and 50 mg/kg (200 µmol/kg), respectively, by oral gavage, a higher modeled bioavailability was reported for BPS than BPA (57.4% vs. 0.5%, respectively). It should be noted that 72 hours prior to the oral dose, animals were administered a 5 mg/kg intravenous dose of BPS (Gayrard et al. 2019).

3.1.2 Dermal dosing

Dermal absorption and bioavailability of BPS were demonstrated to be relatively lower in humans and human skin models compared to oral dosing, and highly dependent on vehicle.

In women dosed dermally with 1 mg/kg BPS in phosphate buffer with carboxymethylcellulose for 6 hours, absorption was generally undetectable for most time points, with T_{max} observed in individual participants between 5 and 8 hours (Khmiri et al. 2020).

In an *in vitro* study where 25 µg/cm^2 BPS (dissolved in water) was applied unoccluded to fresh human skin in diffusion cells for 24 hours, 0.2–0.4% of the applied dose was recovered in the receptor fluid (absorbed dose) and 11.4% was recovered in the receptor fluid plus skin including the *stratum corneum* (potentially absorbed dose) compared to 25% and 40%, respectively, of an applied BPA dose using the same dosing regimen. Of note, the *stratum corneum* is not always included in the potentially absorbed dose due to high cellular turnover. The maximum flux (absorption rate) for BPS was 0.006 µg/cm^2/hour compared to 0.67 µg/cm^2/hour for BPA (Reale et al. 2021). In another absorption study using diffusion cells, 20 µg/cm^2 of BPA or BPS in three different vehicles was applied to unoccluded human skin samples for up to 40 hours. The cumulative absorbed dose of BPS in the receptor fluid at 40 hours post-application was 0.011 (0.06%), 0.041 (0.2%), and 0.256 (1.3%) µg/cm^2 in acetone, water, and artificial sebum vehicles, respectively, compared to 5.7%, 40.9%, and 2.7% for BPA. The potentially absorbed dose of BPS in skin (including the *stratum corneum*) was 20%, 47%, and 27% in acetone, water, and sebum, respectively, and flux at steady state was low in all vehicles, but highest in artificial sebum, with 0.0003, 0.0010, and 0.0106 µg/cm^2/hour in acetone, water, and sebum, respectively. Comparatively, BPA

had a higher flux at steady state in all media (Champmartin et al. 2020). In another human skin *in vitro* model, skin permeability of a 1.5 or 7.7 μg/cm^2 application of isotope-labeled BPA and BPS was assessed. At both dose levels, 6–8% of the BPS dose was recovered in the receptor fluid (absorbed dose) and 16–17% was recovered in the skin (potentially absorbed dose) compared to 43–46% of the BPA dose in the receptor fluid and 13–14% in the skin at 25 hours. This study used a reconstructed human epidermis and applied BPS with BPA as a mixture; these factors likely account for the differences in results with the studies using whole human skin (Liu and Martin 2019). One study reported changes in absorption and flux when 20 μg/cm^2 BPS in acetone, water, and artificial sebum was applied unoccluded and occluded (to mimic clothing) to human skin diffusion cells for 40 hours. When BPS was dissolved in acetone and water, occlusion resulted in six-fold and four-fold increases in absorption flux and cumulative absorption compared to that of unoccluded skin. When BPS was solubilized in artificial sebum, there was no effect of occlusion on absorption flux or cumulative absorption (Marquet et al. 2024).

3.2 Distribution

Once absorbed into circulation, BPS is distributed throughout the body (Khmiri et al. 2020; Oh et al. 2018). BPS has been detected in human cord blood (Liu et al. 2017), amniotic fluid (Tuzimski et al. 2023), and the placenta (Zhu et al. 2023). BPS has been also detected in human colostrum and breast milk samples (Iribarne-Durán et al. 2022; Luo et al. 2021; Niu et al. 2021; Zhang et al. 2024). In men and women administered a single oral dose of 8.75 μg/kg BPS, the estimated volume of distribution was 205 L, indicating extensive distribution to peripheral tissues (Oh et al. 2018).

Single-dose gavage studies in rats reported extensive biliary excretion within the first two hours of dosing, with significant reuptake in the gut (i.e., enterohepatic recirculation) (BASF 2019b; Waidyanatha et al. 2018). In rats after a single gavage administration, BPS has been detected in gastrointestinal tissues, liver, kidney, heart, spleen, lung, and muscle (Mao et al. 2022). In rats, the BASF (2019b) study reported the highest tissue concentrations in the gastrointestinal tract after 1 hour in the 300 mg/kg dose group. In male rats, after the gastrointestinal tract, the highest residues in the 300 mg/kg dose group were found in the kidney, liver, and plasma. Similar results were observed in male and female mice after a single gavage dose of 150 mg/kg BPS (Waidyanatha et al. 2018) and in rats continuously administered a gavage dose of 500 μg/kg/day BPS for 31 days (Mao et al. 2022). BPS did not accumulate in tissues or blood over time in rats and mice administered BPS as a single dose (Mao et al. 2022; BASF 2019b; Waidyanatha et al. 2018).

3.2.1 Placental transfer

There is evidence that BPS can cross the placenta in humans and animals. BPS has been detected in human placental tissue, amniotic fluid samples, and cord blood (Abrantes-Soares et al. 2022; Liu et al. 2017; Pan et al. 2020; Tuzimski et al. 2023; B Zhang et al. 2020; Zhu et al. 2023).

In a study of pregnant women in China, BPS was detected in four maternal plasma samples (< 0.04–0.07 ng/mL) and seven cord serum samples (< 0.03 – 0.12 ng/mL) (Liu et al. 2017). In another study from China of 48 matched maternal-fetal pairs, including maternal plasma, cord plasma, and placental samples, median levels of BPS in maternal plasma (10.1 pg/g, ww [wet weight]) were higher than levels in cord plasma (5.8 pg/g, ww) and lower than in the placenta (19.0 pg/g, ww), suggesting that the placenta can accumulate BPS (Pan et al. 2020).

Placental BPS transfer was reported in human term placenta perfused *ex vivo* with 1 or 5 µM radiolabeled BPS. The placental BPS and BPS glucuronide transfer ratios into the fetal compartment were lower than into the maternal compartment (3.18% vs. 5.85% BPS, respectively; 0.34% vs. 3.97% BPS glucuronide, respectively) (Grandin et al. 2019). In another *ex vivo* human placental perfusion model from term placentas, 5 µM BPS had a lower placental transfer ratio of 2.45% compared to several bisphenols used at the same concentration, including BPA (25.7%) that transferred principally by passive diffusion (Gély et al. 2021).

BPS was also detected in amniotic fluid and fetal plasma in samples collected from pregnant ewes administered BPS via injection (Gingrich et al. 2019; Grandin et al. 2018).

In ewes, the BPS maternal and fetal plasma half-lives were 3.7 and 402 hours, respectively, after a single sc injection of 0.5 mg/kg BPS to the pregnant ewe on approximately GD 122. However, fetal C_{max} was lower than maternal (18.5 ng/mL vs. 643.1 ng/mL, respectively) (Gingrich et al. 2019). In pregnant sheep administered an intravenous dose of 5 mg/kg BPS with a 17.5 mg BPS-glucuronide-d8 dose to the fetus, the fetal half-lives were 1.92 and 93.6 hours for BPS and BPS-glucuronide, respectively, and maternal half-lives were 2.37 and 5.22 hours for BPS and BPS glucuronide, respectively (Grandin 2018).

3.2.2 Breast milk transfer

BPS has been measured in human breast milk in populations around the world (Iribarne-Durán et al. 2022; Luo et al. 2021).

3.3 Metabolism

BPS undergoes metabolism via sulfation, glucuronidation, and hydroxylation to form BPS-sulfate, BPS-glucuronide, and hydroxylated BPS (Waidyanatha et al. 2018). Figure 3, adapted from Waidyanatha et al. (2018), depicts the main metabolic pathways and metabolites for BPS in humans, rats, and mice (Oh et al. 2018; Sonker et al. 2021; Waidyanatha et al. 2018). Studies indicate that BPS-glucuronide is the primary metabolite of BPS formed in humans (Khmiri et al. 2020; Oh et al. 2018), rats (Mao et al. 2022; Waidyanatha et al. 2018), and mice (Waidyanatha et al. 2018). A recent study in Chinese participants (59% females) reported that in 79 paired human serum and whole blood samples, the mean levels of BPS metabolites were higher for BPS-sulfonate (approximately 0.4 ng/ml) than BPS-glucuronide (0.1 ng/ml) and unconjugated BPS (0.1–0.2 ng/ml) in serum and whole blood. In this study, BPS was detectable in 49% of serum and 78% of whole blood samples. BPS-glucuronide and BPS-sulfonate had higher detection frequency than BPS in serum (68–74% vs. 49%) and whole blood (84-86% vs. 78%) (Z Fu et al. 2024).

In an *in vitro* study in HepaRG cells, a human hepatic cell line, 85.8% of BPS was metabolized to BPS-glucuronide and 10.5% to BPS-sulfate (Oh et al. 2018). One study found that in isolated hepatocytes from humans, rats, and mice, BPS was metabolized to hydroxylated BPS (humans, rats, mice), BPS-sulfate (humans, rats), BPS-glucuronide (humans, rats), and the sulfate conjugate of hydroxylated BPS (rats) (Waidyanatha et al. 2018).

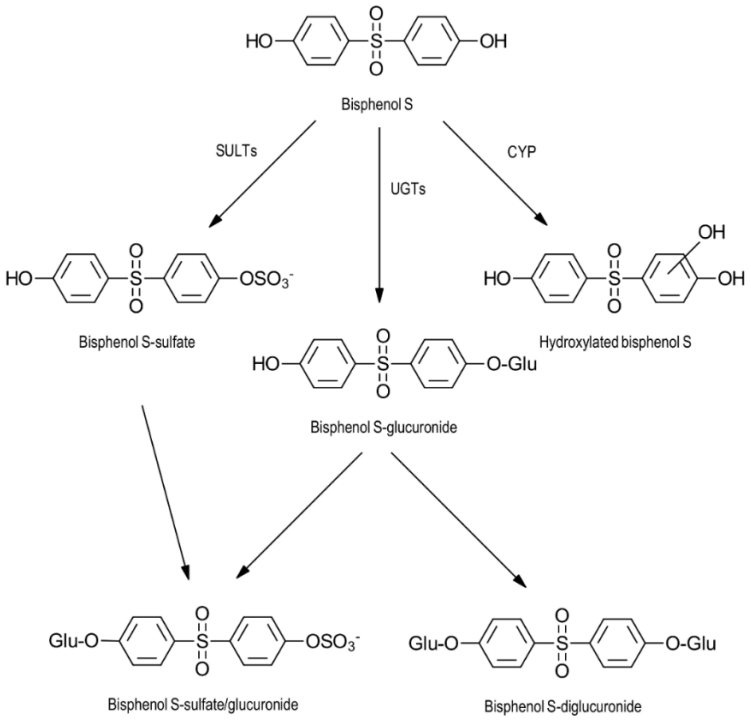
Variability in metabolic capabilities has been reported among different human cell lines (Le Fol et al. 2015), and considerable interindividual variation in the metabolism of BPS was observed in a study conducted in women, with the percentage of a single administered dose recovered in urine as BPS-glucuronide over 72 hours ranging from 37 to 72% (Khmiri et al. 2020). Another single-dose study conducted in adult men and women reported that the percentage of the dose recovered in urine as total BPS over 48 hours was lower in women (59–77%) compared to men (67–104%) (Oh et al. 2018).

Comparative metabolism studies in male and female rats and mice administered a single gavage dose of BPS reported that BPS-glucuronide accounted for approximately 40–50% of the administered dose in both rats and mice, while BPS-sulfate accounted for approximately 18–21% of the administered dose in mice and 4% in rats at 150 mg/kg (Waidyanatha et al. 2018).

In a dermal absorption *in vitro* model using human skin, little metabolism was observed when a 20 μg/cm^2 dose of BPS in acetone, water, or artificial sebum was applied to human skin diffusion cells for 40 hours. The majority (85–93%) of the BPS in the

receptor fluid was unmetabolized, indicating minimal metabolism within the skin compartment (Champmartin et al. 2020).

Figure 3 Proposed metabolism of BPS in rodents



Abbreviations: SULTs sulfotransferases; UGTs = uridine 5′-diphospho-glucuronosyl-transferase; CYP= cytochrome P450 enzyme (Adapted from Waidyanatha et al. (2018)).

3.4 Excretion

Studies in humans and animals indicate that BPS is excreted in the urine, bile, feces, breast milk, and, to a minor extent, in expired air after oral exposure. Free and total BPS were detected in the urine of men who handled BPS-containing paper followed by hand washing at 2 hours post-exposure (Liu and Martin 2019). In humans, BPS is excreted primarily via urine as BPS-glucuronide. In one study, urinary excretion of a single oral dose of total BPS was 92% in men and 70% in women after 48 hours, with an estimated elimination half-life of 6.9 hours, representing metabolism and excretion (Oh et al. 2018). Another study in women estimated an elimination half-life of a single oral BPS dose of around 8 to 9 hours for free and BPS-glucuronide, respectively, and reported that urinary excretion was almost complete after 72 hours (Khmiri et al. 2020). In the dermal exposure study in men, 78% of urine samples had detectable total BPS after two days (Liu and Martin 2019). BPS is also primarily excreted via urine in mice, rats, and sheep. No substantial species or sex differences in urinary BPS excretion were

identified in studies of male and female rats and mice administered a single gavage dose of BPS, with approximately 67–70% of an administered dose of 150 mg/kg excreted within 72 hours (Waidyanatha et al. 2018). Greater variability was reported for fecal excretion, however, with 22%, 16%, 12%, and 17% of the administered dose excreted by male rats, female rats, male mice, and female mice, respectively, within 72 hours (Waidyanatha et al. 2018).

In male and female rats administered a single gavage dose of 30 or 300 mg/kg radiolabeled BPS, urinary and fecal excretion accounted for approximately 60% and 43%, respectively, in males in the 30 mg/kg group; 48% and 44%, respectively, in males in the 300 mg/kg group; 51% and 41%, respectively, in females in the 30 mg/kg group; and 39% and 56%, respectively, in females in the 300 mg/kg group. In this study, high biliary excretion was demonstrated in bile duct-cannulated rats administered the same single doses of BPS, accounting for approximately 44–56% and 38–46% of the dose in males and females, respectively. In addition, less than 2% of the 30 mg/kg oral dose of BPS was detected in exhaled air (BASF 2019b).

In plasma, the elimination half-life in rats was 4.11 hours in females and 8.06 hours in males after a single oral dose of free BPS at 110 mg/kg. The elimination half-life in male mice was 2.86 hours at 34 mg/kg and 4.21 hours at 340 mg/kg, and in male rats was 5.77 hours at 34 mg/kg and 11.9 hours at 340 mg/kg after a single gavage dose of free BPS (Waidyanatha et al. 2020). In the piglet study by Gayrard et al. (2019), the urinary excretion of BPS as BPS-glucuronide was 86.5% with approximately half of the dose eliminated by 3 hours.

4 DEVELOPMENTAL TOXICITY

Studies on the developmental toxicity of BPS evaluated potential adverse effects of preconceptional or prenatal exposure on the developing offspring. Some animal studies with combined prenatal and postnatal exposure were also reviewed. The available evidence is summarized in the following order: evidence from human epidemiologic studies, evidence from whole animal *in vivo* mammalian and non-mammalian studies, and evidence from studies most often employing *in vitro* experimental designs, which help inform consideration of mechanisms of action.

4.1 Studies in Humans

OEHHA identified 65 epidemiologic studies of possible effects of BPS on fetal development for inclusion. These studies assessed associations between individual-level exposure and developmental outcomes using cohort, case-control, or cross-

sectional designs. Included studies presented adjusted measures of association, reported original data analyses with details about methods, and were published in peer-reviewed journals. These included 27 studies on birth outcomes, eight studies on infant growth, thirteen studies on neurodevelopment, seven studies on immune function, nine studies on endocrine and cardiometabolic outcomes, two studies on bone mass and bone mineral density, and two studies on offspring reproductive development. Three of the included studies are counted in both the birth outcomes and infant growth sections because multiple outcomes were examined.

In addition to the 65 included studies, there were 18 studies from the developmental toxicity literature search full-text review that were excluded. Three studies were excluded because the authors reported that BPS was detected in too few samples to analyze thus measures of association were not reported (Barkoski et al. 2019; Buke Sahin et al. 2024; Kolatorova et al. 2018). Five studies were excluded because BPS was measured after gestation (Jang et al. 2021; Jin et al. 2020; Kim et al. 2022; Lee et al. 2024; Sigvaldsen et al. 2024). Five studies were excluded from the epidemiological section because the researchers didn't evaluate a specific developmental outcome (Blaauwendraad et al. 2021; J Chen et al. 2024; Kelley et al. 2019; McCabe et al. 2020; L Wang et al. 2021); however, some are summarized in the mechanistic section, see Section 4.3. One study was excluded because BPS was predicted from dietary exposure and not directly measured (Ramírez et al. 2024). Two studies were excluded because they did not report adjusted measures of association (Pan et al. 2024; Zhang et al. 2024). Two studies were excluded because associations specific to BPS, independent from a mixture of chemicals, were not reported (J Fu et al. 2024; Karthikeyan et al. 2024).

The included studies determined BPS exposure through levels of BPS measured in urine (58 studies), serum (5 studies), placenta (1 study), or cord blood (1 study) samples. Most studies measured BPS as total BPS and did not differentiate between free or conjugated forms. For more information on BPS metabolism, see Section 3, Pharmacokinetics of BPS. As discussed in the exposure section, Appendix B Table B.1 presents the ranges of limits of detection (LOD), percent of samples with BPS detected, and sample matrices for all studies that examined developmental outcomes.

All but one of the studies included measurement of additional bisphenols, most often bisphenol A (BPA) and bisphenol F (BPF). The correlations between BPS and other bisphenols varied. In general, most studies showed weak to moderate correlations between BPS and other bisphenols. It is important to note that because many studies examined BPS along with other chemical exposures, BPS was not the only exposure of interest.

Estimation of an unbiased association between BPS and developmental outcomes requires adjustment for potential confounding variables. Covariates included in the study adjustment sets are listed in Table 4.1.1. The most frequently adjusted variables were maternal age, pre-pregnancy body mass index (BMI), parity and/or gravidity, exposure to smoking, markers of socioeconomic status (e.g., household income, occupation, maternal education), and offspring sex. Most adjustment sets were comprehensive, though bias due to unmeasured or residual confounding is possible in observational research.

A review of the studies is ordered by outcome in the following discussion. Key elements of each study are presented in Table 4.1.1. Statistically significant results (α = 0.05) in all the tables are shown in bold along with p-values and confidence intervals as available.

4.1.1 Birth Outcomes

Gestational length

Twelve studies estimated associations between gestational or preconception (one study) BPS exposure with outcomes of preterm birth and gestational age. Preterm birth is defined as birth prior to 37 weeks gestation and was analyzed as a binary variable, while gestational age is defined as the length of time from the last menstrual period through birth and was analyzed as a continuous variable (in days or weeks).

Several studies reported associations with BPS in the direction of shorter gestational length and increased risk of preterm birth. The strongest associations were observed in studies that measured BPS preconceptionally or during trimester one (TM1). For example, Mustieles et al. (2020) reported 3.33 (95% Confidence Interval [CI]: 1.13 to 8.80) times higher odds of preterm birth per 1-unit increase of preconception natural log-transformed (ln) BPS (Mustieles et al. 2020). In a cohort from Guangxi, China, Liang et al. (2021) observed 2-fold increases in the odds of preterm birth in high and middle (vs. low) tertiles of TM1 BPS exposure (High vs. Low odds ratio [OR] = 2.07, 95% CI 1.24 to 3.46; Middle vs. Low OR = 1.93, 95% CI 1.15 to 3.25) (Liang et al. 2021b). These associations were slightly stronger for pregnancies with male infants compared to female infants (Liang et al. 2021b). Three other prospective cohort studies estimated positive, but not statistically significant, associations between TM1 BPS and preterm birth with ORs of 1.63 (95% CI: 0.84 to 3.24) (Sol et al. 2021), 1.41 (95% CI: 0.48 to 4.10) (Huang et al. 2019), and 1.25 (95% CI: 0.82 to 1.89) (Zhang et al. 2021). Note that the latter two studies also examined associations with BPS measured in other trimesters and the directions of reported ORs were mixed and estimates were imprecise (Huang et al. 2019; Zhang et al. 2021). Lastly, in the National Institutes of Health Environmental Influences on Child Health Outcomes (ECHO) study that harmonized

data from 11 unique cohorts with birth years 1998–2023 (n = 3,619), one-unit increases in TM1 BPS were associated with shorter gestation length in pregnancies with female fetuses (Beta coefficient [β]: −0.31 weeks, 95% CI: −0.59 to −0.03) and among Non-Hispanic White individuals (β: −0.43 weeks, 95% CI: −0.72 to −0.14) (Trasande et al. 2023). Racial and ethnic group stratified associations between TM1 BPS and preterm birth were not statistically significant, but of the same magnitude to those presented above (Trasande et al. 2023).

Two studies reported positive associations between late-pregnancy BPS exposure and shorter gestational age and preterm birth. A study from China by Yang et al. (2021) reported that the highest versus lowest tertile of BPS exposure measured after 34 weeks was associated with shorter gestational length (β: −0.23 weeks, 95% CI: −0.37 to −0.09) (Yang et al. 2021). This finding was strongest in pregnancies with female fetuses where the second and highest tertiles of exposure were associated with shorter gestational length by 0.32 and 0.46 weeks, respectively (β: −0.32 weeks [95% CI: −0.53 to −0.11] and β:−0.46 weeks [95% CI: −0.66 to −0.25]) (Yang et al. 2021). A nested case-control study by Aung et al. (2019) showed results in a similar direction, where BPS detected at 35 weeks was associated with 2.05 (95% CI: 1.09 to 3.89) times the odds of preterm birth. BPS measured at earlier points in pregnancy (medians ranged from 9.7 to 26 weeks) was not associated with preterm birth. However, this study was limited by the small proportion of samples above the LOD (20.1%) (Aung et al. 2019).

Findings from the Puerto Rico Testsite for Exploring Contamination Threats (PROTECT) cohort raise the possibility that effects of BPS may vary by maternal psychosocial stress. In an analysis of the full cohort, the authors reported no associations with number of gestation days or risk of preterm birth per interquartile range (IQR) increase of BPS measured during trimester two (TM2) (Aker et al. 2019b). However, in a second study, they stratified their analyses by maternal report of negative life events, a marker of maternal psychosocial stress, and reported shorter gestational length per IQR increase of TM2 BPS (β: −3.15 days, 95% CI: −6.06 to −0.24) among women reporting the most negative life events (Aker et al. 2020). This potential interaction between BPS exposure and psychosocial stress has not been examined in other studies.

Contrary to the direction of all the findings presented above, Wan et al. (2018) observed that a 1-unit increase in ln BPS measured at the delivery visit was associated with longer gestational length by 0.66 days (95% CI: 0.29 to 1.04) (Wan et al. 2018).

Lastly, three studies examined the non-linearity of the dose-response of BPS with gestation length. One observed an inverted U-shaped dose response for risk of preterm birth (Liang et al. 2021b), one observed a possible U-shaped association with

gestational age (S Kim et al. 2021), and one observed no evidence of non-linearity with gestational age (Yang et al. 2021).

Fetal size

Seven studies examined fetal growth *in utero*. The timing of gestational BPS exposure varied, and several studies were limited to analysis of BPS exposure as a binary (detect/no detect) variable, in part, due to low BPS detection frequencies across samples. Outcomes were measured by ultrasound from 16 to 35 weeks and included fetal weight, head circumference, femur length, abdominal circumference, and biparietal diameter.

Fetal weight

Four studies examined associations with estimated fetal weight (Bommarito et al. 2024; Ferguson et al. 2018; Kim et al. 2024; Sol et al. 2021). Analyzing 2006–2008 data from the LIFECODES cohort in Boston, Ferguson et al. (2018) modeled associations between BPS (detected vs. not detected) and repeated measures of fetal weight (inclusive of birthweight). They reported decreased fetal weight in male offspring only (β: −0.25 change in z-score, 95% CI: −0.49 to −0.02) (Ferguson et al. 2018). A second study analyzed 2008–2018 data from the same LIFECODES cohort and reported a similar, marginally significant, association with fetal weight in all offspring (β: −0.11 change in z-score, 95% CI: −0.23 to 0.01) (Bommarito et al. 2024). Sol et al. (2021) analyzed data from the Generation R Study in the Netherlands, showing associations between TM1 BPS (detected vs. not detected) and larger fetal weight at TM2 (β: 0.12 standard deviation score [SDS], 95% CI: 0.02 to 0.23) and trimester 3 (TM3) (β: 0.16 SDS, 95% CI: 0.06 to 0.26). In a study from Korea, Kim et al. (2024) reported no associations between TM2 urine BPS and TM2 fetal weight, though it is important to note that this last study was not comparable to the others because the sample was restricted to 107 women with “high-risk factors,” including gestational diabetes and preterm birth. If these risk factors are on the causal pathway from BPS to fetal weight, restriction of the sample to women with these risk factors would bias estimates towards the null.

Fetal head circumference

Six studies examined associations with fetal head circumference, two of which reported significant associations with increased head circumference. Ferguson et al. (2018) reported an association between gestational BPS (detect vs. no detect) and larger head circumference in girls only (specific estimate not reported). Sol et al. (2021) reported associations between TM1 BPS and larger head circumference measured in TM2 (β: 0.15 SDS, 95% CI: 0.05 to 0.26) and TM3 (β: 0.12 SDS, 95% CI: 0.02 to 0.23), which aligned with observations of larger fetal weight reported at the same time points.

Conversely, Bommarito et al. (2024) reported a marginally significant decrease in head circumference (β: −0.07 change in z-score, 95% CI: −0.18 to 0.04) in pregnancies with detected vs. not detected BPS. Three other studies reported no associations with head circumference (Goodrich et al. 2019; Jedynak et al. 2022; Zhou et al. 2020).

Fetal femur length

Five studies examined associations with femur length, of which three reported statistically significant findings. A cohort study in France measured BPS in urine at TM2 and TM3 and reported that compared to participants with BPS below the LOD, those with detectable BPS at either time point had longer femur length at 32 weeks (β: 0.20 SDS, 95% CI: 0.02 to 0.37) (Jedynak et al. 2022). A US cohort study reported associations between gestational BPS (detected vs. not detected) and longer femur length at 32 weeks in female fetuses only (Ferguson et al. 2018). A similar association with longer femur length, though not statistically significant, was reported in a cross-sectional study from China that measured urinary BPS and fetal growth at ≥ 35 weeks (Tertile 2 vs. 1, β: 0.70 centimeters [cm], 95% CI: −0.008 to 1.41; Tertile 3 vs. 1, β: 0.23 cm, 95% CI: −0.48 to 0.93) (Zhou et al. 2020). Conversely, Bommarito et al. 2024 reported an association with shorter femur length when comparing individuals with detectable versus non-detectable BPS (β: −0.15 change in z-score, 95% CI: −0.27 to −0.04). One other study reported no associations with femur length (Goodrich et al. 2019).

Fetal abdominal circumference and biparietal diameter.

Five studies reported no associations with abdominal circumference (Bommarito et al. 2024; Ferguson et al. 2018; Goodrich et al. 2019; Jedynak et al. 2022; Zhou et al. 2020) and three studies reported no associations with biparietal diameter (Goodrich et al. 2019; Jedynak et al. 2022; Zhou et al. 2020).

Birth Size

Eighteen studies measured associations between BPS and birth size. Most studies reported multiple effect estimates, corresponding to analyses of different periods of exposure assessment (e.g., trimester-specific estimates) and different outcomes. The following summary paragraphs are organized by outcome.

Birthweight

Multiple studies observed associations between BPS exposure and lower birthweight. Data from a US cohort study observed that 1-unit increases in TM1 ln BPS exposure were associated with lower birthweight by 150.42 grams (95% CI: −294.85 to −6.00) (Goodrich et al. 2019). After categorizing the BPS exposure as detected (37% of samples) versus not detected, they reported a similar association with birthweight

(−220.10 grams, 95% CI: −424.94 to −15.26). The study sample size was small (n = 56), yielding imprecise estimates and a limited set of adjustment variables (Goodrich et al. 2019). A prospective cohort study in China measured BPS in all three trimesters and reported that IQR increases in TM1 and TM2 BPS were associated with lower birthweight by 32 and 38 grams, respectively, after mutual adjustment for BPA and BPF (TM1: 95% CI: −60 to −5; TM2: 95% CI: −68 to −8) (Hu et al. 2019). Four additional studies reported associations between gestational BPS exposure and lower birthweight of similar magnitude (βs ranged from −28 to −67 grams), but confidence intervals were wide and crossed the null value (S Kim et al. 2021; J Liang et al. 2020; Mustieles et al. 2018; Stevens et al. 2023).

Findings from the large ECHO study that harmonized data from 11 unique cohorts with birth years 1998–2023 (n = 3,619) raise the possibility that the effects of BPS on birth size could vary by racial or ethnic group. For example, this study reported that average gestational BPS was not associated with changes in birthweight in the full sample (β: −0.90 grams, 95% CI: −49.34 to 47.55), but 1-unit increases in BPS were associated with lower birthweight in non-Hispanic White participants (β: − 65.2 grams, 95% CI: −128.8 to −1.7) and higher birthweight in Hispanic participants (β: 97.9 grams, 95% CI: 11.7 to 184.0) (Trasande et al. 2023). No other studies presented results stratified by racial or ethnic group.

Two cohort studies reported associations between BPS exposure and increased birthweight (Mustieles et al. 2018; J Wang et al. 2021), though findings from these studies were not directly comparable to those presented above due to differences in study design. For example, Mustieles et al. (2018) measured BPS before conception. In a prospective birth cohort study from Boston, they reported higher birthweight by 144 grams (95% CI: 2 to 286) per 1-unit increase in maternal preconception ln BPS. When examining gestational exposure to BPS in the same model, they reported an association with lower birthweight that was not statistically significant but consistent in magnitude to decreases reported in the previously mentioned studies (−67 grams, 95% CI: −210 to 76). Both models adjusted for paternal exposure to BPS. Only 73 individuals had measurements of both preconception and gestational BPS, thus estimates were imprecise and unstable across models with different covariate sets (Mustieles et al. 2018). The second study by J Wang et al. (2021) is the only study that included non-singleton pregnancies, hypothesizing that within-twin pair birthweight differences would be larger in pregnancies with more BPS exposure. They reported null associations for all within-twin pair analyses. In supplementary analyses, they examined between-twin pair differences in birthweight and reported that middle and high tertiles (vs. low) of TM2 BPS exposure and the middle tertile (vs. low) of TM3 BPS exposure were associated with higher birthweight with effect estimates ranging from 66 to 117 grams (J Wang et al. 2021).

Two studies examined potential non-linearity of the dose-response of BPS with birthweight. One observed a U-shaped association for BPS using a BKMR analysis (S Kim et al. 2021) and one reported no evidence of non-linearity using a restricted cubic spline analysis (Yang et al. 2021).

Two studies analyzed birthweight as a binary variable of low birthweight (< 2500 grams). In the ECHO study, Trasande et al. (2023) reported that per unit increases in TM3 BPS were associated with increased odds (OR: 1.77, 95% CI: 1.07 to 2.93) of having a low birthweight baby, with a stronger association observed in pregnancies with male fetuses (OR: 3.2, 95% CI: 1.26 to 8.12) (Trasande et al. 2023). The second study, by Yang et al. (2021) reported no associations between urine BPS measured at the delivery encounter with low birthweight in a cohort in China.

Other studies reported no associations between BPS and birthweight (Aker et al. 2019b; Jedynak et al. 2022; Kim et al. 2024; X Li et al. 2024; Wan et al. 2018).

Birthweight z-score

Six studies analyzed birthweight as a continuous z-score, which is birthweight standardized for gestational age and sex. Pooled data from the ECHO study showed that per unit increases in TM1 urinary BPS were associated with lower birthweight z-scores (β: −0.24, 95% CI: −0.44 to −0.03) among non-Hispanic White individuals and TM2 urinary BPS levels were associated with higher birthweight z-scores in pregnancies with male fetuses (β: 0.14, 95% CI: 0.001 to 0.28) and among non-Hispanic Black individuals (β: 0.26, 95% CI: 0.03 to 0.49) (Trasande et al. 2023). Other studies reported no associations between BPS and birthweight z-score (Aker et al. 2019a; Bommarito et al. 2024; Y Chen et al. 2024; Ferguson et al. 2018; J Liang et al. 2020).

Five studies analyzed birthweight z-scores as the binary variables of small-for-gestational age (SGA; birthweight <10th percentile) or large-for-gestational age (LGA; birthweight > 90th percentile). A study from the Puerto Rico PROTECT cohort reported no differences in continuous birthweight z-score, but 1.82 times higher odds of SGA (95% CI: 1.17 to 2.84) per IQR increase in visit 3 (24–28-weeks) BPS exposure and 1.62 times higher odds of LGA (95% CI: 1.06 to 2.45) per IQR increase in all visits (16–28-weeks) average BPS exposure (Aker et al. 2019b). Thus, the associations between BPS and birth size appeared most evident at extremes of the birthweight distribution, however, the authors caution over-interpretation until the findings are reproduced in other cohorts. The ECHO study that harmonized data from 11 unique cohorts, inclusive of the PROTECT cohort, reported that one-unit increases in TM3 BPS were associated with higher odds of SGA (OR: 1.52, 95% CI: 1.08 to 2.13), with stronger associations observed in pregnancies with male fetuses and in non-Hispanic White individuals

(Trasande et al. 2023). The same study reported a significant association between TM2 BPS and higher odds of LGA among Hispanic individuals (OR: 1.96, 95% CI: 1.11 to 3.45). A third study reported null associations for SGA (Wan et al. 2018) and a fourth reported lower odds of SGA with detectable versus not detectable TM1 BPS exposure (OR: 0.56, 95% CI: 0.38 to 0.84) (Sol et al. 2021). The fifth study examined associations with BPS categorized as detected versus not detected during pregnancy and reported small non-significant positive associations for SGA and LGA (Bommarito et al. 2024).

Weight-for-length measures

Three studies analyzed associations between gestational BPS and ponderal index, which is calculated as weight in kilograms divided by length in meters-cubed times one hundred (kg/m^3 x 100) and is used as a proxy for adiposity. Hu et al. (2019) analyzed data from a cohort in Wuhan, China with urine BPS levels measured in all three trimesters. For TM1, they reported that per IQR increases in BPS were associated with a smaller ponderal index (β: −0.16 kg/m^3, 95% CI: −0.32 to 0.01). There was no effect on birth length observed at the same point, suggesting that the change in ponderal index was driven by the association with lower birthweight (β: −32 grams, 95% CI: −60 to −5) (Hu et al. 2019). Liang et al. (2020) reported a similar non-significant association between TM1 serum BPS and ponderal index (β: −0.30 kg/m^3, 95% CI: −0.68 to 0.08) with no effect on birth length in a cohort from Guangxi Province, China (J Liang et al. 2020). The third study also used data from a study of births in China but with BPS measured in urine at the delivery encounter. In that study, there was no association between BPS and ponderal index (Yang et al. 2021).

The fourth study to include a weight-for-length outcome was Chen et al. (2024), which assessed associations between TM3 urinary BPS and BMI z-score in a cohort from Shanghai, China. They reported a non-significant association in the direction of lower BMI z-score (β: −0.18 z-score, 95% CI: −0.50 to 0.14) comparing individuals with detectable vs. undetectable BPS (Y Chen et al. 2024).

Adiposity

There are two studies that directly measured adiposity at birth. Y Chen et al. (2024) reported that pregnancies with BPS detected at TM3 had more abdominal skinfold thickness (β: 0.21 millimeter [mm], 95% CI: 0.04 to 0.38), a measure of regional subcutaneous fatness, compared to pregnancies without BPS detected. In a mixture model, an IQR increase in BPS was associated with larger abdominal skinfold thickness in male infants when other bisphenols were held at their 25^{th} and 50^{th} percentiles (Y Chen et al. 2024). Stevens et al. (2023) analyzed associations with fat and lean mass measured by whole body air displacement plethysmography and reported no statistically significant associations.

Other Birth Outcomes

A prospective birth cohort from the Guangxi Province in China examined associations between TM1 BPS and cord blood leukocyte telomere length measured at birth. The study observed an overall linear negative association between BPS and percent change in telomere length, with effect modification by maternal age such that the association was stronger for maternal age at or above 28 years (β: −3.19 percent; 95% CI: −6.08 to −0.21). There was no significant change in telomere length observed when maternal age was less than 28 years (β: 0.64 percent; 95% CI: −2.25 to 3.61) (Liang et al. 2021a).

One population-based case-control study from Northern China reported no associations between BPS measured in placental samples at delivery and neural tube defects (Zhu et al. 2023).

4.1.2 Infant Growth

Five studies assessed associations between BPS and infant growth trajectories, though, heterogeneity in the methodologies used to characterize infant growth trajectories and the ages of included infants made it difficult to synthesize results across studies. Analyzing data from a prospective birth cohort in China, Y. Chen et al. (2024) reported that, in females, detected vs. not detected TM3 BPS was associated with increased risk of rapid growth from birth to 6 months (risk ratio [RR]: 1.70, 95% CI: 1.17 to 2.49) and from birth to 12 months (RR: 1.91, 95% CI: 1.07 to 3.42). They defined rapid growth as a change in weight-for-age z-score > 0.67. Another study from China measured offspring BMI growth trajectories, which were derived from BMI-for-age z-scores measured from birth to 24 months and categorized as low-stable, low-increasing, moderate-increasing, and moderate-stable (reference category). They reported that TM1 BPS exposure was associated with higher odds of a ‘low-increasing’ growth trajectory (i.e., small size at birth and grew to meet the average growth curve by 12 months), with the largest association observed when comparing quartile [Q] 2 to Q1 BPS (OR: 1.88, 95% CI: 1.01 to 3.53). When analyzing BPS exposure averaged across gestation, Q2 vs. Q1 BPS was associated with higher odds (OR: 2.17, 95% CI: 1.31 to 3.59) of a ‘moderate increasing’ trajectory (i.e., average size at birth and increased in size through 6 months). No associations were observed for TM2 or TM3 BPS (Xiong et al. 2023a). Other studies did not observe statistically significant associations between gestational BPS and infant growth trajectories from birth to 5 months (Stevens et al. 2023), birth to six or twelve months (X Li et al. 2024), or from birth to 2 years (Blaauwendraad et al. 2024).

Seven studies measured associations between gestational BPS and infant size at varying points after birth. Blaauwendraad et al. (2024) assessed associations between

trimester-specific urinary BPS levels and child weight, height, triceps skinfold, and subscapular skin fold measured repeatedly from birth to four years. They observed that per unit increases in TM3 BPS were associated with smaller subscapular skinfold (β: −0.09 SDS, 95% CI: −0.18 to 0.00). Lv et al. (2024) examined associations between urine BPS measured in all three trimesters and offspring BMI z-score measured at 2 years. They reported that average BPS (%Δ: 7.39, 95% CI: 0.35 to 14.42, p = 0.04) and TM1 BPS (%Δ 5.66,95% CI: 0.26 to 11.06, p = 0.04) were associated with larger offspring BMI z-score at 2 years.

Other studies measured outcomes in younger infants only. Y. Chen et al. (2024) reported that TM3 BPS was associated with larger subscapular skin fold (β: 0.95 mm, 95% CI: 0.31 to 1.59), larger abdominal skinfold thickness (β: 0.87 mm, 95% CI: 0.18 to 1.57), and larger arm circumference (β: 0.40 cm, 95% CI: 0.08 to 0.72) at 6 months. The study by Y. Chen et al. (2024) was limited to analysis of BPS as detected versus not detected because over two-thirds of the sample had BPS levels below the LOD. Ouidir et al. (2024) reported associations in a similar direction. For example, individuals with BPS above the limit of quantification (LOQ) in TM2 had larger BMI at 3 months (β: 0.41 kg/m^2, 95% CI: 0.11 to 0.70) and 36 months (β: 0.29 kg/m^2, 95% CI: 0.01 to 0.56), and larger weight and height at both points compared to those with BPS levels below the LOD. Colombini et al. (2025) reported that BPS measured in TM2 in the highest category (> LOQ) was associated with higher child fat mass percent at 3 years compared to the lowest category of BPS exposure (< LOD) (β: 1.49 percent (95% CI: 0.65 to 2.32). Two other studies reported no associations between TM3 BPS and offspring weight at 6 and 12 months (X Li et al. 2024) or between TM2 BPS and weight, fat mass, and lean mass at five months (Stevens et al. 2023).

4.1.3 Neurodevelopment

The neurodevelopmental outcomes examined and ages of offspring at assessment varied across thirteen studies.

Two prospective birth cohort studies assessed associations between BPS and early infant neurodevelopment. One study analyzed data from two cohorts included in the ECHO study (IKIDS and ECHO-PROTECT) that had measures of infant non-nutritive suck before 8 weeks of age. Non-nutritive suck was used as an index of central nervous system integrity and thought to be predictive of subsequent child neurodevelopment. Prenatal BPS levels were not associated with patterns of non-nutritive suck in either cohort (Woodbury et al. 2025). Data from a subset of infants (n = 151) enrolled in the SEPAGES cohort in Grenoble, France showed that BPS detection in TM2 was associated with reduced reaction time (β: -16.0 milliseconds, 95% CI: -31.9 to -0.1) on an infant eye tracking task at 24 months. The authors reported that negative

associations with reaction time can be predictive of higher intelligence quotient (IQ) scores and are shown to be shorter in children with autism spectrum disorder. However, the sample size was small and there were a large percentage of samples with BPS below the LOD (> 70%) (Rolland et al. 2025).

Three prospective birth cohort studies assessed associations between BPS and Bayley Scales of Infant Development at 24 months. The first study from China by Jiang et al. (2020) observed lower psychomotor development index (PDI) scores with higher gestational BPS exposure (defined by averaging TM1, TM2, and TM3 BPS levels). For example, the highest levels of BPS exposure (Q4 vs. Q1) were associated with lower PDI scores by 5.52 points (95% CI: −10.06 to −0.99). When examining trimester-specific associations, only TM3 BPS exposure was significantly associated with offspring PDI scores [Q4 vs. Q1: β: −4.9 (95% CI: −9.4 to −0.4); Q3 vs. Q1: β: −4.8 (95% CI: −9.3 to −0.2)]. For the second outcome examined, mental development index (MDI), there was a significant interaction between BPS exposure and trimester such that per-unit increases in TM1 ln BPS were associated with better MDI scores (β: 2.88 95% CI: 0.27 to 5.50) and per-unit increases in TM3 ln BPS were associated with worse MDI scores (β: −1.51 95% CI: −4.37 to 1.35) (Jiang et al. 2020). The second birth cohort study examining Bayley Scales of Infant Development outcomes at 24 months measured TM2 exposure and reported null associations for cognitive, language, motor, social emotional, and adaptive behavior subscales (Liu et al. 2021). The third study that analyzed associations with BPS and Bayley Scales of Infant Development at 24 months reported an interaction with socioeconomic status such that TM2 BPS was negatively associated with cognitive development in the high socioeconomic status group only [β: −1.57 (95% CI: −2.74 to −0.41); p-interaction = 0.003] (Zhou et al. 2025). An additional study examining associations between TM2 BPS and a different measure of neurodevelopment at ages 2 and 4 years reported no associations between BPS and executive function scores of inhibitory control, flexibility, and emergent metacognition (England-Mason et al. 2021).

Three studies assessed associations between gestational BPS exposure and socioemotional behavioral development. A US cohort study by Geiger et al. (2023) reported evidence of effect modification by child sex such that for female children ages 2–3 years, higher BPS exposure (estimated from five pooled urine samples collected between 16 and 38 weeks gestation) was associated with a 3.92 percent (95% CI: 1.16 to 13.27) increase in emotionally reactive behavior score and a 13.96 point (95% CI: 2.16 to 25.76) increase in internalizing behavioral problems score, where higher scores correspond to worse outcomes. The emotionally reactive behavior score is a subscale of the internalizing behavioral problems score that specifically assesses problems with emotion regulation. No associations were observed with the internalizing behavioral problem scales among males or for externalizing behavioral problem scales for either

sex. A prospective cohort study in France reported that detectable BPS exposure in TM3 was associated with worse child social behavior and autistic traits measured by the Social Responsiveness Scale at age 3 (β: 3.82, 95% CI: 0.94 to 6.70, p = 0.01) (Mustieles et al. 2023). When examining individual subscales, TM3 BPS exposure was associated with poorer scores on the social awareness, social cognition, and social communication subscales. However, these results should be considered in light of low BPS detection frequencies (28% with BPS > LOD) (Mustieles et al. 2023). The third study assessed associations between TM1 urine BPS and offspring behavioral problems measured at age 4. The instrument used had four scales: emotional problems, hyperactivity/inattention, conduct problems, and peer problems. When analyzed as binary outcomes, higher levels of BPS exposure were associated with increased odds of emotional problems (OR: 1.16, 95% CI: 1.01 to 1.34). There was no evidence of effect modification by child sex (Lei et al. 2024).

Three studies assessed associations between BPS and IQ and its subscales at ages 6–7. One study reported that BPS was associated with a non-significant decrease in working memory (β: −1.76, 95% CI: −3.85 to 0.33) and no differences in full scale IQ, verbal comprehension, perceptual reasoning, or processing speed (Bornehag et al. 2021). The other studies reported no differences in IQ, verbal comprehension, perceptual reasoning (Chen et al. 2023) and nonverbal IQ (van den Dries et al. 2020).

One study assessed associations between TM1 serum BPS levels and vision acuity and visual impairment in children ages 2–6 and reported no significant associations (J Li et al. 2024).

4.1.4 Immune Function and Related Outcomes

Six individual studies and one meta-analysis (which pooled data from four birth cohorts) examined associations between gestational BPS exposure and offspring immune function. Results from the six individual studies are presented first, by study outcome, followed by a summary of the meta-analysis. The outcomes analyzed in the individual studies were asthma (five studies), wheeze (two studies), lung function (two studies), bronchiolitis (one study), bronchitis (one study), food allergies (one study), atopic dermatitis (one study), allergic rhinitis (one study), and eczema (one study). Outcomes analyzed in the meta-analysis were asthma, wheeze, and lung function. Across all studies, offspring age at assessment varied from 2 months to 13 years.

Coiffier et al. (2023) reported that BPS detected in TM2 or TM3 (vs. not detected) was associated with 1.89 (95% CI: 1.05 to 3.38) times higher odds of asthma among offspring at age 3. The exposure was categorized in this way because over half of the participants had BPS levels measured below the LOD (Coiffier et al. 2023). In a study from Japan, Kuraoka et al. (2024) observed that individuals in the top 10% of TM1 BPS

exposure had non-significantly higher odds of asthma at age 4 (OR: 1.28, 95% CI: 0.93 to 1.77) compared to those in the remaining 90%. Two other studies reported that associations between gestational BPS and asthma vary by sex, but in inconsistent directions. One US study reported 1.65 (95% CI: 1.01 to 2.69) times higher odds of asthma with BPS (detected in TM1, TM2, or TM3 vs. not detected) among males at age 6 (Gaylord et al. 2023) and a study from Rotterdam, Netherlands reported 1.89 (95% CI: 1.09 to 3.28) times higher odds of asthma per IQR increase in averaged gestational BPS exposure among girls at age 13 (Karramass et al. 2023). Similar to the Coiffier et al. (2023) study, the studies by Kuraoka et al. (2024), Gaylord et al. (2023), and Karramass et al. (2023) were limited by low detection of BPS, with percentages of participants with BPS levels below the LOD as high as 85%, 49% and 81%, respectively. Two studies additionally examined wheezing and reported no significant associations; Coiffier et al. (2023) reported no associations between BPS detected in TM2 or TM3 (vs. never) and wheezing measured at age 3 and Gaylord et al. (2023) reported no associations between BPS detected in any trimester (vs. not detected) and wheezing at age 6.

Coiffier et al. (2023) and Karramass et al. (2023) additionally examined associations between gestational BPS and objectively measured indices of lung function. These variables were analyzed as continuous measures such that changes reflect shifting of the distribution of lung function scores including at levels below thresholds for clinical diagnosis. Data from the prospective cohort in Rotterdam, Netherlands showed that IQR increases in gestational BPS exposure were associated with lower forced vital capacity and lower forced expiratory volume at 13 years (Karramass et al. 2023). Conversely, in the prospective cohort from Grenoble, France, detectable gestational BPS exposure (versus not detected) was associated with greater lung volume defined by higher functional residual capacity and higher tidal volume at 2 months of age (Coiffier et al. 2023). The latter finding was unexpected considering BPS was associated with higher risk of asthma and bronchiolitis among the same study participants assessed at 3 years. When the authors discussed these findings, they mentioned low detection of BPS and lack of recency of study data (2014–2017) in this sample (Coiffier et al. 2023).

Data for other clinical respiratory and atopic outcomes were limited to one study each. In the prospective cohort from Grenoble, France, BPS detected during gestation (vs. not detected) was associated with higher odds of bronchiolitis (OR: 1.56, 95% CI: 1.01 to 2.38) and no differences in the odds of bronchitis at 3 years (Coiffier et al. 2023). Maternal BPS measured around the time of birth was not associated with incidence of infantile eczema at 6 and 12 months of age in a prospective cohort from China (Li et al. 2021) and detectable BPS in any trimester was not associated with risk of food allergy at age 6 in a prospective cohort from the US (Gaylord et al. 2023).

In another study where the National Institutes of Health ECHO study harmonized data from nine unique cohorts with birth years 1998–2017 (n = 599–889), Miller et al. (2025) analyzed prenatal BPS exposure and associations with the immune outcomes of atopic dermatitis (at age 0–3), allergic rhinitis (at age 5–9), and asthma (at age 5–9). There were no significant associations between BPS exposure and any outcome for the full sample. For girls only, a standard deviation increase in BPS exposure was associated with reduced odds of atopic dermatitis (OR: 0.64, 95% CI 0.44 to 0.93) (Miller et al. 2025).

Finally, one meta-analysis pooled data from four European cohort studies that measured gestational BPS exposure and compared differences (BPS detected vs. not detected) in offspring outcomes between ages 7 and 11. Abellan et al. (2022) reported no differences in asthma risk, no differences in lung function parameters, and decreased odds of late and persistent wheeze patterns (OR: 0.43, 95% CI: 0.19 to 1.00 and OR: 0.56, 95% CI: 0.35 to 0.90, respectively). Similar to some of the previously mentioned studies, the meta-analysis was limited by low BPS detection in the included cohorts (percentage of participants with BPS below LOD by study: 90%, 83%, 70%, 29%) (Abellan et al. 2022).

4.1.5 Endocrine and Metabolic Effects

Several studies examined offspring outcomes related to the metabolic syndrome, which refers to a cluster of conditions — central adiposity, high triglycerides, low high-density lipoprotein (HDL), high blood pressure, and high fasting glucose— that are associated with heart disease and diabetes. A prospective birth cohort in Rotterdam, Netherlands investigated associations between TM1 and TM2 BPS exposure and markers of cardiometabolic health at ages 9–10 (Sol et al. 2020). They reported that IQR increases in TM1 BPS exposure were associated with significant decreases in insulin and glucose for male children (β: −0.13 SDS, 95% CI: −0.25 to −0.02 and −0.15 SDS, 95% CI: −0.26 to −0.03) with no differences observed in female children. Sol et al. (2020) also found that IQR increases in TM2 BPS exposure were associated with lower odds of high low-density lipoprotein (LDL) cholesterol in males (OR: 0.69, 95% CI: 0.47 to 0.99). Many statistical tests were carried out and these associations did not remain statistically significant after multiple testing adjustment. Also, there were no associations with triglycerides, total cholesterol, or HDL cholesterol in females or males (Sol et al. 2020). Lastly, a prospective study did not find associations between TM1 BPS and offspring BMI at five years (Svensson et al. 2023).

Analyzing data from the Generation R study, Blaauwendraad et al. (2022a) averaged urinary BPS levels collected in each trimester and assessed associations with offspring carotid intima-media thickness and distensibility measured by ultrasonography at

10 years. There was a marginally statistically significant association with greater carotid distensibility, a marker of worse arterial health (β: 0.09, 95% CI: −0.02 to 0.19, p = 0.098) (Blaauwendraad et al. 2022a).

Four studies examined associations between gestational exposure to BPS and offspring thyroid hormone levels at birth with mixed results. In a cohort from Shanghai, China, there was a significant interaction between BPS and newborn sex such that BPS was associated with lower thyroid stimulating hormone (TSH) levels (and non-significantly lower total thyroxine (TT4) and free thyroxine (FT4) levels) in male newborns only (Xi et al. 2023). However, this study was limited by low BPS detection rates because over 50% of sample participants had BPS below the LOD. The second study, with BPS detected in over 80% of participant samples, reported increases in neonatal TSH associated with BPS exposure measured in each trimester (Xiong et al. 2023b). A third study reported associations between cord blood BPS levels and lower follicle-stimulating hormone among women with normal pre-pregnancy BMI and among pregnancies with cesarean deliveries only (Bigambo et al. 2024). One other study reported no associations between BPS and thyroid hormones measured in cord blood and in serum at 5 years of age (Derakhshan et al. 2021).

Another study examined associations between BPS and digit ratio, defined as the ratio of lengths of the second and fourth fingers, and hypothesized to be an indicator of disrupted gestational sex hormones. Urinary BPS measured in TM3 was not associated with higher digit ratios at age 4 in boys and girls. There was a marginal association observed between BPS and digit ratio in girls, which attenuated after adjustment for other bisphenols (Z Wang et al. 2021).

A prospective birth cohort from Shanghai, China reported that TM3 BPS at or above the median (compared to < LOD) was associated with higher kisspeptin levels in male children at age 6 (β: 63.43 ng/g, 95% CI: 25.20 to 101.65) (Wang et al. 2022). This association was smaller and not statistically significant in female children (β: 23.22 ng/g, 95% CI: −23.23 to 69.68) (Wang et al. 2022).

4.1.6 Bone Mass and Mineral Density

Two studies examined associations between gestational BPS and bone mass and mineral density. BPS measured in TM1 in a prospective birth cohort from the Netherlands was associated with lower offspring bone mineral density and area adjusted bone mineral content measured at age 10 (β: −6.08 mg/cm^2, 95% CI: −9.97 to −2.19; β: −0.12 grams 95% CI: −0.20 to −0.04 respectively), but not at age 6 (van Zwol-Janssens et al. 2020). BPS measured in TM1 in a prospective birth cohort from China was similarly associated with decreased bone mineral density, but only in boys ages 3 to 6 years. For example, the highest tertile of BPS exposure was associated with

6.17 times (95% CI: 1.45 to 33.79) the odds of low bone mineral density (i.e., bone mineral density z-score ≤ −1) compared to the lowest tertile exposure (Liang et al. 2023).

4.1.7 Offspring Reproductive Development

One study analyzed data from the Generation R birth cohort in Rotterdam, Netherlands to assess associations between average gestational exposure to BPS and offspring reproductive development at 10 and 13 years. BPS was associated with delayed onset of menstruation by 0.17 years, on average, among female offspring that had already menstruated (β: 0.17 years, 95% CI: 0.02 to 0.31). There were no significant associations between BPS and female ovarian volume, male testicular volume, or other indices of pubertal development in either sex (Blaauwendraad et al. 2022b).

One study analyzed late pregnancy BPS exposure measured between 27 and 37 weeks and children's anogenital distance (AGD) at birth, 6, 12, and 48 months (Chen et al. 2025). In girls, detected (vs. not detected) BPS was associated with greater odds of having rapid AGD growth (OR: 2.94, 95% CI: 1.35 to 6.40). These girls also had significantly longer anus-clitoris distance (β: 4.06, 95% CI: 0.43 to 7.69) and anus-fourchette distance (β: 3.25, 95% CI: 0.76 to 5.73) at 48 months (Chen et al. 2025).

Table 4.1.1 BPS Epidemiologic studies of developmental toxicity

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
Birth Outcomes					
Aker et al. 2019b Puerto Rico 2011–2017 Prospective cohort study Puerto Rico Testsite for Exploring Contamination Threats Program (PROTECT) Cohort Study sample size (n) = 922, The number of people included in each analysis varied from 329 and 540 depending on data availability at that visit. Mean (standard deviation [SD]) maternal age in years: 26.70 (5.5) Inclusion criteria: singleton, > 18 years, lived in region, no oral contraceptives within 3 months prior to getting pregnant, no *in vitro* fertilization, no known medical health complications (including diabetes, hypertension, etc.).	Urine spot samples Adjusted for specific gravity (SG) Limit of detection (LOD): 0.1 % < LOD: 6.1 (all visits), 5.5 (visit 1), 6.9 (visit 2), 5.7 (visit 3) Values below the LOD were calculated as LOD÷√2. Geometric mean (GM) ± geometric standard deviation (GSD): 0.46 ± 3.2 (all visits), 0.47 ± 3.3 (visit 1), 0.45 ± 3.0 (visit 2), 0.45 ± 3.2 (visit 3) Percentiles (all visits, visit 1, visit 2, visit 3): 25th: 0.20, 0.20, 0.20, 0.20 50th: 0.40, 0.40, 0.40, 0.40 75th: 0.90, 0.99, 0.90, 0.90 Timing of samples: Visit 1: 16–20 weeks Visit 2: 20–24 weeks Visit 3: 24–28 weeks	Gestational age (days), preterm birth (< 37 weeks) Birthweight z-score, small-for-gestational age (SGA, < 10th percentile), large-for-gestational age (LGA, > 90th percentile)	All visits average BPS, per interquartile range (IQR) increase: Birthweight, Beta estimate (*β*): 0.05 (95% Confidence Interval [CI]: -0.09, 0.20), p-value (p) = 0.46 SGA, odds ratio (OR): 1.49 (95% CI: 0.97, 2.29), p = 0.07 **LGA, OR: 1.62 (95% CI: 1.06, 2.45), p = 0.02** Gestational age, β: -0.52 (95% CI: -2.14, 1.09), p = 0.53 Preterm birth, OR: 1.08 (95% CI: 0.70, 1.66), p = 0.72 Visit 1 BPS, per IQR increase: Birthweight, β: 0.08 (95% CI: -0.07, 0.24), p = 0.28 SGA, OR: 0.91 (95% CI: 0.57, 1.46), p = 0.70 LGA, OR: 1.49 (95% CI: 0.99, 2.25), p = 0.06 Gestational age, β: -0.58 (95% CI: -2.27, 1.11), p = 0.5 Preterm birth, OR: 1.07 (95% CI: 0.69, 1.66), p = 0.72 Visit 2 BPS, per IQR increase: Birthweight, β: 0.03 (95% CI: -0.13, 0.18), p = 0.73 SGA, OR: 1.40 (95% CI: 0.89, 2.22), p = 0.14 LGA, OR: 1.33 (95% CI: 0.88, 2.01), p = 0.18 Gestational age, β: -0.27 (95% CI: -2.02, 1.47), p = 0.76 Preterm birth, OR: 1.11 (95% CI: 0.71, 1.75), p = 0.64 Visit 3 BPS, per IQR increase: Birthweight, β: 0.02 (95% CI: -0.15, 0.19), p = 0.80 **SGA, OR: 1.82 (95% CI: 1.17, 2.84), p = 0.01** LGA, OR: 1.46 (95% CI: 0.86, 2.49), p = 0.16 Gestational age, β: 0.44 (95% CI: -1.34, 2.23), p = 0.63 Preterm birth, OR: 0.98 (95% CI: 0.57, 1.69), p = 0.95 No significant associations with birthweight z-score. No evidence of interaction with infant sex for any outcome.	Models adjusted for: SG, maternal age, insurance type, alcohol use, and exposure to second-hand smoke. Effect modification examined: infant sex. Other bisphenols measured: Bisphenol A (BPA), Bisphenol F (BPF).	Detectable 3rd trimester (TM3) BPF levels associated with lower odds of preterm birth. Regarding findings for both SGA and LGA, authors stated, "these results are difficult to explain. Therefore, we caution over-interpretation..." The n for BPS analyses was smaller than "other urinary biomarkers because [it was] added to the analytic panel mid-way through the study." Correlations between BPS and other bisphenols: BPA (Spearman correlation coefficient (ρ) = 0.33), BPF (ρ = 0.02).

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
Aker et al. 2020 Puerto Rico 2011–2017 Prospective cohort study PROTECT Cohort n = 752, n = 540 with measured BPS Median (IQR) maternal age in years: 26 (22, 31) Inclusion criteria: singleton, lived in region, no oral contraception use within three months prior to pregnancy, no *in vitro* fertilization, no known medical complications (including diabetes, hypertension, etc.).	Urine spot samples Adjusted for SG LOD: 0.1 % < LOD: 6.1 (all visits), 5.5 (visit 1), 6.9 (visit 2), 5.7 (visit 3) Values below the LOD were calculated as LOD÷√2. GM ± GSD: 0.46 ± 3.2 (all visits), 0.47 ± 3.3 (visit 1), 0.45 ± 3.0 (visit 2), 0.45 ± 3.2 (visit 3) Percentiles (all visits, visit 1, visit 2, visit 3): 25th: 0.20, 0.20, 0.20, 0.20 50th: 0.40, 0.40, 0.40, 0.40 75th: 0.90, 0.99, 0.90, 0.90 Timing of samples: Visit 1: 16–20 weeks Visit 2: 20–24 weeks Visit 3: 24–28 weeks	Gestational length (days)	All visits average BPS, per IQR increase: β: -0.52 (95% CI -2.14, 1.09), p = 0.53 By total life event score (TLES): For mothers reporting negative life events (TLES < -1): **β: -3.15 (95% CI: -6.06, -0.24), p=0.04** For mothers reporting neutral life events (TLES = -1 to 1): β: -0.54 (95% CI: 3.82, 2.74), p=0.75 For mothers reporting positive life events (TLES > 1): β: 1.62 (95% CI: -0.96, 4.20), p=0.22 p-interaction for BPS*TLES = 0.06 By infant sex and TLES score: Among mothers with male infants and TLES < -1: **β: -5.06 (95% CI: -9.4, -0.72), p=0.03** Among mothers with female infant and TLES < -1: β: -0.79 (95% CI: -6.14, 4.55), p=0.77	Models adjusted for: SG, maternal age, insurance type, alcohol use, and exposure to second-hand smoke. Effect modification examined: TLES and infant sex. Other bisphenols measured: BPA and BPF.	Authors hypothesize a "two-hit" theory of maternal stress with chemical exposure. This sample includes the same individuals as Aker 2019. BPS percentiles from Aker 2019. Correlations between BPS and other bisphenols: BPA (ρ = 0.33), BPF (ρ = 0.02). Intraclass correlation coefficient (ICC) for BPS: 0.17 (95% CI: 0.10, 0.24). After stratification by sex, "associations with BPA and BPS were only observed among males. However, the sample sizes for each group in this analysis were relatively small (60-90 women), so caution must be taken when interpreting."

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
Aung et al. 2019 Boston, Massachusetts 2006–2008 Nested case-control study LIFECODES birth cohort n =130 cases, 350 controls Median (minimum-maximum) maternal age in years: Cases: 32.7 (20.9–50.2) Controls: 31.9 (18.3–48.7) Inclusion criteria: ages 18–50, delivery at recruitment hospital, first trimester, singleton, no medical protocol requiring delivery prior to 37 weeks (for cases).	Urine spot samples Adjusted for SG LOD: 0.4 % < LOD: 79.4 (all samples) Values below the LOD were calculated as LOD÷√2. Percentiles (all samples): 75th: < LOD 90th: 1.2 95th: 2.10 Timing of samples (median (IQR¥)): Visit 1: 9.7 (3.28) weeks Visit 2: 17.9 (1.71) weeks Visit 3: 26.0 (1.89) weeks Visit 4: 35.0 (1.28) weeks	Spontaneous or placental preterm birth (< 37 weeks)	Visits 1–3 BPS, detected vs. not detected: OR: 0.92 (95% CI: 0.59, 1.45), p = 0.73 With added adjustment for BPA, OR 0.83 (95% CI 0.52, 1.31), p = 0.42 Visit 1 BPS, detected vs. not detected: OR: 0.93 (95% CI: 0.53, 1.63), p = 0.81 Visit 2 BPS, detected vs. not detected: OR: 1.08 (95% CI: 0.63, 1.83), p = 0.78 Visit 3 BPS, detected vs. not detected: OR: 1.33 (95% CI: 0.72, 2.45), p = 0.36 Visit 4 BPS, detected vs. not detected: **OR: 2.05 (95% CI: 1.09,3.89), p = 0.03** Visit 4 OR slightly stronger when examining placental [OR: 3.45, 95% CI: 0.98, 12.2)] versus spontaneous [OR: 2.23, 94% CI: 0.98, 12.2)} preterm births. No evidence of interaction with infant sex.	Models adjusted for: maternal age, SG, race/ethnicity, pre-pregnancy body mass index (BMI), health insurance, education level. "Visits 1–3" model additionally adjusted for BPA in supplementary analyses. Effect modification examined: infant sex. Other bisphenols measured: BPA.	Sample size dropped per visit. At visit 4, there were 63 cases and 313 controls. Authors state that associations may "suffer from potential bias due to loss of cases." Correlations between BPS and other bisphenols: SG-adjusted BPA (ρ = -0.06), raw BPA (ρ = 0.28).

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
Bommarito et al. 2024 Boston, Massachusetts 2008–2018 Case-cohort study LIFECODES birth cohort N = 900 Median (IQR) age in years: 32.4 (28.7, 36.3) Inclusion criteria: at least 18 years of age, prenatal care before 16 weeks gestation, plan on delivering at study hospital, singleton pregnancy, live birth, birthweight and gestational age data available in medical record. Sample was enriched for SGA and LGA births.	Urine spot samples Adjusted for SG LOD: 0.4–1.6 % < LOD: 48 Values below the LOD were imputed using multiple imputation by chained equations. Percentiles: not reported for BPS Timing of samples* (median): Visit 1: 10 weeks Visit 2: 26 weeks Visit 3: 35 weeks	Repeated measures of fetal growth between 16 weeks and delivery measured by ultrasound: weight, head circumference, abdominal circumference, femur length. Measures were standardized to gestational-age specific z-scores. Binary variables: SGA, LGA.	Visits 1–3 BPS, detected vs. not detected: Ultrasound measures of fetal growth: Head circumference, β: -0.07 (95% CI: -0.18, 0.04) Abdominal circumference, β: -0.07 (95% CI: -0.19, 0.04) **Femur length, β: -0.15 (95% CI: -0.27, -0.04)** Estimated fetal weight, β: -0.11 (95% CI: -0.23, 0.01) Size at delivery: Birthweight z-score, β: 0.07 (95% CI: -0.10, 0.24) SGA, OR: 1.11 (95% CI: 0.72, 1.72) LGA, OR: 1.25 (95% CI: 0.80, 1.94) No evidence of effect modification by infant sex.	Models adjusted for age, pre-pregnancy BMI, maternal education, race/ethnicity, insurance status, year of conception, parity, alcohol consumption, smoking, season at enrollment, fetal sex assigned at birth. All models were weighted to account for the case-cohort sampling scheme and the number of ultrasounds performed. Effect modification: infant sex. Other bisphenols measured: BPA, BPF.	BPA and BPF were not associated with any outcome. Correlations between BPS and other bisphenols: not reported. Authors stated about SG adjustment: "we corrected for urine dilution using covariate-adjusted standardization"

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
Y Chen et al. 2024 Shanghai, China 2012 Cohort study Shanghai Minhang Birth Cohort Study n = 537 Mean (SD) maternal age in years: 29.0 (3.4) Inclusion criteria: attending first prenatal care visit, no pregnancy complications, singleton, no abortion or still birth.	Urine spot samples Adjusted for creatinine LOD: 0.004 % < LOD: 75.4 Values below the LOD were calculated as LOD÷2. GM: 0.01 µg/g Percentiles (µg/g): 25th: 0.00 50th: 0.01 75th: 0.03 Timing of samples (median (25th, 75th)): 32.1 (27.4, 37.3) weeks	Sex- and age-specific weight z-scores and body mass index z-scores. Scapular skinfold thickness (SST, mm), abdominal skinfold thickness (ABST, mm), waist circumference (WC, cm), and arm circumference (cm) 3 days after birth.	BPS, detect vs. no detect: BMI z-score, β: -0.18 (95% CI: -0.50, 0.14) Weight z-score, β: -0.09 (95% CI: -0.25, 0.14) SST, β: 0.15 (95% CI: -0.08, 0.39) **ABST, β: 0.21 (95% CI: 0.04, 0.38)** WC, β: 0.08 (95% CI: -0.49, 0.66) Arm circumference, β: -0.09 (95% CI: -0.57, 0.39) No significant interaction by infant sex. Bayesian kernal machine regression (BKMR) models: BPS was associated with larger ABST when other bisphenols were held at their 25th and 50th percentiles in males.	Models adjusted for: maternal age at delivery, maternal pre-pregnancy BMI, parity, gestational age, maternal passive smoking during early pregnancy, maternal educational level, family income per capita. Effect modification examined: infant sex. Other bisphenols measured: BPA, BPF, Bisphenol AF (BPAF), Tetrachlorobisphenol A (TCBPA). BKMR models used to estimate effects of BPS as part of a mixture of bisphenols.	There were 1225 live singletons born at delivery, but only 545 maternal urine samples were selected for bisphenol measurements due to "limited funding." Correlations between BPS and other bisphenols: reported as range, r = 0.15–0.43. Study also appears in postnatal growth section with separate outcomes reported.

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
Ferguson et al. 2018 Boston, MA 2006–2008 Prospective birth cohort study LIFECODES birth cohort Maternal age: 29% > 35 years, 39% 30-35 years, 20% 25-30 years, 12% < 25 Years. n = 476, n = 321 with ultrasound measurements. Inclusion criteria: singleton, non-anomalous fetus, deliver at participating hospital, < 15 weeks gestation.	Urine spot samples Adjusted for SG LOD: 0.4 % < LOD: 73.3 Values below the LOD were calculated as LOD÷√2. <u>Percentiles (all samples):</u> 50th: < LOD 75th: 0.59 90th: 0.94 95th: 1.32 <u>Timing of samples</u>: Visit 1: <15 weeks Visit 2: 18 weeks Visit 3: 26 weeks Visit 4: 35 weeks	Birthweight, birth length at delivery. Repeated measures of fetal growth between 16 weeks and delivery measured by ultrasound: weight, head circumference, abdominal circumference, femur length. (median: 32.9, range 19.9 to 40.3 weeks). All outcomes standardized to gestational age specific z-scores.	<u>Visits 1–3 BPS, detected vs. not detected:</u> Birthweight z-score, β: -0.12 (95% CI -0.31, 0.08), p = 0.23 <u>By fetal sex:</u> Male fetal sex: **Fetal weight combined with birthweight: *β*: -0.25 (95% CI: -0.49, -0.02)** Femur length, β: -0.21 (95% CI -0.48, 0.06) Abdominal circumference, β: -0.24 (95% CI -0.50, 0.02) Birthweight z-score, β: -0.19 (95% CI -0.46, 0.07) Birth length, β: -0.35 cm, 95% CI -1.13, 0.43) No association with head circumference. Female fetal sex: **Longer femur length (estimate not reported)** **Larger head circumference (estimate not reported)** No associations with fetal weight, birth length, birthweight, and abdominal circumference. <u>Statistical test for interaction:</u> No evidence of interaction by fetal sex for birthweight z-score (p-interaction = 0.37).	Models adjusted for: study design (via inverse probability weights), maternal age, race/ethnicity, pre-pregnancy BMI, and health insurance provider. Effect modification examined: fetal sex.	Corrigendum was issued in 2019 for error with coding of fetal sex. Results are interpreted based on the corrigendum. "-0.25 standard deviation change in fetal weight for males equates to a decrease in 108 grams in birthweight." Study design adjustment via weighting was conducted because participants were selected into the sample by preterm birth status (1 preterm birth case: 3 controls). Fetal weight and birthweight were combined and analyzed as repeated measures in the same model.

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
Goodrich et al. 2019 Ann Arbor, Michigan 2012–2015 Pilot study from a prospective cohort study, the Michigan Mother-Infant Pairs Study n = 56 Median maternal ages in years (minimum–maximum): 31.5 (26–40) Inclusion criteria for the study:18 years old, natural conception, singleton, 8-14 weeks gestation, and delivered at university hospital. Additional inclusion criteria for this pilot study: only Caucasian, non-Hispanic, non-smoking mothers with full term newborns (>37 weeks gestation).	Urine Spot Samples Adjusted for SG LOD: 0.20 % < LOD: 62.5 Values below the LOD were calculated as LOD÷√2. GM (95% CI): 0.21 (0.18, 0.26) <u>Percentiles</u>: 50th: < LOD 75th: 0.26 95th: 1.13 99th: 1.55 <u>Timing of sample</u>: First trimester (TM1) study visit	Birthweight (grams, g), birth length (millimeters, mm), head circumference (mm), Fenton z-score 2nd Trimester (TM2) fetal anthropometry: head and abdominal circumference (mm), biparietal diameter (mm), femur length (mm)	<u>Continuous BPS, per 1-unit increase natural log (ln) BPS:</u> **Birthweight, β: −150.42 (95% CI: −294.9, −6.0), p = 0.04** **Fenton z-score, β: −0.31 (95% CI: −0.6, 0.002), p = 0.05** Non-significant increase for abdominal circumference, biparietal diameter, and head circumference. Non-significant decrease for femur length. <u>BPS, detected vs. not detected:</u> **Birthweight β: -220.10 (95% CI: -424.9, -15.3), p= 0.04** **Fenton z-score β: -0.51 (95% CI: -0.94, -0.07), p= 0.02**	Birthweight models adjusted for: SG, gestational age, and gender. Fenton z-score models adjusted for: SG. Fetal anthropometry models adjusted for: SG and gender. Other bisphenols measured: BPA and BPF.	Many chemical exposures tested. Authors stated: "Associations would not have remained statistically significant after accounting for multiple comparisons." Limited set of adjustment variables. Correlations between BPS and other bisphenols: BPA (ρ = 0.46), BPF (ρ = 0.12).

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
Hu et al. 2019 Wuhan, China 2013–2015 Prospective cohort study n = 845 Mean (SD) maternal age in years: 27.9 (3.4) Inclusion criteria: first prenatal care visit before 16 weeks gestation, residents of Wuhan, comprehended the Chinese language, give birth at study hospital, singleton birth, no birth defects, no tobacco or alcohol consumed before or during pregnancy.	Urine spot samples Adjusted for SG LOD: 0:04 % < LOD: all samples: 13.2, TM1: 15.7, TM2: 13.5, TM3: 10.4 Values below the LOD were calculated as LOD÷√2. GM (95% CI): All samples: 0.39 (0.37, 0.42), TM1: 0.33 (0.30, 0.38), TM2: 0.39 (0.35, 0.44), TM3: 0.46 (0.41, 0.52) Percentiles (all samples, TM1, TM2, TM3): 25th: 0.13, 0.10, 0.14, 0.17 50th: 0.38, 0.30, 0.39, 0.43 75th: 1.11, 0.95, 1.17, 1.21 95th: 7.36, 6.50, 6.98, 8.07 Timing of samples (Mean (range)): TM1: 13.0 (10–16) weeks TM2: 23.6 (19–27) weeks TM3: 36.0 (32–41) weeks	Birth weight (g), birth length (centimeters, cm), and ponderal index (kg/m^3 x 1000)	Average (Avg.) BPS, per IQR increase: Birthweight, β: -26 (95% CI: -57, 4) Birth length, β: -0.10 (95% CI: -0.21, 0.01) Ponderal index, β: -0.02 (95% CI: -0.19, 0.14) TM1 BPS, per IQR increase: **Birthweight, β: -32 (95% CI: -60, -5)** Birth length, β: -0.05 (95% CI: -0.15, 0.05) Ponderal index, β: -0.16 (95% CI: -0.32, 0.01) TM2 BPS, per IQR increase: **Birthweight, β: -38 (95% CI: -68, -8)** **Birth length, β: -0.13 (95% CI: -0.23, -0.02)** Ponderal index, β: -0.05 (95% CI: -0.23, 0.13) TM3 BPS, per IQR increase: Birthweight, β: -17 (95% CI: -47, 13) Birth length, β: -0.09 (95% CI: -0.20, 0.02) Ponderal index, β: 0.03 (95% CI: -0.14, 0.20) **Significant interaction between BPS and trimester for birthweight (p = 0.04)** Associations were more pronounced in boys, but interaction with infant sex was not significant. No evidence of effect modification by parity, maternal age at recruitment, or maternal pre-pregnancy BMI (p-interaction > 0.05). Similar results were observed when BPS was categorized into quartiles. Statistically significant estimates from quartile analyses were: **TM1 Q4 vs. Q1 Birthweight, β: -67 (95% CI: -134, -1)** **TM2 Q4 vs. Q1 Birthweight, β: -81 (95% CI: -149, -13)** **TM2 Q4 vs. Q1 Birth length, β: -0.23 (95% CI: -0.47, 0)** **Avg. Q4 vs. Q1 Birth length, β: -0.27 (95% CI: -0.53, 0)**	Models adjusted for: gestational age at delivery, maternal age at recruitment, maternal and paternal height, parity, pre-pregnancy BMI, passive smoking during pregnancy, education, folic acid supplementation, infant sex, BPA, BPF. Effect modification examined: trimester, infant sex, parity, maternal age at recruitment, maternal pre-pregnancy BMI. Other bisphenols measured: BPA and BPF.	TM3 BPF was associated with reduced birthweight and ponderal index, although co-adjusting for other bisphenols weakened these associations. Correlations between BPS and other bisphenols: BPA (Pearson correlation coefficient [r] = 0.12), BPF (r = 0.26). ICC for BPS: 0.45 (95% CI: 0.41, 0.49), "fair-to-good reproducibility." Findings were robust to sensitivity analyses adjusting for additional pregnancy complications and restricting to term deliveries.

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
Huang et al. 2019 Wuhan, China 2014–2015 Prospective cohort study n = 850 Mean (SD) maternal age in years: 28.6 (3.4) Inclusion criteria: singleton, completed TM1 ultrasound, < 16 weeks, gave birth in study hospital, no birth defect, no active smoking in pregnancy.	Urine spot samples Adjusted for SG LOD: 0.04 % < LOD: TM1: 37.6, TM2: 35.4, TM3: 31.9 Values below the LOD were calculated as LOD÷√2. GM: TM1: 0.37, TM2: 0.45, TM3: 0.70 <u>Percentiles (TM1, TM2, TM3):</u> 25th: 0.13, 0.16, 0.20 50th: 0.35, 0.47, 0.51 75th: 1.07, 1.39, 1.43 95th: 7.61, 8.25, 9.78 <u>Timing of samples</u> (Mean ± SD): TM1: 13.0 ± 1.1 weeks TM2: 23.6 ± 3.2 weeks TM3: 35.9 ± 3.4 weeks	Gestational age (days), preterm birth (< 37 weeks)	<u>BPS tertiles (cutoffs varied by time point):</u> No statistically significant associations between BPS and odds of preterm birth: TM1 tertile 2 (T2) vs. tertile 1 (T1), OR: 0.95 (95% CI: 0.29 to 3.09) TM1 tertile 3 (T3) vs. T1, OR: 1.41 (95% CI: 0.48 to 4.10) TM2 T2 vs. T1, OR: 1.24 (95% CI: 0.41 to 3.70) TM2 T3 vs. T1, OR: 1.04 (95% CI: 0.34 to 3.22) TM3 T2 vs. T1, OR: 0.67 (95% CI: 0.23 to 1.92) TM3 T3 vs. T1, OR: 0.44 (95% CI: 0.14 to 1.32) No associations between BPS and gestational days (TM-specific β estimates ranged from -0.5 to 1.25). No evidence of interaction between BPA and BPS.	Models adjusted for: maternal age, education, pre-pregnancy BMI, pregnancy weight gain, parity, passive smoking, hypertension during pregnancy, and gestational diabetes. Supplementary analyses included additional adjustment for BPA and interaction between BPA and BPS. Other bisphenols measured: BPA.	BPA was associated with decreases in gestational age and higher odds of preterm birth. BPS exposures increased over pregnancy. ICCs for uncorrected and SG-corrected BPS: 0.20 (95% CI: 0.15, 0.24) and 0.13 (95% CI: 0.09, 0.17), "weakly correlated." Findings did not meaningfully change after adjustment for BPA. Correlations between BPS and other bisphenols not reported. In-text, authors report adjustment for gestational diabetes. In Table 3 footnote, gestational diabetes is not listed as a covariate.

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
Jedynak et al. 2022 Grenoble, France 2014–2017 Prospective cohort study Suivi de l'Exposition à la Pollution Atmosphérique durant la Grossesse et Effet sur la Santé (SEPAGES) cohort n = 478, n ranged from 433 to 475 by analysis Median (IQR) maternal age in years: 32.1 (29.9, 35.2) Inclusion criteria: Singleton, < 19 weeks gestation, ≥ 18 years of age, affiliation with French security system, and deliver at participating hospitals.	Urine samples, 3/day for 7 consecutive days LOD: 0.1 % < LOD: TM2: 75, TM3: 72 Values below LOD were imputed using "fill-in" method of random values below LOD and between LOD and limit of quantification (LOQ). Percentiles (TM2, TM3): 50th: < LOD, < LOD 95th: 3.0, 2.9 Timing of samples: TM2 7-day average: 18 weeks TM3 7-day average: 34 weeks	Prenatal growth: abdominal circumference (mm), biparietal diameter (mm), femoral length (mm), and head circumference (mm) at ultrasound examinations at 22 and 32 weeks. Birth: weight (kg), length (mm), and head circumference (mm). Growth outcomes were standardized by dividing them by the period-specific standard deviation.	TM2 BPS 3-level variable (< LOD, LOD-LOQ, > LOQ): No associations between BPS and fetal growth at 22 weeks. TM2 and TM3 BPS 3-level variable (< LOD, > LOD at TM2 or TM3, > LOD at TM2 and TM3) Femur length at 32 weeks: **Middle vs. Low: β: 0.20 (95% CI: 0.02, 0.37)** High vs. Low: β: 0.11 (95% CI: -0.18, 0.41) No associations with fetal biparietal diameter, abdominal circumference, and head circumference at 32 weeks. No association with birthweight and birth length. No evidence of interaction by sex.	Models adjusted for: maternal height, maternal pre-pregnancy weight, maternal age, education after high school, active smoking during TM2, parity, gestational duration, child sex. Effect modification examined: infant sex. Other bisphenols measured: BPA.	Main analyses included 264 participants for whom urine samples were collected after ultrasound measurement of outcome, excluding these individuals yielded more consistent and larger, but not statistically significant, associations (Supplementary Table 7). LOQ used to classify exposure groups, but LOQ for BPS not reported. Correlations between BPS and other bisphenols not reported. Authors report no adjustment for SG because "biomarker concentrations assessed in equal volume pools correlated well with those assessed in a pool of all urine samples collected over 24h or over a week."

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
S Kim et al. 2021 Seoul, South Korea 2017–2020 Prospective birth cohort Mother and Kids Environmental Health (MAKE) Study n = 180 77% with maternal age ≥ 30 years Inclusion criteria: 18 years of age, singleton birth, ≥ 28 weeks gestation.	Urine spot samples Adjusted for SG LOD: 0.02 % < LOD: 33.9 Values below the LOD were calculated as LOD÷√2. GM (GSD): 0.1 (3.0) Percentiles: 10th: < LOD 25th: 0.03 50th: 0.05 75th: 0.1 90th: 0.2 Max: 1.5 Timing of samples: TM3	Birthweight (g) and gestational age (weeks)	Continuous BPS, per 10-fold increase ln BPS: Birthweight, β: -44.2 (95% CI: -92.7, 4.4), p = 0.07 Gestational age, β: -0.09 (95% CI: -0.30, 0.13), p = 0.43 In univariate exposure-response functions from BKMR models, BPS showed an **inverse u-shape with birthweight** and to a lesser extent for gestational age. Posterior inclusion probability (PIP) for BPS was 0.48 for the birthweight model and 0.25 for the gestational age model.	Models adjusted for: maternal age, education, family income, smoking status, drinking status, BMI, exercise, parity, infant sex, gestational weeks (in the case of birthweight), and other bisphenols. Other bisphenols measured: BPA and BPF. BKMR models used to estimate effects of BPS as part of a mixture of bisphenols.	No significant findings with BPA; BPF was associated with increased birthweight at or above the median value. BPS associations similar when not mutually adjusted for BPA and BPF. Later pregnancy exposure assessment (>28 weeks). Correlations between BPS and other bisphenols (statistical test not indicated): BPA (r = 0.11) and BPF (r = 0.22).

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
Kim et al. 2024 Korea 2022–2023 Prospective birth cohort No Environmental Hazards for Mother-Child (NoE-MoC) cohort n = 107 Mean (SD) maternal age in years: 35.2 (3.7) Inclusion criteria (met any "high-risk factors"): complications in pregnant period (e.g., gestational diabetes, gestational hypertension, preterm birth), > 35 years, pre-pregnancy BMI > 25 kg/m^2, cotinine levels above sample median.	Urine spot samples Adjusted for creatinine. LOD: 0.01 % < LOD: not reported. Values below the LOD were calculated as LOD÷√2. GM: 0.35 (total), 0.29 (TM1), 0.21 (TM2), 1.63 (delivery) <u>Percentiles (Total, TM1, TM2, delivery):</u> 25th: 0.13, 0.12, 0.08, 0.41 50th: 0.37, 0.23, 0.25, 0.65 75th: 0.81, 0.62, 0.47, 1.75 Max: 30.51, 22.09, 30.51, 16.75 <u>Timing of samples</u>: TM1, TM2, delivery	TM2 estimated fetal weight (g). Birthweight (g).	<u>Continuous BPS, per unit increase in TM2 ln BPS:</u> Fetal weight, β: 10.04 (95% CI: -86.04 to 106.1) Birthweight, β: 95.54 (95% CI: -185.3 to 376.3) <u>Mixture:</u> BPS was not associated with fetal growth or birthweight when other bisphenols were held constant in BKMR models.	Models adjusted for: maternal age, pre-pregnancy BMI, education, income, residential area, parity, maternal cotinine level in urine, neonatal sex, and gestational age. Other bisphenols measured: BPA, BPF. BKMR models used to estimate effects of BPS as part of a mixture of bisphenols.	Cohort was restricted to women with "high-risk factors." TM2 BPS – fetal weight associations were cross-sectional. Correlations between BPS and other bisphenols: not reported.

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
X Li et al. 2024 Shenyang, China 2019–2020 Prospective cohort n = 113 43.4% with maternal age ≥ 30 years Inclusion criteria: maternal age >18 years, 37–42 weeks gestation, no stillborn births, no birth defects, no metabolic diseases.	Urine spot samples Adjusted for creatinine. LOQ: 0.1 LOD not reported. % < LOD: 53.98 Values below the LOQ were calculated as LOQ÷√2 GM: 0.12 µg/g Percentiles (µg/g): 25th: 0.07 50th: 0.31 75th: 0.57 Max: 15.34 Timing of samples: TM3	Birthweight (kg)	BPS, ln-transformed continuous variable: Birthweight, β: −0.021 (95% CI: −0.085 to 0.042) In males: β: −0.026 (95% CI: −0.118 to 0.066) In females: β: 0.020 (95% CI: −0.102 to 0.062)	Model adjusted for maternal age, pre-pregnancy BMI, maternal weight gain during pregnancy (less, appropriate, more) and gestational age. Effect modification examined: infant sex. Other bisphenols measured: BPA, BPF.	BPA and BPF were associated with lower birthweight. Correlations between BPS and other bisphenols: BPA (r = 0.443) and BPF (r = 0.263). Study also appears in infant growth section with separate outcomes reported.

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
J Liang et al. 2020 Guangxi Province, China 2015–2018 Prospective birth cohort Guangxi Zhuang Birth Cohort (GZBC) n = 2,023 Mean (SD) maternal age in years: 28.2 (5.6) Included: < 13 weeks gestation, singleton, Zhuang population (mother or father), planned to give birth in participating hospital, no birth defect.	Serum samples LOD: 0.046 % < LOD: 13.1 Values below the LOD were calculated as LOD÷2. GM (GSD): 0.093 (2.427) <u>Percentiles:</u> 25th: 0.096 50th: 0.097 75th: 0.107 95th: 0.307 Max: 139.340 <u>Timing of samples:</u> TM1	Birthweight (g), birth length (cm), ponderal index (kg/m^3 x 1000), and birthweight z-scores	<u>Continuous BPS, per 1-unit increase in ln BPS:</u> Birthweight, β: -33.42 (95% CI: -81.60, 14.76) Birth length, β: 0.06 (95% CI: -0.13, 0.26) Ponderal Index, β: -0.30 (95% CI: -0.68, 0.08) Birthweight z-score, β: -0.05 (95% CI: -0.16, 0.05) No evidence of effect modification by fetal sex for birthweight or ponderal index. Association for birth length stronger among males [β: 0.12 (95% CI: -0.17, 0.41)] compared to females [β: 0.00 (95% CI: -0.25, 0.25)]. Statistical interaction not tested.	Models adjusted for: maternal age, pre-pregnancy BMI, drinking before pregnancy, passive smoking during pregnancy, parity, gravidity, gestational age, and fetal sex. Effect modification examined: fetal sex. Other bisphenols measured: BPA, bisphenol B (BPB), BPF, Tetrabromobisphenol A (TBBPA).	BPA was associated with a significant decrease in birthweight; BPF was associated with decrease in birthweight, ponderal index, and birthweight z-scores with significant *P* trend; TBBPA in male infants showed associations with decreased birthweight, birth length, and birthweight z-scores with significant P trend. Limited variability of BPS exposure with at least one extreme outlier. Correlations between BPS and other bisphenols: not reported.

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
Liang et al. 2021a Guangxi Providence, China 2015–2017 Prospective birth cohort Guangxi Zhuang Birth Cohort n = 801 Mean (SD) maternal age in years: 28.3 (5.6) Included: < 13 weeks gestation, singleton, deliver at study hospital, Zhuang population (mother or father).	Serum samples LOD: 0.046 % < LOD: 9.1 Values below the LOD were calculated as LOD÷2. GM: 0.102 Percentiles: 25th: 0.096 50th: 0.098 75th: 0.110 95: 0.239 Timing of samples: TM1	Telomere length measured from cord blood at birth Analyzed as percent change (%Δ)	Continuous BPS, per doubling of exposure: %Δ, β: -1.32 (95% CI: -3.37, 0.76), p = 0.212 By maternal age: Among maternal age ≥ 28 years: **%Δ, β: -3.19 (95% CI: -6.08, -0.21), p = 0.037.** Among maternal age < 28 years: %Δ, β: 0.64 (95% CI: -2.25, 3.61), p = 0.669 Restricted cubic spline: Linear negative association with relative telomere length, no evidence of non-linear association (**p-overall = 0.041**, p non-linear = 0.169) among mothers aged ≥ 28 years No evidence of effect modification by infant sex.	Models adjusted for: gestational age, infant gender, maternal age, pre-pregnancy BMI, occupation, drinking before pregnancy, passive smoking during pregnancy, parity, hypertensive disorders in pregnancy, and gestational diabetes mellitus. Effect modification examined: maternal age (< 28 vs. ≥ 28 years), infant sex. Other bisphenols measured: BPA, BPB, BPF, TBBPA.	TBBPA was associated with an increase in cord blood telomere length in mothers < 28 years. Sensitivity analyses excluding individuals with gestational diabetes and hypertensive disorders in pregnancy yielded similar results. Limited variability of BPS exposure. Correlations between BPS and other bisphenols: BPA (ρ = 0.01), BPF (ρ = 0.13), TBBPA (ρ = 0.16), BPB (ρ = 0.09).

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
Liang et al. 2021b Guangxi Providence, China 2015–2018 Prospective birth cohort Guangxi Zhuang Birth Cohort n = 2,023 Mean (SD) maternal age in years: non-preterm birth: 28.2 (5.5); preterm birth: 29.1 (5.9) Included: < 13 weeks gestation, singleton, Zhuang population (mother or father), no birth defect.	Serum samples LOD: 0.046 % < LOD: 13.1 Values below the LOD were calculated as LOD÷2. Percentiles: 25th: 0.096 50th: 0.097 75th: 0.107 Timing of samples: First prenatal visit	Preterm birth (< 37 weeks), gestational (gest.) age (weeks)	Continuous BPS, per 1-unit increase in ln BPS: Preterm birth, OR: 1.05 (95% CI: 0.85, 1.29) Gest. weeks, β: -0.04 (95% CI -0.11, 0.03) BPS Tertiles (T) (ranges not provided): **T3 vs. T1, Preterm birth OR: 2.07 (95% CI: 1.24, 3.46)** **T2 vs. T1, Preterm birth OR: 1.93 (95% CI: 1.15, 3.25)** T3 vs. T1, Gest. weeks β: -0.14 (95% CI -0.29, 0.02) T2 vs. T1, Gest. weeks β: -0.08 (95% CI -0.23, 0.08) By fetal sex: For male fetus: **T3 vs. T1, Preterm birth OR: 2.42 (95% CI: 1.17, 5.10)** T2 vs. T1, Preterm birth OR: 1.88 (95% CI: 0.89, 3.98) **T3 vs. T1, Gest. weeks β: −0.23 (95% CI: −0.44, −0.01)** T2 vs. T1, Gest. weeks β: -0.04 (95% CI: -0.25, 0.18) For female fetus: T3 vs. T1, Preterm birth OR: 1.62 (95% CI: 0.77, 3.42) T2 vs. T1, Preterm birth OR: 1.86 (95% CI: 0.89, 3.85) T3 vs. T1, Gest. weeks β: −0.03 (95% CI: −0.25, 0.20) T2 vs. T1, Gest. weeks β: -0.12 (95% CI -0.34, 0.10) Restricted cubic spline: Inverted U-shaped curve for preterm birth **(p-nonlinear: 0.01, p-overall: 0.032)** BKMR and quantile g-computation analysis: "bisphenol mixture was significantly related to an increased risk of preterm birth, and its effects were primarily driven by BPA, BPF, and BPS." Inverse U-shaped curve for BPS observed among male infants after stratification by sex. BPS weight in g-computation model was 29.6%. Group and conditional PIP BPS were 0.76 and 0.14.	Models adjusted for: maternal age, pre-pregnancy BMI, drinking, passive smoking, parity, gravidity, and fetal sex. Effect modification examined: fetal sex. Other bisphenols measured: BPA, BPB, BPF, TBBPA. BKMR models and quantile g-computation used to estimate effects of BPS as part of a mixture of bisphenols.	Increased BPA showed associations with increased risk of preterm birth for female infants; BPF and TBBPA were associated with increased odds for risk of preterm birth for male infants, while BPB reduced odds for risk of preterm birth for male infants. Odds for late preterm birth (34 to <37 weeks) similar. Correlations between BPS and other bisphenols: BPA (ρ = -0.01), BPB (ρ = 0), BPF (ρ = 0.23), TBBPA (ρ = 0.22).

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
Mustieles et al. 2018 Boston, MA 2005–2016 Prospective cohort study Environment and Reproductive Health (EARTH) Study n = 346 infants with BPA measured, and n = 107 for BPS, n = 73 analyzed Mean (SD) maternal age in years: 34.8 (3.9) Inclusion criteria: women ages 18-46, single or couple enrolled at fertility center, followed through pregnancy and delivery, singleton, not taking hormones at study enrollment, planning pregnancy, and prior to conception.	Urine spot samples Adjusted for SG LOD: 0.1 % < LOD: preconception: 47%, prenatal: 45% Values below the LOD were calculated as LOD÷√2. GM (GSD): preconception: 0.45 (0.03), prenatal: 0.33 (0.03) Percentiles: (preconception, prenatal): 25th: 0.29, 0.19 50th: 0.46, 0.31 75th: 0.83, 0.55 Timing of samples (median): Preconception TM1: 6 weeks TM2: 21 weeks TM3: 35 weeks	Birth weight (g) and head circumference (circ.) (cm).	Continuous BPS, per 1-unit increase in ln BPS: Preconception BPS: **Birthweight, β: 144 (95% CI: 2, 286), p = 0.05** Head circ., β: -0.11 (95% CI: -1.2, 0.96), p = 0.84 Effect estimates for preconception BPS and birthweight varied substantially across models with different sets of covariates. Some evidence of sex*preconception BPS interaction for birthweight (p-interaction = 0.10): Males: Birthweight, β: -145 (95% CI: -459, 169) Females: Birthweight, β: 210 (95% CI: -73, 494) Prenatal BPS: Birthweight: β: -67 (95% CI: -210, 76), p = 0.36 Head circ., β: -0.02 (95% CI: -0.99, 0.94), p = 0.96 No evidence of sex*prenatal BPS interaction for birthweight (p-interaction =0.90).	Models adjusted for: maternal age, pre-pregnancy BMI, maternal education, smoking status, assisted reproductive technology, and co-adjustment for preconception or prenatal BPS. Head circ. models additionally adjusted for mode of delivery. Effect modification examined: infant sex. Other bisphenols measured: BPA.	BPA was inversely associated with birthweight and head circ. Study results may be due to "small subsample (n = 73) and low detection frequencies." Authors interpretation, "maternal preconception urinary BPS concentrations were not associated with birthweight or head circumference." Sample limited to sub-fertile couples. Maternal preconception BPS exposure correlated with maternal prenatal BPS exposure (r = 0.24). Correlations between BPS and other bisphenols: not reported.

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
Mustieles et al. 2020 Boston, MA 2005–2018 Prospective cohort study Environment and Reproductive Health (EARTH) Study n = 417, n = 163 with measured BPS Mean (SD) maternal ages in years: 34.7 (4.0) Inclusion criteria: single or couple enrolled at fertility center, followed through pregnancy and delivery, singleton, ages 18-46, enrolled prior to conception.	Urine spot samples Adjusted for SG LOD: 0.1 % < LOD: 19.3 Values below the LOD were calculated as LOD÷√2. GM (GSD): 0.48 (0.03) Percentiles: 25th: 0.32 50th: 0.47 75th: 0.77 Timing of samples: Preconception	Preterm birth (< 37 weeks)	Maternal preconception BPS (per ln unit increase) **RR: 2.42 (95% CI: 1.01, 5.77), p = 0.05** **With added adjustment for prenatal BPS:** **RR: 3.33 (95% CI: 1.13, 8.80), p=0.03** No evidence of interaction by sex (p-interaction = 0.68).	Models adjusted for: maternal age, pre-pregnancy BMI, maternal education, smoking status, assisted reproductive technology, prenatal BPS exposure (in additional model). Effect modification examined: infant sex. Other bisphenols measured: BPA.	Maternal preconception BPA exposure associated with increased risk of preterm birth. Paternal preconception exposure also measured but not analyzed. Maternal preconception BPS exposure weakly correlated with prenatal exposure (ρ = 0.15). Correlations between BPS and other bisphenols: not reported. Effect estimates robust to additional adjustment for study period and number of fertility cycles (in sensitivity analyses). Prenatal BPS was measured but summary statistics were not reported.

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
Sol et al. 2021 Rotterdam, Netherlands 2004–2005 Prospective birth cohort Generation R Study n = 1,379 Mean (SD) maternal age in years: 30.5 (4.8) Inclusion criteria: <18 weeks gestation, singleton.	Urine spot samples Adjusted for creatinine LOD: 0.05 % < LOD: TM1: 32.1, TM2: 70.6 Values below the LOD were calculated as LOD÷√2. Percentiles (TM1, TM2): 25th: 0.03, 0.03 50th: 0.17, 0.03 75th: 0.61, 0.10 Timing of samples (median (25th, 75th)): TM1: 12.9 (12.1, 14.5) weeks TM2: 20.4 (20.4, 20.9) weeks	Fetal head circumference (circ.) (z-score), length (z-score), weight (z-score) measured in TM2 and TM3, preterm birth (< 37 weeks), and SGA	Average BPS, per IQR increase: **Fetal head circ., β: 0.18 (95% CI: 0.01, 0.34)** No associations with fetal length and fetal weight No evidence of interaction with gestational age. TM1 BPS, detected vs. not detected: **TM2 fetal head circ., β: 0.15 (95% CI: 0.05, 0.26)** **TM3 fetal head circ., β: 0.12 (95% CI: 0.02, 0.23)** Birth fetal head circ: β: 0.11 (95% CI: -0.06, 0.29) **TM2 fetal weight, β: 0.12 (95% CI: 0.02, 0.22)** **TM3 fetal weight, β: 0.16 (95% CI: 0.06, 0.26)** Birth fetal weight: β: 0.10 (95% CI: -0.00, 0.21) TM2 fetal length, β: 0.10 (95% CI: -0.01, 0.20) TM3 fetal length, β: 0.09 (95% CI: -0.02, 0.19) Birth fetal length: β: 0.08 (95% CI: -0.07, 0.23) Associations remained significant after correction for multiple testing. **SGA, OR: 0.56 (95% CI: 0.38, 0.84)** Preterm birth, OR: 1.63 (95% CI: 0.84, 3.24) TM2 BPS, detected vs. not detected: No statistically significant associations with preterm birth, SGA, or fetal head circ., length, or weight at any gestational age.	Models adjusted for: fetal sex (except in models for outcomes at birth), maternal age at enrollment, education level, ethnicity, parity, folic acid supplementation, daily caloric intake, pre-pregnancy BMI, smoking, alcohol consumption, and gestational age at growth measurement (for fetal growth models). Effect modification examined: timing of outcome measurement. Other bisphenols measured: BPA and BPF.	BPA was associated with an increase in gestational age at birth, an increase in fetal length in TM2, and a decrease in head circumference in TM3; BPF was associated with lower fetal weight in TM3, lower fetal length and weight at birth, and decreased odds of SGA. TM3 BPS not analyzed because over 80% of samples were < LOD. Concentrations of BPS converted from nanomoles per liter (nmol/L) to ng/mL. Correlations between BPS and other bisphenols: TM1 BPA (r = 0.17), TM2 BPA (r = 0.13), TM1 BPF (r = 0.11).

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
Stevens et al. 2023 Denver, Colorado, USA 2009–2014 Prospective birth cohort Healthy Start Cohort n = 438 Mean (SD) maternal age in years: 28.1 (6.1) Included: ≥ 16 years of age, singleton, < 24 weeks gestation, attended obstetric clinics at university hospital. Excluded: history of stillbirth or extremely preterm, had diabetes, asthma treated with steroids, cancer, or medication-dependent psychiatric illness.	Urine spot samples Adjusted for creatinine LOD: 0.1 % < LOD: 13 Values below the LOD were imputed as the instrument value when possible, or else calculated as ½ the minimum reported value. <u>Percentiles:</u> 25th: 0.2 50th: 0.3 75th: 0.6 <u>Timing of samples:</u> Second study visit: median (25th, 75th) = 27 (25, 29) weeks.	Infant size and body composition: weight, fat mass %, and lean mass (in grams), and fat and lean mass indices (kg/m^2) at 72 hours after delivery and 5 months; Secondary outcome: rapid infant growth from delivery to 5 months.	<u>Continuous BPS, per 1-unit increase in ln BPS:</u> At birth: Weight, β: -28 (95% CI: -67 to 11), p = 0.16 Fat mass %, β: -0.1 (95% CI: -0.48 to 0.28), p = 0.61 Fat mass, β: -5.8 (95% CI: -20 to 8.1), p = 0.41 Lean mass, β: -22 (95% CI: -54 to 9.8), p = 0.17	Models adjusted for: age, race and ethnicity, pre-pregnancy BMI category, highest education level completed, any previous pregnancies, smoking during pregnancy, gestational age at biological sample collection, infant sex, diet during pregnancy, physical activity during pregnancy, and gestational weight gain. 5-month models additionally adjusted for infant age Effect modification examined: sex Other bisphenols measured: BPA Quantile g-computation used to estimate effects of BPS as part of a mixture of chemicals (phenol mixture and phenol + phthalates mixture).	ICC for BPS: 0.25. Correlations between BPS and other bisphenols: BPA (ρ = -0.36). Study was also summarized in the infant growth section.

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
Trasande et al. 2023 United States 1998–2023 Prospective cohort study National Institutes of Health Environmental influences on Child Health Outcomes (ECHO), harmonized data from 11 unique cohorts. n = 3,619 (varied by analysis). Maternal age: 22.9% < 25 years, 58.8% 25-34 years, 18.3% ≥ 35 years. Study inclusion criteria varied by cohort. Inclusion criteria for this analysis: ≥ 1 urinary phenol measurement during index pregnancy, data on gestational age and birthweight, singleton delivery, ≥ 50 participants per cohort.	Urine samples Adjusted for SG or creatinine by cohort. LOD: varied by cohort. % < LOD: less than 50% of samples, exact values from cohorts not reported. Authors reported replacing values below the lower LOD with lower LOD÷√2. Percentiles (Average, TM1, TM2, TM3): 50th (IQR¥): 0.4 (0.6), 0.3 (0.6), 0.4 (0.6), 0.3 (0.6) Timing of samples: TM1, TM2, TM3	Gestational age (weeks), preterm birth (< 37 weeks) Birth length (cm), birthweight (grams), Birthweight z-score, SGA, LGA, low birthweight (< 2,500 grams).	All visits average BPS, per 1-unit increase: Birthweight, β: -0.90 (95% CI: -49.34, 47.55) Birthweight z-score, β: 0.01 (95% CI: -0.10, 0.11) Birth length, β: 0.02 (95% CI: -0.25, 0.30) Gestational age, β: -0.07 (95% CI: -0.24, 0.09) Preterm, OR: 1.01 (95% CI: 0.66, 1.53) SGA, OR: 1.10 (95% CI: 0.80, 1.53) LGA, OR: 1.10 (95% CI: 0.77, 1.56) Low birthweight, OR: 0.86 (95% CI: 0.54, 1.38) Association with gestational age significant in non-Hispanic White group [**β: −0.21 (95% CI: -0.41, -0.01)].** Association with birthweight negative in non-Hispanic White group [**β: -65.2 (95% CI: -128.8, -1.7)] and** positive in Hispanic group [**β: 97.9 (95% CI: 11.7, 184.0)].** Association with birth length **[β: 0.55 (95% CI: 0.06, 1.04))],** birthweight z-score **[β: 0.28 (95% CI: 0.10, 0.46))]** and LGA in Hispanic group [**OR: 1.89 (95% CI: 1.02, 3.48)].** TM1 BPS, per 1-unit increase: Birthweight, β: -17.11 (95% CI: -81.17, 46.96) Birthweight z-score, β: 0.02 (95% CI: -0.11, 0.15) Birth length, β: -0.19 (95% CI: -0.53, 0.15) Gestational age, β: −0.16 (95% CI: -0.38, 0.07) Preterm, OR: 1.06 (95% CI: 0.62, 1.83) SGA, OR: 1.11 (95% CI: 0.75, 1.63) LGA, OR: 0.80 (95% CI: 0.50, 1.28) Low birthweight, OR:1.26 (95% CI: 0.75, 2.12) Association with gestational age significant in female infants [**β: −0.31 (95% CI: -0.59, -0.03)].** Association with gestational age [**β: -0.43 (95% CI: -0.72, -0.14)],** birthweight [**β: -156.6 (95% CI: -245.4, -67.8)],** birthweight z-score **[β: -0.24 (95% CI: -0.44, -0.03)],** birth length **[β: -0.79 (95% CI: -01.32, -0.27)]**, SGA **[OR: 2.1 (95% CI: 1.1, 4.3)]** (continued on next page)	Models adjusted for: maternal race/ethnicity, parity, and education, and child sex; cohort as random effect. birthweight or gestational age model removes parity and child sex from covariates. Effect modification examined: infant sex, race/ethnicity. Other bisphenols measured: BPA, BPF	Correlations between BPS and other bisphenols: < 0.4 (exact coefficient not reported). Authors note that a limitation "of the trimester-specific analyses is that different cohorts/participants contribute to each analysis, making the results difficult to directly compare across trimesters." Two of the 11 cohorts included in this study, the PROTECT cohort and the Healthy Start cohort, were also analyzed by (Aker et al. 2020; Aker et al. 2019b) and (Stevens et al. 2023), respectively.

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
Trasande et al. 2023 continued			and low birthweight **[OR: 4.8 (95% CI: 1.5, 14.9)]** significant in non-Hispanic White group. TM2 BPS, per 1-unit increase: Birthweight, β: 32.376 (95% CI: -16.85, 81.60) **Birthweight z-score, β: 0.11 (95% CI: 0.0004, 0.212)** Birth length, β: 0.14 (95% CI: -0.14, 0.41) Gestational age, β: -0.07 (95% CI: -0.23, 0.10) Preterm, OR: 1.08 (95% CI: 0.72, 1.61) SGA, OR: 0.76 (95% CI: 0.55, 1.06) LGA, OR: 1.18 (95% CI: 0.84, 1.65) Low birthweight, OR: 0.75 (95% CI: 0.48, 1.17) Association with birthweight significant in non-Hispanic Black **[β: 263.2 (95% CI: 0.07, 526.4)]** and Hispanic **[β: 92.1 (95% CI: 11.5, 172.7)]** groups. Association with birthweight z-score significant in male infants; **[β: 0.142 (95% CI: 0.001, 0.283)]** and non-Hispanic Black group **β: 0.26 (95% CI: 0.03, 0.49)]** Association with LGA significant in Hispanic group [**OR: 1.96 (95% CI: 1.11, 3.45)].** TM3 BPS, per 1-unit increase: Birthweight, β: -44.59 (95% CI: -97.21, 8.03) Birthweight z-score, β: -0.10 (95% CI: -0.22,0.01) Birth length, β: -0.21 (95% CI: -0.49, 0.08) Gestational age, β: -0.03 (95% CI: -0.19, 0.14) Preterm, OR: 0.90 (95% CI: 0.53, 1.52) **SGA, OR: 1.52 (95% CI: 1.08, 2.13)** LGA, OR: 0.80 (95% CI: 0.51, 1.27) **Low birthweight, OR: 1.77 (95% CI: 1.07, 2.93)** Association with SGA [**OR: 1.7 (95% CI: 1.02, 2.82)]** and low birthweight [**OR: 3.2 (95% CI: 1.26, 8.12)]** significant in males. Association with SGA significant in non-Hispanic White group [**OR: 2.48 (95% CI: 1.42, 4.32)].**		

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
Wan et al. 2018 Wuhan, China 2012–2014 Cross-sectional study design with participants selected from a prospective birth cohort (Healthy Baby Cohort) n = 985 Mean (SD) maternal age in years: 28.8 (3.7) Inclusion criteria: singleton birth, no birth defect.	Urine spot samples Adjusted for SG LOQ: 0.02 (LOD not reported) % < LOD: 6.3 Values below the LOQ were calculated as LOQ÷√2. GM: 0.17 Percentiles: 25th: 0.07 75th: 0.42 95th: 1.77 Timing of samples: Delivery encounter (32–42 weeks)	Gestation length (days), Preterm delivery (< 37 weeks gestation), Late term delivery (41-42 weeks), birthweight (g), SGA, birth length (cm)	Continuous BPS, per 1-unit increase ln BPS: **Gestation length, β: 0.66 (95% CI: 0.29, 1.04), p < 0.01** No associations with birthweight, birth length, preterm delivery, later term delivery, SGA. No evidence of interaction with infant sex for any outcome. BPS Quartiles: Estimates shown graphically. **Gestation length, Q3 and Q4 vs. Q1 associated with longer gestation length.** No associations between BPS quartiles and birthweight or birth length.	Models adjusted for: maternal age, education, infant sex, pre-pregnancy BMI, parity, passive smoking, gestational age (in birthweight and birth length models), BPA. Effect modification examined: infant sex. Other bisphenols measured: BPA.	BPA associated with lower gestational days for both sexes. Correlations between BPS and other bisphenols: BPA (ρ = -0.10). Mutual adjustment for BPA "did not change the main results."

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
J Wang et al. 2021 Wuhan, China 2013–2016 Prospective birth cohort Wuhan Twin Birth Cohort n = 289 twin pairs Mean (SD) maternal age in years: 30.06 (3.70) Inclusion criteria: Seeking prenatal care < 16 weeks gestation, lived in Wuhan more than 1-year, live births, twin pregnancy, no birth defect, no smoking or alcohol during pregnancy.	Morning urine samples Adjusted for SG LOD: 0.05 % < LOD: All samples: 21.5, TM1: 17.6, TM2: 21.8, TM3: 24.9 Values below the LOD were calculated as LOD÷√2. GM (95% CI): All samples: 0.27 (0.24, 0.29), TM1: 0.28 (0.24, 0.32), TM2: 0.26 (0.21, 0.30), TM3: 0.27 (0.23, 0.32) Percentiles (all samples, TM1, TM2, TM3): 25th: 0.09, 0.09, 0.09, 0.09 50th: 0.29, 0.29, 0.24, 0.30 75th: 0.73, 0.71, 0.80, 0.72 Timing of samples: TM1: 12–16 weeks TM2: 20–28 weeks TM3: 28–42 weeks	Birth length (cm) and weight (g) differences between and within twins	Within-twin pair differences: No associations with within twin differences in birthweight or length. Between-twin pair differences (supplementary materials): TM1 BPS tertiles (< 0.12, 0.12-0.48, > 0.48) No associations with birthweight TM2 BPS tertiles (< 0.12, 0.12-0.48, > 0.48) Associations with birthweight: **T2 vs. T1, β: 108.93 (95% CI: 46.82, 171.05)** **T3 vs. T1, β: 65.55 (95% CI: 4.39, 126.71)** ***P* trend: 0.03** TM3 BPS tertiles (< 0.12, 0.12-0.48, > 0.48) Associations with birthweight: **T2 vs. T1, β: 117.33 (95% CI: 53.65, 181.01)** T3 vs. T1, β: 49.46 (95% CI: -12.32, 111.24) *P* trend: 0.13 No association with birth length in any model.	Models adjusted for: maternal age, pre-pregnancy BMI, gestational age, household income, maternal folic acid supplementation, education, and passive smoking. Other bisphenols measured: BPA and BPF.	BPA levels were positively associated with birthweight and birth length differences across pregnancy trimesters based on within and between twin pairs; TM3 BPF tertile 2 vs. 1 associated with lower birthweight and height. ICC for BPS: 0.41, "moderate reproducibility." Did not consider differences by sex within or between twin pairs. Correlations between BPS and other bisphenols: BPA (ρ = 0.09), BPF (ρ = 0.27).

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
Yang et al. 2021 Wuhan and Xiaogan, China 2011–2013 Cross-sectional study design with participants selected from a prospective birth cohort n = 1197 Mean (SD) maternal age in years: 28.49 (4.70) Inclusion criteria: Singleton, over 18 years, resided in study areas over 1 year.	Urine spot samples Adjusted for creatinine LOD: 0.03 % < LOD: 52.1 Values below the LOD were calculated as LOD÷√2. Mean: 0.40 Median: < LOD Timing of samples: Delivery encounter (35–47 weeks)	Birthweight (g), birth length (cm), gestational age (weeks), ponderal index (kg/m^3 x 100), low birthweight < 2,500 g, and preterm birth < 37 weeks	BPS 3-level variable (low: < LOD, middle: LOD-0.16 ng/mL, high: > 0.16 ng/mL): Gestational age: Middle vs. low, β: -0.11 (95% CI: -0.25, 0.04) **High vs. Low, β: -0.23 (95% CI: -0.37, -0.09)** ***P* trend: 0.01** No significant associations with birthweight, birth length, ponderal index, low birthweight, or preterm birth. By infant sex: Gestational age for female infants: **Middle vs. low, β: -0.32 (95% CI: -0.53, -0.11)** **High vs. low, β: -0.46 (95% CI: -0.66, -0.25)** ***P* trend: < 0.01** Gestational age for male infants: Middle vs. low, β: 0.06 (95% CI: -0.13, 0.25) High vs. low, β: -0.07 (95% CI: -0.26, 0.13) *P* trend 0.63 Marginally significant association between BPS and higher ponderal index in boys (*P* trend: 0.07), but not girls (*P* trend: 0.43). Restricted cubic spline: no evidence of non-linear association with gestational age **(p-overall = 0.04**, p-nonlinear = 0.92)**.** For males: p-overall = 0.99. **For females: p-overall = 0.01.** Contribution of BPS to BKMR model mixture not reported.	Models adjusted for: urinary creatinine, maternal age, pre-pregnancy BMI, gestational weight gain, parity, household income, study city, education, infant sex, and gestational age (in birthweight, birth length, and ponderal index models). Effect modification examined: infant sex. Other bisphenols measured: BPA and BPF. BKMR models used to estimate effects of BPS as part of a mixture of bisphenols.	BPA and BPF associated with decreased birth length for all infants and increased ponderal index for girls. BPA and BPF had a non-linear association with birth length. Odds ratios presented for low birthweight and preterm birth uninterpretable and outside plausible range (Supplementary Table 4). Specific estimates presented are for a sample restricted to deliveries between 37–42 weeks; consistent pattern to examination of all deliveries 35–47 weeks. Correlations between BPS and other bisphenols: not reported.

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
Zhang et al. 2021 Boston, MA 2005–2018 Prospective cohort study Environment and Reproductive Health (EARTH) Study n = 386; n =156, 123, and 131 for early, middle, and late pregnancy analyses Mean (SD) maternal age in years: 34.7 (3.9) Inclusion criteria: single or couple enrolled at fertility center, followed through pregnancy and delivery, singleton, enrolled preconception.	Urine spot samples Adjusted for SG LOD: 0.1 % < LOD: TM1: 27.6, TM2: 32.5, TM3: 21.4 Values below the LOD were calculated as LOD÷√2. GM: TM1: 0.35, TM2: 0.33, TM3: 0.39 Percentiles (TM1, TM2, TM3): 25th: 0.19, 0.16, 0.20 50th: 0.33, 0.28, 0.35 75th: 0.66, 0.58, 0.70 Timing of samples: TM1: 6 weeks TM2: 21 weeks TM3: 34 weeks	Preterm birth (< 37 weeks)	Continuous BPS, per 1-unit increase ln TM1 BPS: Risk ratio (RR): 1.25 (95% CI: 0.82, 1.89), p = 0.30 Continuous BPS, per 1-unit increase ln TM2 BPS: RR: 1.31 (95% CI: 0.46, 3.75), p = 0.61 Continuous BPS, per 1-unit increase ln TM3 BPS: RR: 0.63 (95% CI: 0.35, 1.14), p = 0.12	Models adjusted for: maternal age, pre-pregnancy BMI, maternal education, assisted reproductive technology, and ethnicity. Other bisphenols measured: BPA.	TM2 BPA exposure associated with increased risk of preterm birth driven by female fetus sex. Low numbers of BPS measurements impacted the analyses for this study. Smoking status not adjusted for in BPS models due to convergence issues. ICC for BPS: 0.16, "relatively low" reproducibility. Correlations between BPS and other bisphenols: not reported.

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
Zhou et al. 2020 Wuhan, China 2011–2012 Cross-sectional study design with participants selected from a prospective birth cohort n = 322 Mean (SD) maternal age in years: 28.7 (4.2) Inclusion criteria: Lived in Wuhan ≥ 1 year, ≥18 years old, singleton, and gave birth at study hospital.	Morning urine samples Adjusted for creatinine LOD: 0.03 % < LOD: 47.5 Values below the LOD were calculated as LOD÷√2. GM (creatinine adjusted): 0.08 µg/g <u>Percentiles (creatinine adjusted)</u>: 25th: 0.02 µg/g 50th: 0.04 µg/g 75th: 0.22 µg/g 90th: 1.17 µg/g <u>Timing of samples</u>: Late pregnancy: ≥ 35 weeks	Fetal growth measured in late pregnancy (≥ 35 weeks) by ultrasound: biparietal diameter (mm), head circumference (mm), femur length (mm), and abdominal circumference (mm)	<u>BPS tertiles (ranges not provided):</u> No associations with biparietal diameter, head circumference, abdominal circumference. Marginally significant association with longer femur length: Tertile 2 vs. 1, β: 0.70 (95% CI: -0.008, 1.41) Tertile 3 vs. 1, β: 0.23 (95% CI: -0.48, 0.93) Tertile 2 vs. 1 estimate was significant before mutual adjustment for other bisphenols (Figure 1, specific estimate not shown). No evidence of interaction by fetal sex.	Models adjusted for: creatinine, maternal age, maternal height, gestational age, weight gain during pregnancy, parity, infant's sex, education, household income, passive smoking, BPA, and BPF. Effect modification examined: fetal sex. Other bisphenols measured: BPA and BPF.	BPA had a weak positive association with fetal growth for all measured parameters; BPF in males was associated with longer femur length and smaller abdominal circumference. This sample is a subset of individuals included in Yang et al 2020, which looked at birthweight, length, ponderal index. Correlations between BPS and other bisphenols: BPA (ρ = 0.16), BPF (ρ = 0.15).

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
Zhu et al. 2023 Northern China 2010–2016 Case-control study (population based) n = 122 cases, n = 164 controls Maternal age: 41 % < 25, 31% 25-29, 28% ≥ 30 years. Inclusion criteria as stated by authors: "the case group was composed of fetuses from mothers whose labor was induced due to prenatal diagnosis of anencephaly, encephalocele, or spina bifida. The controls were infants without congenital malformations".	Placental samples Adjusted for SG LOD: 0.002 ng/g % < LOD: not reported Percentiles (cases / controls): 25th: 1.70, 1.70 ng/g 50th: 1.81, 1.83 ng/g 75th: 3.36, 3.40 ng/g Timing of samples: Placental samples at delivery or termination of neural tube defect-affected pregnancies	Neural tube defects	BPS, high vs. low (median cutoff): No association with neural tube defects: OR: 1.18 (95% CI: 0.48, 2.89) No evidence of significant interaction by fetal sex (p = 0.80) or folic acid supplementation (p = 0.82). Weighted quantiles sum mixture was associated with higher odds of neural tube defects [OR: 4.34 (95% CI: 1.69, 11.20)]. The contribution of BPS to the mixture was small (weight = 6.84%).	Models adjusted for: maternal age, BMI, gestation weeks at delivery, periconceptional use of folic acid, smoking during pregnancy, and history of birth defects. Other bisphenols measured: BPA, Bisphenol Z (BPZ), BPF, BPB, BPAF, Bisphenol P (BPP), Bisphenol AP (BPAP), fluorene-9-bisphenol and TBBPA. Effect modification examined: folic acid supplementation and fetal sex. Weighted quantiles sum regression to evaluate effects of the bisphenol mixture.	BPA and BPZ associated with increased risks for neural tube defects. Placental samples used. BPS not measured during critical period for malformations. Correlations between BPS and other bisphenols: positively correlated with BPB and negatively correlated with other bisphenols (exact ρ not reported).

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
Infant Growth					
Blaauwendraad et al. 2024 New York City, US 2016–2019 Prospective birth cohort New York University Children's Health and Environment Study (NYU CHES) n = 1091 n varied by outcome: weight (n = 1091), body mass index (BMI) (n = 672), triceps skin fold (n = 558), subscapular skinfold (n = 415). Mean maternal age (SD) in years: 31.8 (5.6) Inclusion criteria: 18 years or older, < 18 weeks gestation, fluent in English or Spanish, planned delivery at NYU hospital, bisphenols and phthalates measured at least once in pregnancy.	Urine spot samples Adjusted for creatinine LOD: not reported % < LOD: TM1: 18.5, TM2: 20.3, TM3: 18.6 Values below the LOD were calculated as LOD÷√2. <u>Percentiles (TM1, TM2, TM3):</u> 25th: 0.10, 0.11, 0.10 50th: 0.59, 0.62, 0.60 75th: 6.49, 6.33, 5.71 <u>Timing of samples:</u> TM1 10.8 (3.2) weeks TM2 20.7 (2.15) weeks TM3 29.2 (3.7) weeks	Child weight, height, triceps skinfold, and subscapular skinfold from birth to 4 years, analyzed as repeated measures. Outcome standardized to sex-specific z-scores. Growth patterns 0 to 2 years: growth deceleration, normal growth, growth acceleration	<u>Per unit increase in BPS, all time points:</u> Weight, β: 0.03 (95% CI: -0.02 to 0.08) BMI, β: 0.03 (95% CI: -0.05 to 0.11) Triceps skinfold, β: 0.04 (95% CI: -0.05 to 0.14) Subscapular skinfold, β: -0.08 (95% CI: -0.18 to 0.02) <u>Per unit increase in TM1 BPS:</u> Weight, β: -0.02 (95% CI: -0.06 to 0.02) BMI, β: -0.05 (95% CI: -0.12 to 0.02) Triceps skinfold, β: 0.05 (95% CI: -0.03 to 0.12) Subscapular skinfold, β: -0.04 (95% CI: -0.12 to 0.04) <u>Per unit increase in TM2 BPS:</u> Weight, β: 0.05 (95% CI: 0.00 to 0.09) BMI, β: 0.00 (95% CI: -0.07 to 0.08) Triceps skinfold, β: -0.01 (95% CI: -0.09 to 0.08) Subscapular skinfold, β: -0.05 (95% CI: -0.15 to 0.05) <u>Per unit increase in TM3 BPS:</u> Weight, β: 0.04 (95% CI: -0.01 to 0.08) BMI, β: 0.04 (95% CI: -0.02 to 0.11) Triceps skinfold, β: 0.01 (95% CI: -0.06 to 0.09) **Subscapular skinfold, β: -0.09 (95% CI: -0.18 to 0.00)** No associations were statistically significant with false discovery rate p-value adjustment. No associations when outcomes were analyzed by time point instead of as repeated measures. BPS was not associated with growth patterns.	Models adjusted for race, education, marital status, insurance, parity, body mass index, alcohol and tobacco use. Other bisphenols measured: BPA. Effect modification examined: child sex.	Correlations between BPS and other bisphenols: BPA (positive; specific estimate not reported). It is possible that BPS percentiles reported are the 5th, 50th, and 95th percentiles. Not specified in paper.

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
Y Chen et al. 2024 Shanghai, China 2012 Cohort study Shanghai Minhang Birth Cohort Study n = 537 Mean (SD) maternal age in years: 29.0 (3.4) Inclusion criteria: attending first prenatal care visit, no pregnancy complications, singleton, no abortion or still birth.	Urine spot samples Adjusted for creatinine LOD: 0.004 % < LOD: 75.4 Values below the LOD were calculated as LOD÷2. GM: 0.01 µg/g Percentiles (µg/g): 25th: 0.00 50th: 0.01 75th: 0.03 Timing of samples (median (25^{th}, 75^{th})): 32.1 (27.4, 37.3) weeks	Outcomes measured at 6 and 12 months. Sex- and age-specific weight z-scores and body mass index z-scores. Scapular skinfold thickness (SST, mm), abdominal skinfold thickness (ABST, mm), waist circumference (WC, cm), and arm circumference (cm). Rapid postnatal growth (weight z-score from birth to 6 or 12 months > 0.67) Overweight (BMI z-score at 6 or 12 months > 85^{th} percentile).	<u>BPS, detected vs. not detected:</u> <u>At 6 months:</u> BMI z-score, β: 0.36 (95% CI: -0.05, 0.77) Weight z-score, β: 0.16 (95% CI: -0.10, 0.42) **SST, β: 0.95 (95% CI: 0.31, 1.59)** **ABST, β: 0.87 (95% CI: 0.18, 1.57)** WC, β: 0.47 (95% CI: -0.23, 1.16) **Arm circumference, β: 0.40 (95% CI: 0.08, 0.72)** **Rapid growth in females, RR: 1.70 (95% CI: 1.17, 2.49)** Rapid growth in males, RR: 0.98 (95% CI: 0.70,1.38) Overweight in females, RR: 2.35 (95% CI: 0.90, 6.10) Overweight in males, RR: 1.16 (95% CI: 0.46, 2.94) <u>At 12 months:</u> BMI z-score, β: 0.10 (95% CI: -0.23, 0.44) Weight z-score, β: 0.06 (95% CI: -0.15, 0.26) SST, β: 0.49 (95% CI: -0.04,1.03) ABST, β: 0.32 (95% CI: -0.26, 0.90) WC, β: 0.20 (95% CI: -0.54, 0.94) AC, β: 0.28 (95% CI: -0.08, 0.63) **Rapid growth in females, RR: 1.91 (95% CI: 1.07, 3.42)** Rapid growth in males, RR: 1.29 (95% CI: 0.85,1.95). **Overweight in females, RR: 2.46 (95% CI: 1.13, 5.34)** Overweight in males, RR: 0.54 (95% CI: 0.21, 1.37) BKMR: IQR increase in BPS associated with larger WC and arm circumference at 6 months when other bisphenols held at their 25^{th}, 50^{th}, and 75^{th} percentiles in females.	Models adjusted for: maternal age at delivery, maternal pre-pregnancy BMI, parity, gestational age, maternal passive smoking during early pregnancy, maternal educational level, family income per capita. Effect modification examined: infant sex. Other bisphenols measured: BPA, BPF, BPAF, TCBPA. BKMR models used to estimate effects of BPS as part of a mixture of bisphenols.	There were 1225 live singletons born at delivery, but only 545 were selected for bisphenol measurements due to "limited funding." Correlations between BPS and other bisphenols: reported as range, r = 0.15–0.43). Study also appears in birth outcomes section with separate outcomes reported.

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
Colombini et al. 2025 Grenoble, France 2014–2017 Prospective cohort study Suivi de l'Exposition à la Pollution Atmosphérique durant la Grossesse et Effet sur la Santé (SEPAGES) cohort N = 484, n = 379 children with measurements at 3 years Maternal age: 29% ≥ 35 years. Inclusion criteria: < 19 weeks gestation, > 18 years of age, singleton, planning to give birth at one of the four maternity wards in study area.	Urine spot samples Three urine samples a day during seven consecutive days. Adjusted for SG (in model) LOD: 0.1 LOQ: 0.4 % < LOD: 73 (TM2), 73 (TM3) Values < LOD imputed by random values between 0–LOD and LOD–LOQ. Percentiles (TM2, TM3): 5th: 0.1, 0.1 50th: 0.1, 0.1 95th: 3.68, 2.76 Timing of samples: TM2: 16–19 weeks TM3: 32–35 weeks	Child fat free mass (kg), fat mass percent at 3 years	BPS categorized as <LOD (ref), LOD-LOQ, and > LOQ: TM2 BPS: **> LOQ: β =1.49 (95% CI: 0.65 to 2.32) p = < 0.01** LOD–LOQ: β = -1.08 (95% CI: -2.65 to 0.50) p = 0.18 TM3 BPS: > LOQ: β =0.12 (95% CI: -0.74 to 0.99]) p = 0.78 LOD–LOQ: β = 0.36 (95% CI: -1.2 to 1.93) p = 0.65 No evidence of effect modification by infant sex.	Models adjusted for: mother pre-pregnancy weight, mother height, mother age at conception, mother education, mother parity, father weight, father height, duration, breastfeeding, child history of passive smoking and child sex. Effect modification examined: infant sex. Other bisphenols measured: BPA	BPA was not significantly associated with child fat mass percentage at 3 years. Correlation between BPA and BPS was not reported.

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
X Li et al. 2024 Shenyang, China 2019–2020 Prospective cohort n = 113 43.4% with maternal age ≥ 30 years Inclusion criteria: maternal age >18 years, 37–42 weeks gestation, no stillborn births, no birth defects, no metabolic diseases.	Urine spot samples Adjusted for creatinine. LOQ: 0.1 LOD not reported. % < LOD: 53.98 Values below the LOQ were calculated as LOQ÷√2 GM: 0.12 µg/g Percentiles (µg/g): 25th: 0.07 50th: 0.31 75th: 0.57 Max: 15.34 Timing of samples: TM3	Weight at 6 and 12 months. 0 to 6 month, and 0-to-12-month growth rates.	BPS, ln-transformed continuous variable: At 6 months: Weight, β: 0.020 (95% CI: -0.164 to 0.205) Weight in boys, β: -0.115 (95% CI: −0.409 to 0.179) Weight in girls, β: 0.053 (95% CI: −0.170 to 0.276) 0-to-6-month growth rate, β: 0.009 (95% CI: −0.021 to 0.039) At 12 months: Weight, β: -0.146 (95% CI: -0.374 to 0.082) Weight in boys, β: -0.259 (95% CI: −0.638 to 0.120) Weight in girls, β: -0.052 (95% CI: −0.307 to 0.203) 6-to-12-month growth rate, β: −0.011 (95% CI: −0.032 to 0.011)	Models adjusted for maternal age, pre-pregnancy BMI, maternal weight gain during pregnancy and gestational age. Models for outcomes measured at 6 months also adjusted for exclusive breastfeeding from birth to 6 months. Effect modification examined: infant sex. Other bisphenols measured: BPA, BPF.	BPA and BPF were associated with faster 0 to 6 month growth rate. Correlations between BPS and other bisphenols: BPA (r = 0.443) and BPF (r = 0.263). Study also appears in birth outcome section with separate outcomes reported.

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
Lv et al. 2024 Wuhan, China 2013–2016 Prospective Cohort N = 1978 Mean (SD) maternal age in years: 28.4 (3.2) Inclusion criteria: residents of Wuhan planning to give birth at study hospital, singleton, volunteer to donate biological samples during prenatal period.	Urine spot samples Adjusted for SG LOD: 0.01–0.04 (exact LOD not reported) % < LOD: TM1: 15.1, TM2: 11.9, TM3: 10.2 GM: TM1: 0.59 , TM2: 0.55, TM: 0.67 Values below the LOD were calculated as LOD÷2 Percentiles (TM1, TM2, TM3): 25th: < LOD, < LOD, 0.23 50th: 0.53, 0.53, 0.53 75th: 2.42, 1.50, 2.12 Timing of samples: TM1: 13 ± 1.1 weeks TM2: 23.6 ± 3.2 weeks TM3: 35.9 ± 3.4 weeks	Offspring BMI z-score at 2 years.	BPS, ln-transformed continuous variable: **Average BPS, %Δ: 7.39 (95% CI: 0.35 to 14.42) p = 0.04** **TM1, %Δ 5.66 (95% CI: 0.26 to 11.06) p = 0.04** TM2, %Δ: 1.67 (95% CI: -4.95 to 8.29) TM3, %Δ: 2.87 (95% CI: -3.17 to 8.91) Mixture analyses: WQS index was associated with increase in BMI z-score, with BPS listed as a dominant contributor. BKMR model also showed positive trend between chemical mixture and BMI z-score.	Models adjusted for: maternal age, pre-pregnancy BMI, parity, maternal education, gestational age, infant sex, household income, breastfeeding, and passive smoking during pregnancy duration. Other bisphenols measured: BPA, BPAF WQS regression and BKMR analyses were run to examine mixture of 16 endocrine disrupting chemicals.	Neither BPA nor BPAF were associated with BMI z-score at 2 years. ICC (95% CI) for BPS: 0.01 (0.00, 0.84). Correlations between BPS and other bisphenols: BPA (r = 0.12–0.17), BPAF (r = 0.04–0.32).

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
Ouidir et al. 2024 Grenoble, France 2014–2017 Prospective birth cohort Suivi de l'Exposition à la Pollution Atmosphérique durant la Grossesse et Effet sur la Santé (SEPAGES) cohort n = 364 Mean (25^{th}, 75^{th}) maternal age in years: 32.3 (30.0, 35.2) Inclusion criteria: < 18 weeks gestation, 18 years of age, singleton, enrolled in French social security system, speak and write French, plan to give birth in Grenoble urban areas, plan to live in area for 2 years.	3 urine samples per day (morning, midday, evening) during 7 consecutive days, pooled. Adjusted for SG LOD: 0.10 LOQ: 0.40 % <LOD: 72.3 (TM2), 72 (TM3) Values below the LOD were calculated as LOD÷√2. <u>Percentiles (TM2, TM3):</u> 5^{th}: 0.10, 0.10 50^{th}: 0.10, 0.10 95^{th}: 2.86, 2.76 <u>Timing of samples:</u> Median (25^{th}, 75^{th}) TM2: 18 (16, 19) weeks, TM3: 34 (32, 35) weeks.	Weight, height, and head circumference measured at birth, 2, 12, and 36 months. Jenss-Bayley growth model was used to estimate predicted weight, height, head circumference, and BMI at 3 and 36 months.	<u>3-level BPS, < LOD, LOD to LOQ, > LOQ</u> TM2 BPS > LOQ associated with higher BMI at 3 months **(β: 0.41 kg/m^2 (95% CI: 0.11 to 0.70)** and at 36 months (**β: 0.29 kg/m^2 (95% CI: 0.01 to 0.56)**, and with higher weight and height at both 3 and 36 months (p-values ranged from 0.001 to 0.05) [values not reported]. A similar association was observed with TM3 BPS and predicted BMI, weight, and head circumference at 3 months (p-values ranged from 0.02 to 0.08) [values not reported]. <u>BKMR models:</u> Prenatal mixture of exposures was not associated with infant growth.	Models adjusted for: maternal age, maternal pre-pregnancy weight, maternal pre-pregnancy height, parity, breastfeeding status, maternal education, child sex, infant history of passive smoking. Effect modification examined: child sex. Other bisphenols measured: BPA, BPAF, BPB, BPF. Principal component analysis and BMKR models used to estimate effects of BPS as part of a mixture of bisphenols.	BPAF, BPB, BPF excluded from analysis due to quantification < 5%. Correlations between BPS and other bisphenols: positive correlation with BPA (specific estimates not reported).

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
Stevens et al. 2023 Denver, Colorado, USA 2009–2014 Prospective birth cohort Healthy Start Cohort n = 438 Mean (SD) maternal age in years: 28.1 (6.1) Included: ≥ 16 years of age, singleton, < 24 weeks gestation, attending obstetric university clinic Excluded: history of stillbirth or extremely preterm, had diabetes, asthma treated with steroids, cancer, or medication-dependent psychiatric illness.	Urine spot samples Adjusted for creatinine LOD: 0.1 % < LOD: 13 Values below the LOD were imputed as the instrument value when possible, or else calculated as ½ the minimum reported value. <u>Percentiles:</u> 25th: 0.2 50th: 0.3 75th: 0.6 <u>Timing of samples:</u> Second study visit: median (25th, 75th) = 27 (25, 29) weeks.	Infant size and body composition: weight, fat mass %, and lean mass (in grams), and fat and lean mass indices (kg/m^2) at 72 hours after delivery and 5 months; Secondary outcome: rapid infant growth from delivery to 5 months.	<u>Continuous BPS, per 1-unit increase in ln BPS:</u> At five months: Weight, β*:* -18 (95% CI: -110, 75) p = 0.70 Fat mass %, β*:* -0.22 (95% CI: -0.82, 0.38) p = 0.48 Fat mass, β*:* -21 (95% CI: -77, 35) p = 0.45 Lean mass, β*:* 2.9 (95% CI: -61, 67) p = 0.93 No associations with rapid growth through 5 months. No evidence of interaction by infant sex. Phenol mixture not associated with body composition at five months. Phenol and phthalate mixture associated with lower fat mass percentage and fat mass at five months.	Models adjusted for: age, race and ethnicity, pre-pregnancy BMI category, highest education level completed, any previous pregnancies, smoking during pregnancy, gestational age at biological sample collection, infant sex, diet during pregnancy, physical activity during pregnancy, and gestational weight gain. 5-month models additionally adjusted for infant age Effect modification examined: sex Other bisphenols measured: BPA Quantile g-computation used to estimate effects of BPS as part of a mixture of chemicals (phenol mixture and phenol + phthalates mixture).	ICC for BPS: 0.25. Correlation between BPS and BPA (ρ = -0.36). Study was also summarized in birth outcome section.

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
Xiong et al. 2023a Wuhan, Hubei Province, China 2013–2015 Prospective cohort study Wuhan Healthy Baby Cohort n = 826 Maternal age: 7.0% < 25 years, 86.9% 24-34 years, 6.1% ≥ 35 years Inclusion criteria: living in Wuhan for > 2 years, < 16 weeks gestation, singleton pregnancy, planned to receive prenatal care and deliver at current hospital. Additional inclusion criteria for this analysis: full term (37–41 weeks), normal birthweight (2500–4000 g), no congenital disability, attended at least four of eight follow-up visits.	Urine spot samples Adjusted for SG Total concentrations (free and conjugated) measured. LOD: 0.04 % < LOD: TM1: 15.3(, TM2: 13.1, TM3: 12 Values below the LOD were calculated as LOD÷2 GM ± GSD: 0.55 ± 4.4 (TM1), 0.52 ± 3.9 (TM2), 0.55 ± 4.0 (TM3) <u>Percentiles (TM1, TM2, TM3):</u> 25th: 0.12, 0.15, 0.15 50th: 0.35, 0.41, 0.39 75th: 1.11, 1.18, 1.10 <u>Timing of samples</u>: TM1: 12–16 weeks TM2: 22–26 weeks TM3: 32–36 weeks	BMI growth trajectory within first 2 years estimated from BMI-for-age z-scores measured at 0, 1, 3, 6, 8, 12, 18, and 24 months. Categories included: 'low-stable', 'low-increasing', 'moderate-stable' (reference category), and 'moderate-increasing.'	<u>TM1 BPS, quartiles:</u> Higher odds of having a 'low-increasing' versus a 'moderate-stable' growth trajectory: **Q2 vs. Q1, OR: 1.88 (95% CI: 1.01, 3.53)** Q3 vs. Q1, OR: 1.76 (95% CI: 0.93, 3.35) Q4 vs. Q1, OR: 1.47 (95% CI: 0.74, 2.92) No significant associations for other growth trajectories. No significant associations with TM2 or TM3 BPS. <u>Average BPS, quartiles:</u> Higher odds of having a 'moderate-increasing' versus a 'moderate-stable' growth trajectory: **Q2 vs. Q1 OR: 2.17 (95% CI: 1.31, 3.59)** Q3 vs. Q1 OR: 1.19 (95% CI: 0.70, 2.02) Q4 vs. Q1 OR: 1.14 (95% CI: 0.67, 1.95) No significant associations for other growth trajectories. No evidence of effect modification by infant sex. Significant associations in girls: Higher odds of having a 'moderate increasing' trajectory: **Q2 vs. Q1, OR 2.46 95% CI (1.13, 5.38)** Significant associations in boys: Higher odds of having a 'moderate increasing' trajectory: **Q2 vs. Q1, OR 2.11 95% CI (1.05, 4.24)**	Models adjusted for: maternal age, education, second-hand smoke exposure during pregnancy, pre-pregnancy BMI, parity, cesarean section, infant sex, gestational age, feeding patterns within six months of age, BPA, and BPF. Effect modification examined: infant sex Other bisphenols measured: BPA, BPF	BPA in TM2 and BPF in TM3 associated with an increased likelihood of the 'low-increasing' trajectory pattern. ICC (95% CI) for BPS: 0.31 (0.22, 0.39) Correlations between BPS and other bisphenols: BPA (ρ = 0.16), BPF (ρ = 0.26).

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
Neurodevelopmental Outcomes					
Bornehag et al. 2021 Värmland county, Sweden 2007–2010 Prospective birth cohort Swedish Environmental Longitudinal Mother and Child, Asthma and Allergy (SELMA) Study n = 803 Mean (SD) maternal age in years: 31.4 (4.7) Inclusion criteria: singleton, TM1 prenatal care clinic, resident in county.	First morning void urine samples Adjusted for creatinine LOD: 0.03 % < LOD: 2.6 Reported (measured) concentrations were used for values below LOD. GM (95% CI): 0.07 (0.06, 0.07) Percentiles: 25th: 0.04 50th: 0.07 75th: 0.12 Max: 5.13 Timing of samples: Median: 10 weeks	Cognitive function of children at 7 years measured by the Wechsler Intelligence Scale for Children IV (WISC-IV). Full Scale intelligence quotient (IQ) and four subscales: verbal comprehension, perceptual reasoning, working memory, processing speed.	Continuous BPS, per 1-unit increase ln TM1 BPS: Working memory β: -1.76 (95% CI: -3.85, 0.33), p = 0.10 No associations with full scale IQ, verbal comprehension, perceptual reasoning, processing speed (estimates were around the null value). Tertiles analysis of BPS showed similar results. No evidence of effect modification by sex for any outcome.	Models adjusted for: child sex, maternal age, education, IQ, weight, and smoking. Effect modification examined: child sex. Other bisphenols measured: BPA and BPF.	The authors stated: "Prenatal BPF exposure was associated with decreased full-scale IQ, as well as with a decrease in all four sub scales covering verbal comprehension, perceptual reasoning, working memory and processing speed". Results for BPF were highlighted in males rather than females. Correlations between BPS and other bisphenols: BPA (r = 0.18), BPF (r = 0.10).

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
Chen et al. 2023 Shanghai, China 2012 Prospective birth cohort Shanghai-Minhang Birth Cohort Study n = 1225 births in cohort, n = 561 at age six follow-up, n = 424 included in analysis. Mean maternal age (SD): 29.1 (3.3) Inclusion criteria: Pregnant women recruited at first prenatal care visit, singleton, receiving care at the Minhang Maternal and Child Health Hospital in Shanghai.	Urine spot samples Adjusted for creatinine LOD: 0.004 % < LOD: 76.4 Values below the LOD were calculated as LOD÷2. GM: < LOD <u>Percentiles (creatinine corrected)</u>: 25th: 0.00 µg/g 50th: 0.01 µg/g 75th: 0.02 µg/g <u>Timing of samples:</u> TM3 (range 27.4–37.3 weeks)	Children's cognitive function with the Wechsler Intelligence Scale for Children, Fourth Edition (C-WISC-IV) at age 6. Scales: full scale IQ, perceptual reasoning index, verbal comprehension index.	<u>BPS, detected vs. not detected:</u> No associations with full scale IQ, perceptual reasoning index, or verbal comprehension index. No evidence of effect modification by child sex. Quantile g-computation models: mixture associated with lower full-scale IQ and lower verbal comprehension index in boys. BPA and BPF "contributed most of the negative associations." BKMR models: No significant single-exposure effect for BPS. PIP for BPS ranged from 0.13 to 0.40 across models.	Models adjusted for: maternal educational levels, pre-pregnancy BMI, parity, passive smoking during early pregnancy, age at delivery, gestational weeks, non-verbal IQ, paternal educational levels, household income, and Home Observation for Measurement of the Environment score. Effect modification examined: child sex. Other bisphenols measured: BPA, BPF, BPAF, and TCBPA. BKMR models and quantile g-computation used to estimate effects of BPS as part of a mixture of bisphenols.	BPA and BPF associated with decreased IQ scores in boys, while TCBPA associated with increased IQ scores in boys. BPA and TCBPA associated with increased IQ scores in girls. Low BPS variability among subgroup with detectable BPS. Correlations between BPS and other bisphenols: BPA (ρ = 0.18), BPF (ρ = 0.28), BPAF (ρ = 0.18), TCBPA (ρ = 0.03).

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
England-Mason et al. 2021 Alberta, Canada 2009–2012 Prospective birth cohort Alberta Pregnancy Outcomes and Nutrition (APrON) Cohort n = 310 Mean (SD) maternal age in years: 32.2 (3.7) Inclusion criteria: maternal age > 16 years, < 27 weeks gestation, living in Calgary or Edmonton, breastfeeding during postnatal period, completed Behavior Rating Inventory of Executive Function-Preschool Version (BRIEF-P) tests when child was 2-4 years, had not been diagnosed with a neurological or neurodevelopmental disorder.	Urine spot samples Adjusted for creatinine LOD: 0.10 % < LOD: 39.0 Values below the LOD were calculated as LOD÷√2. GM: 0.22 µg/g <u>Percentiles (creatinine adjusted):</u> Maximum: 23.18 µg/g <u>Timing of samples</u>: TM2 (17.0 ± 2.1 weeks)	BRIEF-P measured as standardized T scores of inhibitory self-control, flexibility, and emergent metacognition for children 2 and 4 years of age	No significant results for BPS and executive function. No evidence of interaction by sex.	Models adjusted for: ethnicity, education, marital status, household income, mother's age, body weight/height, alcohol and tobacco use, physical/mental illnesses, infant feeding habits (i.e., breastfeeding status, breastfeeding frequency, formula use frequency), and birth outcomes such as birthweight, gestational age, and sex. Effect modification examined: child sex. Other bisphenols measured: BPA.	The authors stated: "Higher maternal postnatal BPA concentrations predicted increasing difficulties from age 2 to 4 in the domains of inhibitory self-control and emergent metacognition in female, but not male children." BPS also measured 3 months post-partum (2.7 ± 0.6 months). Correlations between BPS and other bisphenols: not reported.

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
Geiger et al. 2023 2010–2012 Champaign-Urbana, Illinois Prospective birth cohort Illinois Kids Development Study (IKIDS) n = 157 women enrolled, n = 68 analyzed Mean (SD) maternal age in years: 29.7 (3.0) Inclusion criteria: enrolled 16-19 weeks gestation, 18-40 years of age, fluent in English, singleton, living near clinic within 1 year of birth, term delivery, no chronic medical conditions, no medically complex pregnancies.	First-morning and spot urine samples Adjusted for SG LOD: 0.1 % < LOD: 0.7 Values below the LOD were given instrumental-reading values, no imputation. Mean ± SD: 0.4 ± 0.5 <u>Percentiles:</u> Min: 0.1 50th: 0.3 Max: 3.5 <u>Timing of samples</u>: Pooled urine samples from five time points during pregnancy: two first--morning samples at 16–19 weeks and 34–38 weeks gestation and three spot samples collected at prenatal visits occurring at 19-34 weeks	Child Behavior Checklist (CBCL) preschool version at 26-28 months of age. Subscales: internalizing (reactivity, anxious/depression, somatic complaints, and withdrawing) and externalizing (attention issues, aggressiveness) behaviors and sleep problems. Syndrome scale outcomes were modeled as %Δ.	<u>Continuous BPS, per 1-unit increase BPS:</u> Internalizing behaviors, β: 1.6 (95% CI: -2.5, 5.8), p = 0.43 Externalizing behaviors, β: 1.4 (95% CI: -6.7, 4.0), p = 0.61 Marginally significant interaction by child sex for internalizing behaviors (p-interaction = 0.06). Among females: **Internalizing behaviors,** **β: 14.0 points (95% CI: 2.2, 25.8) p = 0.02** **Emotionally reactive problem scale,** **β: 3.92 %Δ (95% CI: 1.16, 13.27), *p* =0.03** Among males: Internalizing behaviors, β: 1.6 points (95% CI: -2.5, 5.8), p = 0.43 Emotionally reactive problem scale, β: 1.4 %Δ (95% CI: 0.86, 2.15) No child sex* BPS interaction for externalizing behaviors Significant interaction by child sex for anxious-depressed scale (stratified estimates not presented). No evidence of a non-linear relationship for any outcome.	Models adjusted for: child sex, number of siblings, maternal age, child age at time of outcome measurement. Effect modification examined: child sex. Other bisphenols measured: BPA.	BPA was associated with scores on syndrome scales of anxious-depressed, aggressive, and sleep problems modified by sex. Notable loss to follow-up, 81 individuals removed from analytic file because of missing CBCL data; mean BPS in excluded sample higher than in analytic sample (1.0, SD 4.7). Correlations between BPS and other bisphenols: "weakly correlated" (ρ = 0.15).

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
Jiang et al. 2020 Wuhan, China 2014–2015 Prospective birth cohort n= 456 Maternal age: 78.9% 25-34 years 14.7% < 25 years 6.4% ≥ 35 years. Inclusion criteria: Comprehended Chinese language, < 16 weeks gestation, plans to delivery at study hospital, singleton, no maternal smoking, term delivery.	Urine spot samples Adjusted for SG LOD: 0.2 % < LOD: TM1: 18.2, TM2: 14.7, TM3: 11.8 Values below the LOD were calculated as LOD÷√2. Percentiles (averaged, TM1, TM2, TM3): 25th: all < LOD 50th: 0.37, 0.34, 0.42, 0.39 75th: 0.89, 1.18, 1.20, 1.11 Timing of samples: TM1 TM2 TM3	Bayley Scales of Infant Development at 24 months of age. Subscores for mental development index (MDI) and psychomotor development index (PDI) age-standardized	Continuous Averaged BPS, per 1-unit increase ln BPS: PDI β: – 2.56 (95% CI: -5.30, 0.19), p = 0.07 MDI β: 0.80 (95% CI: -2.68, 4.28), p = 0.65 Averaged BPS Quartiles: Q4 vs. Q1, PDI **β: -5.52 (95% CI: -10.06, -0.99), p = 0.02** Q3 vs. Q1, PDI β: -2.92 (95% CI: -7.49, 1.64), p = 0.21 Q2 vs. Q1, PDI β: -0.75 (95% CI: -5.28, 3.79), p = 0.75 ***P* trend: 0.01** No significant associations between BPS quartiles and MDI scores. No evidence of interaction by child sex. Statistically significant interaction by trimester for **MDI (p = 0.04)** but not for PDI (p = 0.27). By trimester (per 1-unit increase in ln BPS): **TM1: MDI β: 2.88 (95% CI: 0.27, 5.50), p = 0.03** TM2: MDI β: -0.34 (95% CI: -3.17, 2.50), p = 0.82 TM3: MDI β: -1.51 (95% CI: -4.37, 1.35), p = 0.30 Quartile analyses by trimester showed similar results. Statistically significant estimates were: **TM1:** **Q3 vs. Q1, MDI β: 6.98 (95% CI: 1.23, 12.73), p = 0.02** **TM3:** **Q3 vs. Q1, PDI β: −4.8 (95% CI: −9.3, −0.2), p = 0.04** **Q4 vs. Q1, PDI β: −4.9 (95% CI: −9.4, −0.4), p = 0.03**	Models adjusted for: maternal age, pre-pregnancy BMI, maternal education, passive smoking, gestational age, child sex, and breastfeeding duration. Effect modification examined: trimester of exposure, infant sex. Other bisphenols measured: BPA and BPF.	TM2 BPA was associated with lower MDI scores. Averaged BPA exposure was associated with lower PDI scores for infant boys. ICC (95% CI) for BPS: 0.44 (0.39, 0.50), "fair reproducibility." Correlations between BPS and other bisphenols: BPA (ρ = 0.14), BPF (ρ = 0.21).

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
Lei et al. 2024 2013–2016 Shanghai, China Prospective birth cohort Shanghai Birth Cohort n = 600 Mean (SD) maternal age in years: 28.6 (3.8) Inclusion criteria: singleton, live birth, phenols measured in early pregnancy, participated in 4-year follow-up.	Urine spot sample Adjusted for creatinine LOD: 0.003 % < LOD: 23.5 Values below the LOD were calculated as LOD÷√2. <u>Percentiles:</u> 25th: 0.01 50th: 0.02 75th: 0.08 Max: 6.59 <u>Timing of samples:</u> TM1, < 16 weeks	Behavioral problems measured by Strengths and Difficulties Questionnaire at age 4. Subscales: hyperactivity or inattention, conduct problems, emotional problems, peer problems.	<u>Associations per unit increase in BPS:</u> <u>Behavioral problems analyzed as continuous scores:</u> Hyperactivity/inattention, β: 0.12 (95% CI: -0.01 to 0.25) Conduct problems, β: 0.03 (95% CI: -0.04 to 0.10) Emotional problems, β: 0.06 (95% CI: -0.03, 0.16) Peer problems, β: 0.01 (95% CI: -0.08, 0.09) No evidence of effect modification by child sex. <u>Behavioral problems analyzed as binary variables:</u> Hyperactivity/inattention, OR: 1.15 (95% CI: 1.00 to 1.32) Conduct problems, OR: 1.14 (95% CI: 0.99 to 1.32) **Emotional problems, OR: 1.16 (95% CI: 1.01 to 1.34)** Peer problems, OR: 0.96 (96% CI: 0.82 to 1.13) <u>Mixture:</u> Mixture was associated with worse emotional problems, hyperactivity/inattention and peer problems in boys, and worse peer problems in girls. BPS was the third most weighted chemical in the model for peer problems in girls.	Models adjusted for maternal age, pre-pregnancy BMI, maternal education level, economic status, maternal smoking during pregnancy, parity, and phenol by sex interaction. Alcohol use was not included as a covariate because only two women reported prenatal alcohol use. Effect modification: child sex. Other bisphenols measured: BPA, BPAF, BPAP, BPZ, BPB, BPP. Weighted quantile sum regression used to estimate effects of BPS as part of a mixture of phenols.	All false discovery rate adjusted p-values were > 0.05. Correlations between BPS and other bisphenols: BPA (ρ = 0.08), BPAP (ρ = -0.01), BPP (ρ = 0.01).

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
J Li et al. 2024 2015–2017 Guangxi, China Prospective cohort Guangxi Zhuang Birth Cohort n = 744 Maternal age: 27% ≤ 24 years 34.4% 25–20 years 23.7% 30–34 years 14.9% ≥ 35 years. Inclusion criteria: < 13 weeks gestation, singleton, Zhuang population (mother or father), planned to give birth in participating hospital, no birth defect. Exclusion criteria: no follow-up data, vision acuity out of measurement range.	Serum LOD: range 0.046–0.507 (as reported in paper, BPS LOD as 0.046 from Liang et al. 2020) % < LOD: 14.1 Values below the LOD were calculated as LOD÷√2. GM: 0.086 Percentiles: 25th: 0.096 50th: 0.096 75th: 0.104 95th: 0.183 Timing of samples: TM1	Vision acuity and visual impairment at ages 2–5.	Continuous BPS, per 1-unit increase ln BPS: Left eye visual acuity, β: 0.008 (95% CI: -0.021 to 0.037) Right eye visual acuity, β: 0.011 (95% CI -0.017 to 0.039) BPS tertiles: Visual impairment: Moderate vs. low BPS, OR: 1.17 (95% CI: 0.56 to 2.47) High vs. low BPS, OR: 0.85 (95% CI: 0.39 to 1.87) Stronger associations, though estimates were imprecise, with visual impairment among girls. BKMR models: Higher bisphenol mixture levels were associated with lower risk of visual impairment (PIP for BPS = 0.0838). BPS not associated with outcomes when other bisphenols were held at their 25th, 50th, or 75th percentiles.	Models adjusted for: duration of breastfeeding, child age, child sex, house lighting condition, maternal folic acid supplement, illness in pregnancy, mode of delivery, outdoor exercise time, and passive smoking during pregnancy. Other bisphenols measured: BPA, BPB, BPF, TBBPA Effect modification: child sex BKMR and quantile g-computation models used to estimate effects of BPS as part of a mixture of bisphenols.	Tertile thresholds to define low, moderate, and high levels of BPS for visual impairment models were not defined. Low variability in BPS exposure. Correlations between BPS and other bisphenols: BPA (ρ = -0.20), BPF (ρ = 0.17), BPB (ρ = -0.03), TBBPA (ρ = 0.14).

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
Liu et al. 2021 2009–2012 Alberta, Canada Prospective birth cohort APrON study n = 394 Median (25^{th}, 75^{th}) maternal age in years: 31 (29, 34) years Inclusion criteria: before 18 weeks gestation, resided in Calgary, had TM2 urine samples, non-smokers or quitting smoking, no genetic disorder.	Urine spot samples Adjusted for creatinine LOD: 0.10 % < LOD: 42 Values below the LOD were calculated as LOD÷√2. GM: 0.23 µg/g Percentiles (creatinine adjusted): 25^{th}: < LOD 50^{th}: 0.20 µg/g 75th: 0.40 µg/g 95th: 1.6 µg/g Timing of samples (mean [SD]): 17 (1.7) weeks	Bayley Scales of Infant Development-III measured at age 2 in children. Subscales: cognitive language, motor, social emotional, adaptive behavior	Continuous BPS, per 1-unit increase ln BPS: BPS not associated with cognitive, language, motor, social emotional, or adaptive behavior scores. No evidence of effect modification by child sex Significant interaction with maternal selenium levels in motor score models **($p = 0.026$)** By maternal selenium levels: Selenium ≥ median: Motor scores, β: 0.72 (95% CI: -3.4, 4.8), p = 0.73 Selenium < median: Motor scores, β: -4.0 (95% CI: -8.2, 0.17), p = 0.06 No significant interaction with maternal cadmium or copper levels, and no significant interactions between selenium levels and BPS for other outcomes.	Models adjusted for: child sex, family income, ethnicity, maternal nutrients, heavy metals, and BPA. Effect modification examined: child sex, maternal selenium levels, maternal cadmium levels, maternal copper levels. Other bisphenols measured: BPA.	BPA was not associated with cognitive scores besides a significant interaction with child sex for social emotional problems. β coefficient for BPS and motor development was statistically significant in the model that included interaction terms, but not in the main effects model. Correlation between BPS and: BPA (ρ = 0.17).

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
Mustieles et al. 2023 Grenoble, France 2014–2017 Prospective cohort study Suivi de l'Exposition à la Pollution Atmosphérique durant la Grossesse et Effet sur la Santé (SEPAGES) cohort n = 406 Mean maternal ages (SD): 32.6 (3.9) Inclusion criteria: singleton pregnancy, < 19 weeks gestation, > 18 years of age, affiliated to French national security system, delivery in Grenoble maternity clinic.	Morning, midday, and evening urine samples (7-consecutive days) Adjusted for SG LOD: 0.10 LOQ: 0.40 % < LOD: TM2: 74% , TM3: 72% Values below the LOD were singly imputed by randomly selecting values between 0 and the LOD. <u>Percentiles (TM2, TM3)</u> 50th: < LOD, < LOD 75th: 0.21, 0.26 <u>Timing of samples:</u> TM2: median 17 weeks TM3: median 33 weeks	Child social behavior and autistic traits using the Social Responsiveness Scale, age 3. Five subscales: social awareness, social cognition, social communication, social motivation, and restricted interests and repetitive behaviors.	<u>TM2 BPS, detected vs. not detected:</u> Non-significant decreases in total score, and social cognition, social communication, and social motivation subscales. Non-significant increases in social awareness and restricted interests and repetitive behaviors subscales. <u>TM3 BPS, detected vs. not detected:</u> **Total score, β: 3.82 (95% CI: 0.94, 6.70), *p* = 0.01** **Social awareness, β: 0.89 (95% CI: 0.30, 1.48), *p* < 0.01** **Social cognition, β: 1.02 (95% CI: 0.30, 1.74), *p* = 0.01** **Social communication, β: 1.25 (95% CI: 0.15, 2.35), *p* = 0.03** Non-significant increases in social motivation and restricted interests and repetitive behaviors subscales. No evidence of effect modification by child sex. Phenol/phthalate chemical mixture: No associations between overall mixture at TM2 or TM3 and Social Responsiveness Scales.	Models adjusted for: maternal age, employment, breastfeeding, multivitamin intake, pre-pregnancy BMI, education, anxiety/depression score at TM3, active smoking, passive tobacco exposure, parity, mode of childcare, family environment, child sex, and child age at outcome evaluation. Effect modification examined: child sex. Other bisphenols measured: BPA, BPF, BPB, BPAF. Bayesian Weighted Quantile Sum Regression used to estimate effects of BPS as part of a mixture of phenols and phthalates.	Higher scores on Social Responsiveness Scale correspond to worse outcomes. Correlations between BPS and other bisphenols: not reported. Results from models without adjustment for employment, breastfeeding, and multivitamin intake were similar.

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
Rolland et al. 2025 Grenoble, France 2014–2017 Prospective cohort Suivi de l'Exposition à la Pollution Atmosphérique durant la Grossesse et Effet sur la Santé (SEPAGES) cohort N = 484, n = 151 participated in eye tracking experiment. Median (Q1, Q3) maternal age: 32.1 (30.0, 35.0) years. Inclusion criteria: less than 19 weeks pregnant, over 18 years old, fluent in French, affiliated with the national social security system, planning to deliver in area's maternity clinics, singleton pregnancy.	Urine samples Morning, midday, and evening samples (7-consecutive days) LOD: 0.1 LOQ: 0.4 % < LOD: TM2: 72, TM3: 70 Values below the LOD were imputed using distribution-based methods. <u>Percentiles (TM2, TM3):</u> 5th: < LOD, < LOD 50th: < LOD, < LOD 95th: 1.0, 1.0 <u>Timing of samples:</u> TM2 7-day average: 18 weeks TM3 7-day average: 34 weeks	Infant eye tracking at 24 months. Computed outcomes were: (1) mean fixation duration (milliseconds), (2) novelty preference (%), (3) percent time looking at the eyes (%), (4) mean reaction time (milliseconds)	<u>TM2 BPS, detected vs. not detected:</u> Fixation duration, β: 0.56 (95% CI: -4.24, 5.36) Novelty preference, β: -1.22 (95% CI: -12.87, 10.42) Looking at eyes, β: 23.18 (95% CI: -4.61, 50.97) **Reaction time, β: -16.04 (95% CI: -31.94, -0.14)** <u>TM3 BPS, detected vs. not detected:</u> Fixation duration, β: 3.23 (95% CI: -1.55, 8.01) Novelty preference, β: 0.69 (95% CI: -11.09,12.48) Looking at eyes, β: 8.29 (95% CI: -19.58,36.16) Reaction time, β: 1.56 (95% CI: -14.65,17.78) No evidence of effect modification by child sex.	Models adjusted for: maternal age, maternal tobacco consumption, maternal cognitive function, parity, maternal professional status, breastfeeding duration, child sex, experiment time of day. Covariates considered but not retained: maternal education, gestational age at birth, child age at assessment, maternal depression. Effect modification examined: child sex Other bisphenols measured: BPA	BPA was not associated with any outcome. Authors report that "the relatively limited sample size for the eye-tracking sub-study can be partly explained by a delayed setup (starting in September 2017)" Authors report that the negative association with reaction time is "a measure predictive of higher IQ scores shown to be shorter in children with [autism spectrum disorder] current literature is insufficient to draw firm conclusions" Correlation between BPS and BPA was not reported.

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
van den Dries et al. 2020 Rotterdam, Netherlands 2004–2006 Prospective birth cohort Generation R Study n = 2,083 mothers enrolled during pregnancy, n = 1,405 children followed up at 6 years of age, n = 1,282 analyzed Maternal age: 43% were 30–35 years. Inclusion criteria: resided in Rotterdam, Netherlands, pregnant with a delivery date between April 2002 and January 2006.	Urine spot samples Adjusted for creatinine LOD: 0.05 % < LOD: early pregnancy: 32.2, mid pregnancy: 70.2, late pregnancy:81.0 Values below the LOD were calculated as LOD÷√2. <u>Percentiles (early, mid, and late pregnancy):</u> 25th: 0, 0, 0 50th: 0.2, 0, 0 75th: 0.6, 0.1, 0 max: 28.4, 20.0, 46.7 <u>Timing of samples (median (range)):</u> early pregnancy: 13.3 (6.5-17.9) weeks, mid pregnancy: 20.4 (18.1-24.9) weeks, late pregnancy: 30.3 (27.4-34.5) weeks.	Children's nonverbal IQ at age 6 assessed by Mosaics and Categories subtests from the Snijders-Oomen Nonverbal Intelligence Test–Revised (SON-R)	No significant results between BPS and children's nonverbal IQ scores at age 6. No evidence of effect modification by sex.	Models adjusted for: maternal age, maternal nonverbal IQ, sex of child, age of the child at assessment, ethnicity, education, income, marital status, maternal alcohol consumption, BMI, parity, and smoking. Effect modification examined: child sex. Other bisphenols measured: BPA, BPZ, BPB, BPF, BPAF, BPAP, and BPP.	Multiple imputation for missing bisphenol concentrations (n = 13) and covariate data. Values below LOD were given the value of 0, perhaps due to rounding by the journal or authors. Analysis specific to BPS included as supplementary material; primary analyses examined associations with total bisphenol concentrations. Correlations between BPS and other bisphenols: not reported.

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
Woodbury et al. 2025 Puerto Rico and Illinois, US 2017–2019 Two prospective cohort studies from ECHO consortium: IKIDS and ECHO-PROTECT N = 217 Maternal age: 20.3% 18–25 years, 34.1% 26–30 years, 27.2% 31–34 years, 18.4% 35-42 years IKIDS eligibility criteria: no child already enrolled, 18–40 years of age, not a high risk pregnancy, singleton pregnancy, fluent in English, resided near university and planned to remain in area. PROTECT eligibility criteria: 18–40 years of age, < 20 weeks gestation, residence in study area, no oral contraceptive use in three months before pregnancy, no in-vitro fertilization, no major preexisting medical conditions. Additional eligibility criteria for this analysis: agreed to participate in ECHO, infant born ≥37 weeks gestation.	Urine samples Adjusted with SG LOD: 0.1 % < LOD: < 25%. Values below the LOD were assigned machine-read values or were calculated as LOD÷√2. <u>Percentiles (ECHO-PROTECT, IKIDS):</u> 50th (IQR): 0.53 (0.65), 0.40 (0.43). <u>Timing of samples:</u> IKIDS: first-morning samples at 10–14, 16–18, 22–24, 28–30, and 34–36 weeks. ECHO-PROTECT: 18 ± 2, 22 ± 2, and 26 ± 2 weeks.	Non-nutritive sucking in 1–8-week-old infants Outcomes computed were sucking burst duration (seconds), peak amplitude (cmH_20), intra-burst frequency (Hz), the number of suck cycles per burst, the number of suck cycles per minute, and bursts per minute.	<u>Averaged BPS levels:</u> NNS duration, β: 0.331 (95% CI: -0.272, 0.933) NNS frequency, β: -0.004 (95% CI: -0.044, 0.036) NNS amplitude, β: -0.426 (95% CI: -1.526, 0.674) NNS bursts/min, β: 0.068 (95% CI: -0.308, 0.444) NNS cycles/min, β: 2.110 (95% CI: -2.196, 6.416) NNS cycles/bursts. β: 0.637 (95% CI: -2.696, 3.970) Mixture: BPS did not strongly contribute to mixture for any outcome.	Models adjusted for: infant age at assessment and sex, and maternal age and education with study site included as a random intercept. Other bisphenols measured: BPA, BPF. BKMR and quantile g-computation models used to estimate effects of BPS as part of a mixture of phenols.	Non-nutritive sucking was used as a measure of early neurodevelopment and is thought to relate to "subsequent motor skills, balance, cognition, and language" Correlation between BPS and other bisphenols: BPA (ρ = 0.30), BPF (ρ = 0.08).

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
Zhou et al. 2025 South Africa 2012–2015 Prospective cohort South African Drakenstein Child Health Study N = 545 Maternal age mean (SD) in years: 27 (6.1) Inclusion criteria: 20–28 weeks gestation, born at Paarl Hospital, data available for all study variables.	Urine spot samples No mention of adjustment for dilution. LOD: 0.5 % < LOD: 61.1 Values below the LOD were calculated as LOD÷√2. <u>Percentiles:</u> 25th: 0.14 50th: 0.32 75th: 0.94 <u>Timing of samples:</u> TM2	Neurodevelop-ment at 2 years assessed by Bayley Scales of Infant and Toddler Development, third edition (BSID-III). Cognitive composite score.	<u>Continuous BPS, per unit increase:</u> No significant association between BPS and neurodevelopment score (exact estimate not reported) By prenatal tobacco exposure: BPS negatively associated with cognitive development among non-smokers (p-interaction = 0.07) By socioeconomic status (SES): Low SES, β: 0.92 (95% CI: -0.04, 1.87) **High SES, β: -1.57 (95% CI: -2.74, -0.41)** **P-interaction = < 0.01.** No evidence of effect modification by child sex, prenatal tobacco exposure, or ethnicity (Black African vs. Mixed Ancestry). Mixture models: BPS did not contribute significantly to mixtures, no evidence of non-linearity.	Models adjusted for: maternal HIV status, maternal age, ethnicity, prenatal tobacco exposure, child sex, and socioeconomic status quartile. Effect modification examined: prenatal tobacco exposure, child sex, socioeconomic status, ethnicity. BKMR models, weighted quantile sum regression, quantile-based g-computation, and unsupervised clustering used to examine BPS as a mixture of phenols. Other bisphenols measured: BPA	BPA was negatively associated with worse cognitive scores in males. Correlation between BPS and BPA: r = 0.28.

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
Immune function and related outcomes					
Abellan et al. 2022 1999–2010 Meta-analysis of data from 8 prospective cohorts across Europe (4 had measurements of BPS) n = 3,007, n ranged from 757 to 1806 by outcome Mean (SD) maternal age in years: 31.3 (4.5) Inclusion criteria: Varied from cohort to cohort.	Urine spot samples Adjusted for creatinine LOD: By study: 0.05, 0.05, 0.10, 0.33 % < LOD: 51 (overall) By study: 29%, 70%, 83%, 90%. Timing of samples: At least one urine sample over pregnancy, varied by cohort	Current presentation of asthma, wheeze and lung function at ages 7–11. Wheezing patterns from 1 to 11 years. Lung Function: forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), mid expiratory flow (25–75%)	BPS, detected vs. not detected: **Late wheeze, OR: 0.43, (95% CI: 0.19, 1.00)** **Persistent wheeze, OR: 0.56 (95% CI: 0.35, 0.90)** No associations with current asthma, early wheeze, wheeze in last year, or lung function parameters. No statistically significant interactions by sex.	Models adjust for: maternal age, education, pre-pregnancy BMI, smoking during pregnancy, child age, ethnicity, child's age and sex. Lung function models adjusted for the same covariates except child's age and sex. Effect modification examined: child's sex. Other bisphenols measured: BPA and BPF.	BPA was associated with higher odds of asthma and wheeze in girls. Meta-analysis of 4 cohorts, authors did not collect the data but were given individual participant data. Late wheezing pattern corresponds to wheezing > 4 years. Persistent wheezing pattern corresponds to wheezing ≤ 4 years and > 4 years. Correlations between BPS and other bisphenols: not reported.

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
Coiffier et al. 2023 Grenoble, France Suivi de l'Exposition à la Pollution Atmosphérique durant la Grossesse et Effet sur la Santé (SEPAGES) cohort 2014–2017 Prospective cohort n = 457, n ranged from 281 to 442 by outcome Mean (SD) maternal age in years: 32.5 (3.9) Inclusion criteria: < 19 gestational weeks, > 18 years old, singleton pregnancy, planning to give birth in study clinic (criteria pulled from cited reference, not included in publication).	Pooled urine samples, 3 samples/day for one week No report of adjustment for SG or creatinine. LOD: 0.1 % < LOD: 56.0 No mention of imputation for values < LOD. <u>Percentiles:</u> 25th: 0.51 50Th:1.28 75th: 2.35 <u>Timing of samples (median):</u> TM2: 18 weeks TM3: 34 weeks	Child lung function at 2 months and 3 years; Child respiratory outcomes at 3 years. Measurements: functional residual capacity (FRC), lung clearance index, resistance at various Hz; ratio of time to peak tidal expiratory flow to expiratory time, tidal volume (V_t). Self-reported: asthma, wheeze, bronchiolitis, and bronchitis	<u>BPS, detected vs. not detected:</u> **FRC, β: 4.71 (95% CI: 1.24, 8.18), *p* =0.01** **V_t, β: 1.43 (95% CI: 0.04, 2.82), *p* =0.04** No statistically significant associations with other lung function parameters. **Asthma, OR: 1.89 (95% CI: 1.05, 3.38), p = 0.03** **Bronchiolitis, OR: 1.56 (95% CI: 1.01, 2.38), p = 0.04** Wheeze, OR: 1.26 (95% CI: 0.82, 1.93), p = 0.29 Bronchitis, OR: 1.18 (95% CI: 0.73, 1.93), p = 0.50 No evidence of effect modification by child's sex	Models adjusted for: pre-pregnancy BMI, maternal age, education level, parental history of rhinitis, parity, season of urine sampling, passive smoking, breastfeeding at 2 months, child's sex, weight, and height. Effect modification examined: child sex. Other bisphenols measured: BPA, BPAF, BPB, BPF.	Very low measurement levels of other bisphenols besides BPA. BPS dichotomized and concentrations were not standardized because of low detection frequency. Authors stated multiple imputation by chained equations for missingness in covariates, results shown based on pooled imputed datasets. Correlations between BPS and other bisphenols: not reported. Main analyses examined clusters of exposure, not associations with single chemicals.

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
Gaylord et al. 2023 Prenatal clinics in San Francisco, CA, Rochester, NY, Seattle, WA, and Minneapolis, MN Started recruitment in 2010, and authors did not report end date Prospective birth cohort The Infant Development and Environment Study (TIDES) n = 501 Mean (SD) maternal age in years: any atopy: 30.4 (6.1), no atopy: 31.8 (5.1) Inclusion criteria: <13 weeks gestation, 18 years of age and older, English as primary language, planned to deliver at the study hospital and no adverse pregnancy risks.	Urine spot samples Adjusted for SG LOD: 0.08 % < LOD: TM1: 48, TM2: 43, TM3: 49 Values below the LOD were calculated as LOD÷√2 Percentiles (TM1, TM2, TM3): 25th: all < LOD 50th: 0.11, 0.13, 0.09 75th: 0.52, 0.58, 0.48 Timing of samples (median): TM1: 12 weeks TM2: 21 weeks TM3: 32 weeks	Childhood atopy via questionnaires: current wheeze, current asthma, ever asthma, and food allergies at age 6	BPS, detected vs. not detected: No associations with wheeze, ever asthma, current asthma, or food allergy By sex: For males: **Current asthma, OR: 1.65 (95% CI: 1.01, 2.69) p = 0.045** For females: Current asthma, OR: 0.76 (95% CI: 0.45, 1.30) By trimester among males: TM1: Current asthma, OR: 1.93 (95% CI: 0.73, 5.09) TM2: Current asthma, OR: 0.79 (95% CI: 0.19, 3.34) TM3: Current asthma, OR: 0.86 (95% CI: 0.28, 2.71)	Models adjusted for: history of parental atopy, maternal education, annual household income, pre-pregnancy BMI, maternal age at enrollment, urinary cotinine, child race/ethnicity, study center, time of urine collection, and BPA. Effect modification examined: child sex. Other bisphenols measured: BPA	Trimester BPA exposure associated with decreased odds of food allergies for females. TM2 BPA exposure associated with increased food allergies for males. Imputation over 50% of sample. Low stability of BPS across pregnancy: TM1 vs. TM2 ρ = 0.26, TM2 vs. TM3 ρ = 0.31, TM1 vs. TM3 ρ = 0.28. Correlations between BPS and other bisphenols: BPA in TM1 (ρ = 0.20), TM2 (ρ = 0.21), and TM3 (ρ = 0.11).

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
Karramass et al. 2023 2004–2005 Rotterdam, Netherlands Generation R Study Prospective cohort n = 1020, n = 761 for lung function and n = 907 for current asthma Mean (SD) maternal age in years: 31.1 (4.6) Inclusion criteria: mothers were ≤18 weeks gestation, living in Rotterdam, Netherlands, singleton pregnancy.	Urine spot samples Adjusted for creatinine LOD: 0.01 % < LOD: TM1: 31.1, TM2: 71.0, TM3: 80.5 Values below the LOD were calculated as LOD÷√2. <u>Percentiles (TM1, TM2, TM3):</u> 25th: 0.03, 0.03, < LOD 50th: 0.2. 0.03, < LOD 75th: 0.6, 0.1, < LOD <u>Timing of samples (median):</u> TM1: 12.9 weeks TM2: 20.4 weeks TM3: 30.2 weeks	Lung function at age 13 by spirometry: FVC, FEV1, Mid-expiratory Flow (25–75%); Forced Expiratory Flow after exhaling 75% of FVC, and reported asthma. Lung function outcomes analyzed as z-scores.	<u>Continuous average BPS, per IQR increase in BPS:</u> No associations with lung function outcomes or asthma. <u>Continuous TM1 BPS, per IQR increase in BPS:</u> No associations with lung function outcomes or asthma. <u>Continuous TM2 BPS, per IQR increase in BPS:</u> **FVC, β: -0.10 (95% CI: -0.19, -0.02)** **FEV1, β: -0.10 (95% CI: -0.18, -0.01)** Statistically significant interaction with child's sex for asthma (p-interaction = 0.019) <u>By child's sex:</u> For boys: **Average, Current asthma OR: 0.56 (95% CI: 0.32, 0.99)** TM1, Current asthma OR: 0.59 (95% CI: 0.33, 1.05) TM2, Current asthma OR: 0.71 (95% CI: 0.43, 1.18) For girls: **Average, Current asthma OR: 1.89 (95% CI: 1.09, 3.28)** TM1, Current asthma **OR: 2.09 (95% CI: 1.14, 3.84)** TM2, Current asthma OR: 1.21 (95% CI: 0.77, 1.91) Associations of BPS with respiratory outcomes were not significant after adjusting for multiple testing, though "effect sizes of these associations were larger than observed for the associations of other bisphenols…"	Models adjusted for: parity, ethnicity, education, folic acid use periconceptional, smoking during pregnancy, pre-pregnancy BMI and Diet Quality score. Effect modification examined: child sex. Other bisphenols measured: BPA and BPF. Quantile-based g-computation used to estimate joint effect of a mixture of bisphenols and phthalate metabolites.	TM3 measurements for BPS very low and not analyzed in models, TM2 imputation for almost 70% of samples. Authors stated multiple imputation by chained equations used for 10 covariates, results shown based on pooled imputed datasets. Exposure concentrations converted from nmol/L to ng/mL. Correlations between BPS and other bisphenols: BPA (r = 0.06, BPF (r =0.03) (cited (Blaauwendraad et al. 2022a)).

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
Kuraoka et al. 2024 2013–2014 Japan Japan Environment and Children's Study Prospective cohort n = 3513 Mean (SD) maternal age in years: 31.6 (4.8) Inclusion criteria: born at term (≥ 37 weeks), born after April 1, 2013, compete data and medical record transcripts from first trimester to 6 months, biospecimens collected at the first, second/third trimester, and delivery, birthweight ≥ 2500 grams, and no delivery complications.	Urine spot samples No report of adjustment for SG or creatinine. LOD: 0.18 % < LOD: 85.7 No reported imputation of values < LOD. Mean ± SD: 1.18 ± 4.42 <u>Percentiles:</u> 50th 0.39 <u>Timing of samples:</u> TM1	Asthma at age 4 measured by maternal report.	<u>BPS, detected vs. not detected:</u> Non-significant odds ratio > 1 (specific estimate not reported) <u>BPS, top 10% vs. remaining 90%:</u> OR: 1.28 (95% CI: 0.93 to 1.77) No evidence of effect modification by child sex.	Models adjusted for: gender, birth information, maternal smoking during pregnancy, paternal smoking during pregnancy, and maternal history of asthma. Effect modification examined: child sex. Other bisphenols measured: BPA, BPF, BPAF.	Sample was restricted to women with no delivery complications, term birth, and birthweight ≥ 2500 grams, which may be variables on the causal pathway. Correlations between BPS and other bisphenols were positive (specific estimates not reported). Reported median is higher than reported LOD. It may be that the median was derived from only the detected samples. Details not reported in study.

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
Li et al. 2021 Shenyang, China 2019–2020 Prospective birth cohort Shenyang Maternal and Child Health Study n = 111 Maternal age: 68% of eczema group and 47% of non-eczema group < 30 years. Inclusion criteria: maternal age > 18 years, singleton, gestational age 37–42 weeks, no history of asphyxia at birth, no malformations or conditions that could affect immune system, no perinatal infection, no artificial insemination, no emergency cesarean section.	Urine spot samples Adjusted for SG and creatinine (separate variables) LOQ: 0.1 (LOD not reported) % < LOQ: 53.2 Values below the LOQ were calculated as LOQ÷2. GM: < LOD <u>Percentiles (SG-adjusted):</u> 25th: < LOD 50th: < LOD 75th: 0.35 75th percentile for creatinine-adjusted BPS was 0.41 (µg/g) <u>Timing of samples</u>: Two days before delivery	Incidence of infantile eczema at 6 and 12 months. Cord blood cytokine concentrations 1 hour after birth.	<u>BPS, at or above LOQ vs. below LOQ:</u> No association between BPS and eczema Associations between BPS and cytokine concentrations were unadjusted.	Models adjusted for: maternal age, primipara, infant sex, cesarean, maternal education, exposure to cigarette smoking during pregnancy, parental positive history of allergy, pet keeping during pregnancy, complications of pregnancy, gestational age and feeding patterns within 4 months. Other bisphenols measured: BPA and BPF.	BPA was associated with an increased risk of infantile eczema and reduced FOXP3 gene expression. Eczema group had noticeably younger maternal age (68% under 30) than no eczema group (47% under 30). Correlations between BPS and other bisphenols: not reported.

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
Miller et al. 2025 United States 1998–2017 9 prospective cohorts ECHO N = 4454, n = 1433 mothers with BPS data, n = 599–889 by outcome. Maternal age: not reported Inclusion criteria: varied by cohort; to be included in this analysis, participants needed to have prenatal urine BPS and child asthma, allergic rhinitis or atopic dermatitis outcome measured.	Urine samples Adjusted for SG or creatinine LOD: varied by cohort. % < LOD: 30.1 Values below the LOD were calculated as LOD÷√2. <u>Percentiles:</u> 25th: 0.10 50th: 0.29 75th: 0.69 <u>Timing of samples:</u> Varied by cohort; averaged across pregnancy	Atopic dermatitis (age 0–3), allergic rhinitis (age 5–9), asthma (age 5–9)	<u>Continuous BPS, per SD increase in ln BPS:</u> Atopic dermatitis, OR: 0.84 (95% CI: 0.67, 1.05) Allergic rhinitis, OR: 0.88 (95% CI: 0.71, 1.09) Asthma, OR: 1.27 (95% CI: 0.87, 1.84) <u>BPS Tertiles:</u> Atopic dermatitis: T3 vs. T1, OR: 0.60 (95% CI: 0.36, 1.00) T2 vs. T1, OR: 1.08 (95% CI: 0.68, 1.73) Allergic rhinitis: T3 vs. T1, OR: 0.87 (95% CI: 0.61, 1.25) T2 vs. T1, OR: 1.15 (95% CI: 0.81, 1.63) Asthma: T3 vs. T1, OR: 1.26 (95% CI: 0.71, 2.22) T2 vs. T1, OR: 1.19 (95% CI: 0.68, 2.08) <u>Continuous BPS, per SD increase in ln BPS:</u> Females: **Atopic dermatitis, OR: 0.64 (95% CI 0.44, 0.93)** Allergic rhinitis, OR: 0.84 (95% CI: 0.63, 1.13) Asthma, OR: 0.86 (95% CI: 0.48, 1.54) Males: Atopic dermatitis, OR: 0.98 (95% CI 0.73, 1.33) Allergic rhinitis, OR: 0.84 (95% CI: 0.62, 1.13) Asthma, OR: 1.23 (95% CI: 0.79, 1.91)	Models adjusted for: birth year ≥ 2012, child sex, child race, gestational age, birthweight, birth delivery method, pregnancy smoking, family income less than $50,000, maternal education higher than high school, parental asthma history, maternal breast feeding, and BMI category closest to age 5 (except for outcome of atopic dermatitis). Effect modification examined: child sex. Other bisphenols measured: BPA, BPF	Neither BPA nor BPF were associated with child outcomes. Correlation between BPS and other bisphenols: not reported.

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
Endocrine and cardiometabolic effects					
Bigambo et al. 2024 Birth years not reported. Cross-sectional Nanjing Medical University Birth Cohort n = 378 Mean maternal age (SD) in years: 29.61 (4.51). Inclusion criteria: no assisted delivery, singleton, no chronic diseases such as heart failure, renal failure, acquired immunodeficiency syndrome (AIDS), and cancer, no missing data on thyroid or sex hormones.	Cord blood LOQ: 0.05 LOD not reported % < LOD: 42.6 Values below the LOQ were calculated as LOQ÷2. GM: 0.117 <u>Percentiles:</u> 25th: 0.035 50th: 0.093 75th: 0.367 Max: 153.598 <u>Timing of samples</u>: Delivery	Sex hormones: follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone Thyroid hormones: free triiodothyronine (FT3), free thyroxine (FT4), thyroid stimulating hormone (TSH), thyroid peroxidase antibody (TPOAb). Measured in cord blood at delivery.	<u>Associations per unit increase in BPS:</u> FT3, β: 0.003 (95% CI: -0.010 to 0.015), p = 0.699 FT4, β: 0.000 (95% CI: -0.007 to 0.007), p = 0.989 TSH, β: -0.018 (95% CI: -0.049 to 0.013), p = 0.260 TPOAb, β: -0.016 (95% CI: -0.051 to 0.020), p = 0.388 FSH, β: -0.036 (95% CI: -0.077 to 0.006), p = 0.090 LH, β: -0.042 ((5% CI: -0.102 to 0.017), p = 0.161 Testosterone, β: 0.018 (95% CI: -0.102 to 0.017), p = 0.220 No evidence of effect modification by sex. <u>By pre-pregnancy BMI:</u> BPS was associated with lower FSH **[β: -0.046 (95% CI: --0.092 to 0.000), p = 0.052]** among people with normal weight BMI. No associations for FSH in other BMI groups. <u>By delivery mode:</u> BPS was associated with lower FSH **[β: -0.071 (95% CI: --0.137 to -0.004), p = 0.039]** among people with cesarean delivery. No associations for FSH among those with natural delivery.	Models adjusted for maternal age and education, pre-pregnancy BMI, passive smoking, parity, gestational age, delivery mode, hypertension, thyroid diseases, gestational diabetes mellitus, and newborn sex. Effect modification examined: child sex, pre-pregnancy BMI, delivery mode. Other bisphenols measured: BPA, BPAF, bisphenol AB. Quantile-based g-computation and BKRM used to estimate joint effect of a mixture of bisphenols.	Correlations between BPS and other bisphenols: not reported.

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
Blaauwendraad et al. 2022a Rotterdam, Netherlands 2004–2005 Prospective birth cohort Generation R n = 935 Mean maternal age (SD) in years: 30.89 (4.59). Inclusion criteria: ≤18 weeks gestation, singleton, urine samples at three time points in pregnancy.	Urine spot samples Adjusted for creatinine LOD: 0.05 % < LOD: TM1: 32.2, TM2: 70.8, TM3: 80.2 Values below the LOD were calculated as LOD÷√2. <u>Percentiles (TM1, TM2, TM3)</u>: 25th: 0.025, < LOD, NA 50th: 0.18, < LOD, NA 75th: 0.58, 0.10, NA <u>Timing of samples (Median (95% CI))</u>: TM1: 12.9 (9.8, 12.7) weeks TM2: 20.4 (18.9, 22.8) weeks TM3: 30.2 (28.8, 32.5) weeks	Carotid Intima-Media Thickness (mm) and Distensibility (kPa-1*10-3) measured by ultrasonography at 10 years.	<u>Average prenatal BPS</u> Carotid intima-media thickness, β: -0.05 (95% CI: -0.16, 0.05) (p = 0.317) Carotid distensibility, β: 0.09 (95% CI: -0.02, 0.19) (p = 0.098) No meaningful differences in estimates when TM1 or TM2 BPS examined separately. No evidence of interaction by child sex.	Carotid intima-media thickness model adjusted for: maternal age, parity, pre-pregnancy BMI, educational level, smoking and alcohol use, child's age and gender. Carotid distensibility model adjusted for: maternal age, parity, ethnicity, pre-pregnancy BMI, education level, smoking and alcohol use, child's age and gender. Other bisphenols measured: BPA, BPF. Effect modification: child sex.	Correlations between BPS and other bisphenols: BPA (ρ = 0.06), BPF (ρ = 0.03). BPA was associated with lower child carotid intima-media thickness. BPS concentrations converted from nmol/L to ng/mL.

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
Derakhshan et al. 2021 Rotterdam, Netherlands 2002–2006 Prospective birth cohort Generation R N = 853 with data on newborn thyroid measurements. N = 882 with data on child thyroid measurements Mean maternal age (SD) in years: 30.5 (4.8) Inclusion criteria: ≤18 weeks gestation, singleton, urine samples at three time points in pregnancy, no pre-existing thyroid disease or history of fertility treatment, no children with chronic diseases or using thyroid medication or growth hormone.	Urine spot samples Adjusted for creatinine LOD: 0.05 % < LOD: TM1: 33.4, TM2: 70.2, TM3: 81.1 Values below the LOD were calculated as LOD÷√2. <u>Percentiles (TM1, TM2, TM3)</u>: 25th: < LOD, < LOD, NA 50th: 0.34, 0.24, NA 75th: 8.83, 1.69, NA <u>Timing of samples:</u> TM1: < 18 weeks TM2: 18–25 weeks TM3: > 25 weeks	Cord blood TSH, FT4 Serum TSH and FT4 in childhood (median age was 5.8 years)	Early pregnancy BPS was not associated with cord blood TSH or FT4 (estimates not reported). Early pregnancy BPS was not associated with childhood thyroid function (estimates not reported).	Cord blood models adjusted for: fetal sex, fetal distress, method of delivery (spontaneous, caesarean section and/or breech extraction), parity, ethnicity, maternal education, BMI, smoking status and urinary creatinine. Childhood models adjusted for: Child's age, BMI, ethnicity, and sex as well as maternal education, smoking status, and urinary creatinine. Effect modification examined: child sex. Other bisphenols measured: BPA, BPF.	BPA was associated with higher cord blood TSH and lower childhood FT4. Correlations between BPS and other bisphenols: BPA (r = -0.04-0.19), BPF (r = 0.06-0.3).

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
Sol et al. 2020 Rotterdam, Netherlands 2004–2005 Prospective birth cohort Generation R Study n = 757 Mean maternal age (SD) in years: 31 (4.6) Mean child age (SD) in years: 9.7 (0.2) Inclusion criteria: ≤18 weeks gestation, singleton.	Urine spot samples Adjusted for creatinine LOD: 0.06 % < LOD: TM1: 30.3, TM2: 70.1 Values below the LOD were calculated as LOD÷√2. <u>TM1 Percentiles (Boys, Girls)</u>: 25th: 0.03, 0.03 50th: 0.20, 0.15 75th: 0.75, 0.58 <u>TM2 Percentiles (Boys, Girls)</u>: 25th: 0.03, 0.03 50th: 0.03, 0.03 75th: 0.13, 0.10 <u>Timing of samples (Median (25th, 75th))</u>: TM1: 12.9 (12.1,14.6) weeks TM2: 20.4 (19.9, 20.9) weeks	Measured non-fasting lipids (total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), cholesterol, triglycerides), glucose, and insulin blood concentrations at ages 9-10 years. Outcomes standardized, interpret *β* estimates as standard deviation changes.	<u>Continuous TM1 BPS, per IQR increase:</u> No statistically significant associations between BPS and triglycerides, total cholesterol, HDL cholesterol, and LDL cholesterol in boys or girls. **Significant interaction between BPS and child's sex in LDL cholesterol model (p = 0.02)**. Marginally significant interaction between BPS and child's sex in total cholesterol model (p = 0.09). <u>By child's sex:</u> For boys: LDL, β*:* 0.11 (95% CI: -0.01, 0.22) Total cholesterol, β*:* 0.06 (95% CI: -0.06, 0.17) For girls: LDL β*:* -0.10 (95% CI: -0.22, 0.02) Total cholesterol, β*:* -0.09 (95% CI: -0.21, 0.03) Associations with insulin and glucose only presented as sex-stratified: For boys: **Insulin, β: -0.13 (95% CI: -0.25, -0.02)** **Glucose, β: -0.15 (95% CI: -0.26, -0.03)** Associations did not remain significant after adjustment for multiple comparisons. For girls: Insulin, β*:* -0.01 (95% CI -0.13, 0.11) Glucose, β*:* -0.02 (95% CI -0.14, 0.10) <u>Continuous TM2 BPS, per IQR increase</u>: No associations with triglycerides, total cholesterol, HDL cholesterol, LDL cholesterol, glucose, or insulin in girls or boys. **High LDL analyzed as a binary variable in boys: OR: 0.69 (95% CI: 0.47, 0.99)**	Models adjusted for: child's age and age- and sex-standardized BMI and maternal age, education, parity, ethnicity, pre-pregnancy BMI, folic acid supplement use, maternal diet quality score, alcohol consumption and smoking habits (specifically in early, mid and late pregnancy). Effect modification examined: child sex. Other bisphenols measured: BPA and BPF.	Significant interaction between TM3 BPA exposure and glucose levels (stronger effects in girls). Detection of BPS was high in TM1 but about 70% were below LOD in TM2 and over 80% in TM3 (TM3 not analyzed). BPS concentrations converted from nmol/L to ng/mL. BPF associated with increased triglycerides and HDL cholesterol and decreased insulin and glucose in boys. Correlations between BPS and other bisphenols: not reported.

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
Svensson et al. 2023 Sweden 2007–2010 Prospective cohort study Swedish Environmental Longitudinal, Mother and child, Asthma and allergy (SELMA) study. N = 1,105 Mean (SD) maternal age in years: 30.6 (4.7) Inclusion criteria: singleton, TM1 prenatal care clinic.	First morning void urine samples Adjusted for creatinine LOD: 0.04 % < LOD: 2.5 Values below the LOD were calculated as ÷√2. GM ± GSD: 0.07 ± 3.0 <u>Percentiles:</u> 25th: 0.03 50th: not reported 75th: 0.12 <u>Timing of samples</u>: TM1: ~ 10 weeks	Offspring BMI kg/m^2, overweight, BMI z-score at 5.5 years.	<u>Per ln increase in non-creatine adjusted BPS</u> β: -0.07 (95% CI: -0.30, 0.15), *p* =0.51 In boys: β: 0.02 (95% CI: -0.27, 0.30), *p* =0.89 In girls: β: -0.19 (95% CI: -0.53, 0.16), *p* =0.29 Similar results for logistic regression analyses modeling odds of overweight. <u>Mixture model</u>: Higher prenatal mixture to endocrine disrupting chemicals was associated with lower BMI and lower odds of overweight among girls with no associations observed in boys. Relative weight of BPS in girl-specific mixture model was 4%.	Models adjusted for: maternal BMI, education, age, smoking, parity, and child's sex and age. Effect modification examined: infant sex Other bisphenols measured: BPA, BPF Weighted quantile sum used to estimate joint effect of a mixture of 26 endocrine disrupting chemicals, including BPS, BPA, and BPF.	Considering contribution of BPS to mixture, authors list BPS as one of the "possible chemicals of concern." Correlations between BPS and other bisphenols: BPA (ρ = 0.18), BPF (ρ = 0.09).

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
Wang et al. 2022 Shanghai, China 2012 Prospective birth cohort Shanghai Minhang Birth Cohort Study n = 528 Mean (SD) maternal age in years: 28.5 (3.4) Inclusion criteria: Pregnant women 12-16 gestational weeks and receiving care at the Minhang Maternal and Child Health Hospital in Shanghai, singleton.	Urine spot samples Adjusted for creatinine LOD: 0.004 % < LOD: 75.8% Values below the LOD were calculated as LOD÷2. GM (95% CI): 0.02 (0.01, 0.02) µg/g <u>Percentiles (creatinine corrected)</u>: 25th: 0.00 µg/g 50th: 0.01 µg/g 75th: 0.03 µg/g <u>Timing of samples</u>: TM3	Urinary levels of total kisspeptin (ng/L), including kisspeptin-54, 14, 13, and 10 in children at age 6	<u>BPS 3-level variable (< LOD, LOD to median 0.01, >0.01):</u> **High vs. Low, β: 46.18 (95% CI: 17.07, 75.28)** Middle vs. Low, β: 18.66 (95% CI: -9.34, 46.66) <u>By child's sex:</u> For boys: **High vs. Low, β: 63.43 (95% CI: 25.20, 101.65)** Middle vs. Low, β: 25.85 (95% CI: -10.75, 62.45) In girls: High vs. Low, β: 23.22 (95% CI: -23.23, 69.68) Middle vs. Low, β: -0.35 (95% CI: -45.14, 44.44) In BKMR models: "overall [bisphenols] mixture was suggestively associated with…higher children's kisspeptin." Conditional PIP for BPS was 0.68.	Models adjusted for: maternal creatinine concentrations, household income, maternal education, age at menarche, maternal age, maternal pre-pregnancy BMI, parity, children's BMI z-score, and child sex. Mutual adjustment for BPA and BPF in sensitivity analyses. Effect modification: child sex. Other bisphenols measured: BPA, BPF, BPAF, TBBPA, TCBPA. BKMR models used to estimate effects of BPS as part of a mixture of bisphenols.	BPA tertile 2 associated with an increase in children's kisspeptin levels. BPF greater than the median was associated with decreased maternal kisspeptin levels in boys. Correlations between BPS and other bisphenols: BPA (ρ = 0.095), BPF (ρ = 0.143), BPAF (ρ = 0.036), TCBPA (ρ = -0.063). Associations did not meaningfully change after mutual adjustment for other bisphenols, or maternal kisspeptin levels.

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
Xi et al. 2023 Shanghai, China 2012 Prospective birth cohort Shanghai Minhang Birth Cohort Study n = 1292 enrolled, n = 258 neonates with exposure and outcome measurements Maternal age: 54.7% were 25-29 years Inclusion criteria: Pregnant women 12-16 gestational weeks and receiving care at the Minhang Maternal and Child Health Hospital in Shanghai.	Urine spot samples Adjusted for creatinine LOD: 0.004 % < LOD: 78.68% Values below the LOD were calculated as LOD÷√2. Percentiles (creatinine corrected): 25th: 0.004 µg/g 50th: 0.007 µg/g 75th: 0.019 µg/g Timing of samples: TM3: 32–36 weeks	Thyroid related hormones in cord blood: FT4 (pmol/L), TSH (µIU/mL), total thyroxine (TT4, nmol/L), total triiodothyronine (TT3, nmol/L), FT3 (pmol/L)	BPS, detected vs. not detected: Non-significant decreases of all thyroid related hormones in cord blood Statistically significant interaction by newborn sex. By newborn sex: For male newborns: **TSH, β: -0.23 (95% CI -0.46, -0.01)** TT4, β: -11.36 (95% CI -22.72, 0.00) FT4, β: -0.75 (95% CI -1.56, 0.06) For female newborns: No associations (estimates reported graphically) In BKMR models, no associations between BPS and outcomes when holding other bisphenols constant. PIP for BPS ranged from 0.02 to 0.05 across outcome models.	Models adjusted for: maternal age, pre-pregnant BMI, education level, family income, parous status, maternal passive smoking, type of delivery, newborn sex. Effect modification examined: newborn sex. Other bisphenols measured: BPA, BPF, BPAF, TBBPA, TCBPA. BKMR models used to estimate effects of BPS as part of a mixture of bisphenols.	BPA associated with decrease in TT4 and FT3 in cord blood. Correlations between BPS and other bisphenols: BPA (ρ = 0.160), BPAF (ρ = 0.487), BPF (ρ = 0.429), TCBPA (ρ = 0.227). Analytic sample size was low because the study "only obtained cord blood samples for women who gave birth during the daytime." Results from sensitivity analyses using inverse probability weighting of censoring to correct for loss to follow-up were similar.
Xiong et al. 2023b) Wuhan, China 2013–2015 Prospective birth cohort Wuhan Healthy Baby Cohort Study n = 904 Mean (SD) maternal age in years: 29.12 (3.27) Inclusion criteria:<16 weeks gestation, singleton pregnancy, receive prenatal	Urine spot samples Adjusted for SG LOD: 0.04 µg/L % < LOD: TM1: 15.49, TM2: 13.05, TM3: 11.28 Values below the LOD were calculated as LOD÷√2. Percentiles (TM1, TM2, TM3) SG adjusted µg/L: 10th: < LOD all	TSH levels measured in heel prick blood samples taken 48–72 hours after birth. Analyzed as %Δ	Continuous BPS, per doubling of exposure: **TM1: %Δ: 5.81 (95% CI: 2.27, 9.46)** **TM2: %Δ: 5.70 (95% CI: 1.99, 9.55)** **TM3: %Δ: 4.36 (95% CI: 0.75, 8.11)** For males: **TM1: %Δ: 4.64 (95% CI: 0.24, 9.23)** TM2: %Δ: 3.77 (95% CI: -0.72, 8.47) TM3: %Δ: 3.97 (95% CI: -0.57, 8.72) For females: **TM1: %Δ: 6.53 (95% CI: 0.82, 12.55)** **TM2: %Δ: 7.68 (95% CI: 1.45, 14.29)** TM3: %Δ: 4.45 (95% CI: -1.33, 10.56) BPS Quartiles:	Models measured: maternal age, educational level, pre-pregnancy BMI, passive smoking status, gestational week, infant sex, birth season and birthweight. Other bisphenols measured: BPA and BPF. Effect modification examined: neonatal sex. Quantile g-computation to estimate co-exposure to three bisphenols in a mixture.	ICC (95% CI) for BPS: 0.12 (0.08, 0.16), "lower level of reproducibility." Correlations between BPS and other bisphenols: BPF in TM1 (ρ = 0.31), TM2 (ρ = 0.35), and TM3 (ρ = 0.26), BPA in TM1 (ρ = 0.17), TM2 (ρ = 0.18), and TM3 (ρ = 0.15).

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
care and deliver at participating hospital, no thyroid disease in baby, no birth defect or stillbirth.	25th: 0.18, 0.18, 0.20 50th: 0.39, 0.37, 0.40 75th: 1.14, 1.11, 1.06 90th: 3.87, 3.31, 3.43 <u>Timing of samples:</u> TM1 TM2 TM3		**TM1: Q2 vs. Q1, %Δ: 37.32 (95% CI: 12.54, 67.57)** **TM1: Q3 vs. Q1, %Δ: 43.00 (95% CI: 16.91, 74.90)** **TM1: Q4 vs. Q1: %Δ: 43.41 (95% CI: 17.25, 75.41)** ***P* trend 0.002** TM2: Q2 vs. Q1, %Δ: 12.52 (95% CI: -7.80, 37.30) TM2: Q3 vs. Q1, %Δ: 10.04 (95% CI: -9.94, 34.46) **TM2: Q4 vs. Q1: %Δ: 33.41 (95% CI: 9.22, 62.96)** ***P* trend 0.007** TM3: Q2 vs. Q1, %Δ: 1.05 (95% CI: -17.19, 22.31) TM3: Q3 vs. Q1, %Δ: -4.22 (95% CI: -21.54, 16.93) **TM3: Q4 vs. Q1: %Δ: 22.11 (95% CI: 0.04, 49.06)** ***P* trend 0.047** For males, statistically significant estimates were: **TM1: Q2 vs. Q1, %Δ: 34.82 (95% CI: 4.59, 73.78)** **TM1: Q3 vs. Q1, %Δ: 32.61 (95% CI: 1.86, 72.65)** For females, statistically significant estimates were: **TM1: Q3 vs. Q1, %Δ: 55.64 (95% CI: 14.08, 112.36)** **TM1: Q4 vs. Q1, %Δ: 57.03 (95% CI: 14.09, 116.14)** Mixture positively associated with TSH levels for TM1 exposure. BPS positively weighted in all models.		

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
Z Wang et al. 2021 Shanghai, China 2012 Prospective birth cohort Shanghai Minhang Birth Cohort Study n = 545, n = 433 at 6 years Mean (SD) maternal age in years: 28.5 (3.4) Inclusion criteria: Receive first prenatal care 12-16 weeks gestation at participating hospital, singleton, no history of major chronic diseases.	Urine spot samples Adjusted for creatinine LOD: 0.004 % < LOD: 75.2 Values below the LOD were calculated as LOD÷2. GM: 0.01 Percentiles: 25th: 0.0 µg/g 50th: 0.01 µg/g 75th: 0.03 µg/g Timing of samples: TM3	Digit ratio measurements, 2D:4D ratios at 4-6 years	BPS, detected vs. not detected: No statistically significant results for BPS and changes in digit ratio measurements in males or females at age 6. Authors report a consistent pattern of higher digit ratios at 4 years. Marginal association in girls (p = 0.054) for right hand 2D:4D that attenuated after mutual adjustment for other bisphenols.	Models adjusted for: household income, maternal education, maternal age, gestational age, parity, maternal pre-pregnancy BMI, maternal pre-pregnancy passive smoking, paternal smoking before conception, paternal drinking before conception, and child's body weight-for-length z-score, creatinine. Effect modification examined: child sex. Other bisphenols measured: BPA, BPF, BPAF, TBBPA, and TCBPA. Supplementary analysis includes mutual adjustment for all bisphenols in the same model.	BPF in all children and BPAF in females associated with higher digit ratio while TCBPA was associated with lower digit ratio at age 4. Authors considered 2D:4D digit ratio "an indicator of disrupted prenatal sex hormones." Low detection rate for BPS. Correlations between BPS and other bisphenols: BPA (ρ = 0.102), BPF (ρ = 0.155), BPAF (ρ = 0.049), TCBPA (ρ = -0.044).

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
Bone mass and mineral density					
Liang et al. 2023 Guangxi Providence, China 2015–2018 Prospective birth cohort Guangxi Zhuang Birth Cohort n = 230 Mean (SD) maternal age in years: 29.4 (5.5) Inclusion criteria: < 13 weeks gestation, singleton, Zhuang population (mother or father), planned to give birth in participating hospital, no birth defect.	Serum samples LOD: 0.046 % < LOD: 13.9 Values below the LOD were calculated as LOD÷2. GM: 0.085 <u>Percentiles:</u> 25th: 0.096 50th: 0.097 75th: 0.106 95th: 0.159 <u>Timing of samples:</u> TM1	Bone mass at ages 3–6. Parameters: speed of sound (SOS) measured by quantitative ultrasonography, bone mass density z-score (BMDZ), low bone mineral density (BMDL, BMDZ ≤ - 1.0)	<u>Per 1-unit increase in ln BPS:</u> SOS, β: - 0.008 (95% CI: -0.017, 0.001) BMDZ, β: -0.157 (95% CI: -0.334, 0.020) BMDL, OR: 1.102 (95% CI: 0.716, 1.698) Associations stronger in boys than girls, though no estimates per 1-unit increase BPS were significant. <u>BPS tertiles:</u> No associations for SOS Associations for BMDZ or BMDL observed only in boys. For girls: BMDZ Middle vs. Low, β: –0.252 (95% CI: –0.740, 0.236) BMDZ High vs. Low, β: –0.138 (95% CI: –0.600, 0.324) BMDL Middle vs. Low, OR: 0.693 (95% CI: 0.166, 2.903) BMDL High vs. Low, OR: 0.706 (95% CI: 0.185, 2.688) For boys: BMDZ Middle vs. Low, β: –0.485 (95% CI: –0.981, 0.009) **BMDZ High vs. Low, β: –0.568 (95% CI: –1.087, –0.050)** **BMDL Middle vs. Low, OR: 4.695 (95% CI: 1.14, 24.38)** **BMDL High vs. Low, OR: 6.165 (95% CI: 1.445, 33.789)** In principal component analysis, BPS was strongest factor in principal component 1 (loading = 0.71), which showed a negative trend with SOS in girls. Conditional PIPs in BKMR models were 0 for SOS, 0.48 for BMDZ, and 0.32 for BMDL. The bisphenol mixture was negatively associated with SOS in girls. Univariate dose-response curves showed an inverse U-shaped curve for BMDL in boys.	Models adjusted for: maternal age, pre-pregnancy BMI, parity, passive smoking, drinking, folic acid, child age, child height-for-age Z score, and child sex. Effect modification examined: sex. Other bisphenols measured: BPA, BPB, BPF, TBBPA Principal component analysis and BMKR models used to estimate effects of BPS as part of a mixture of bisphenols.	Cutoffs used to define BPS tertiles not reported. Correlations between BPS and other bisphenols: not reported.

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
van Zwol-Janssens et al. 2020 Rotterdam, Netherlands 2004–2005 Prospective cohort study Generation R Study n = 1,362, n = 1,335 at 6 years, n = 982 at 10 years Mean (SD) maternal age in years: 30.6 (4.8) Mean (SD) children's age in years: 5.9 (0.2) and 9.7 (0.2) Inclusion criteria: mothers were ≤18 weeks gestation, singleton.	Urine spot samples Adjusted for creatinine LOD: 0.05 % < LOD: TM1: 32.2, TM2: 70.5, TM3: 80.7 Values below the LOD were calculated as LOD÷√2. Percentiles (TM1, TM2, TM3): 25th: 0.03, 0.03, 0.03 50th: 0.17, 0.03, 0.03 75th: 0.61, 0.10, 0.03 Timing of samples (median): TM1: 12.9 weeks TM2: 20.4 weeks TM3: 30.21 weeks	Total body bone mineral density (BMD, mg/cm^2), bone mineral content (BMC), area adjusted bone mineral content (aBMC, g) and bone area (BA) in children at ages 6 and 10 years	TM1 BPS, per IQR increase: BMD at age 6, β: -2.04 (95% CI: -4.55, 0.46), p = 0.11 **BMD at age 10, β: -6.08 (95% CI: -9.97, -2.19), p < 0.01** aBMC at age 6, β: -0.07 (95% CI: -0.14, 0.00), p = 0.06 **aBMC at age 10, β: -0.12 (95% CI: -0.20, -0.04), p < 0.01** No statistically significant associations with TM2 or TM3 BPS and BMD or aBMC at ages 6 and 10. BMC and BA analyses reported in supplementary material. Statistically significant estimates were: TM1 BPS: **BMC at age 10, β: -7.61 (95% CI: -13.98, -1.23), p = 0.02** TM2 BPS: **BA at age 10, β: -3.89 (95% CI: -7.62, -0.16), p = 0.04** Authors report, "we did not observe different associations between child's sex or maternal folic acid supplement use groups."	Models adjusted for: child's age, sex, height and bone-free mass, maternal age, pre-pregnancy BMI, ethnicity and education level, parity, folic acid supplement use during pregnancy, alcohol and smoking habits (specifically during each trimester or during pregnancy) and vitamin D blood concentrations. Effect modification examined: child sex, folic acid supplementation. Other bisphenols measured: BPA and BPF.	TM1 BPF associated with increased bone area at age 10. Averaged BPF levels associated with decrease in BMD and BMC at age 6. Reporting of percentiles for BPS, potentially with many values imputed with LOD÷√2, includes values < LOD. Exposure concentrations converted from nmol/L to ng/mL. Low stability of BPS across pregnancy (ICC = 0.01). Correlations between BPS and other bisphenols: not reported.

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
Female/Male Reproduction (in utero exposure)					
Blaauwendraad et al. 2022b Rotterdam, Netherlands 2004–2005 Prospective cohort study Generation R Study n = 673 boys and n = 524 girls, n for analysis varied by outcome from 286 to 639 Mean (SD) maternal age in years: 30.8 (4.7) Inclusion criteria: mothers were ≤18 weeks gestation, singleton.	Urine spot samples Adjusted for creatinine LOD: 0.15 % < LOD: TM1: 31.5, TM2: 70.3, TM3: 80.0 Values below the LOD were calculated as LOD÷√2. <u>Percentiles (TM1, TM2, TM3):</u> Males: 25th: 0.03, < LOD, < LOD 50th:0.2, < LOD, < LOD 75th: 0.7, < LOD, < LOD Females: 25th: < LOD, < LOD, < LOD 50th: 0.2, < LOD, < LOD 75th: 0.6, 0.08, < LOD <u>Timing of samples (weeks)</u> (median (25th, 75th)): TM1: 12.9 (12.1,14.4) TM2: 20.4 (19.9, 20.9) TM3: 30.2 (29.9, 30.8)	Offspring reproductive development: infant reproductive tract abnormalities, ovarian and testicular volume at 10 years using Magnetic Resonance Imaging and pubertal development and onset of menstruation at 13 years.	<u>Continuous averaged BPS, per IQR increase:</u> For girls: Ovarian volume, β: -0.03 standard deviation score difference (95% CI: -0.16, 0.09), p = 0.622 **Age at first menstruation, β: 0.17 years (95% CI: 0.02, 0.31), p = 0.025** No statistically significant differences in breast development or pubic hair development. For boys: Testicular volume, β: 0.04 standard deviation score difference (95% CI: -0.04, 0.12), p = 0.334 No statistically significant differences in genital development or pubic hair development.	Models adjusted for: maternal age, ethnicity, pre-pregnancy BMI, education level, parity, intake, smoking and alcohol use, breastfeeding, and child's gestational age-adjusted birthweight, and age and age-adjusted BMI at time of measurement. Other bisphenols measured: BPA and BPF Used quantile-based g-computation to assess a chemical mixture of bisphenol and phthalate metabolites.	BPF was not included in the study with low detection levels inTM2. BPA associated with decrease in pubic hair development in boys for "lower than expected for age" Tanner stage. Reporting of percentiles for BPS included values < LOD (potentially with values imputed with LOD÷√2). Exposure concentrations converted from nmol/L to ng/mL. Correlations between BPS and other bisphenols: BPA (r = 0.03), BPF (r = 0.28). Specific birth years were not reported in this study. 2004–2005 were reported as years of BPS data collection in Generation R in other studies.

Reference; study location, period, design, sample*	Exposure matrix and concentration (ng/mL)†	Outcomes	Results	Covariates, other bisphenols analyzed	Comments†
Chen et al. 2025 Shanghai, China 2012 Prospective cohort study Shanghai-Minhang Birth Cohort Study N=1225, n=545 included in study, n = 456 with estimated AGD trajectories. Maternal average age: 28.98 ± 3.41 years. Inclusion criteria: singleton, 12−16 weeks gestation, gave birth at study hospital.	Urine spot samples Adjusted for creatinine LOD: 0.004 % < LOD: 75.23 Values < LOD imputed with LOD÷√2 GM (GSD): 0.01 (0.00) µg/g Percentiles: 25th: 0.00 µg/g 50th: 0.01 µg/g 75th: 0.03 µg/g Timing of samples: 27−37 weeks	Children's anogenital distance (AGD) at birth, 6, 12, and 48 months. [AGD: boys, AGD_{AP} (anus-penis), AGD_{AS} (anus-scrotum); girls, AGD_{AC} (anus-clitoris), AGD_{AF} (anus-fourchette)]	BPS detected vs not detected: No statistically significant associations between BPS and AGD measured at birth or 6, or 12 months. For girls at 48 months: **AGD_{AC}: β: 4.06 (95% CI: 0.43, 7.69)** **AGD_{AF}: β: 3.25 (95% CI: 0.76, 5.73)** **Rapid AGD growth: OR: 2.94 (95% CI: 1.35, 6.40) p = 0.0067** For boys at 48 months: AGD_{AC}: β: -1.54 (95% CI: -4.33, 1.24) AGD_{AF}: β: -1.61 (95% CI: -3.98, 0.76) Rapid AGD growth: non-significant estimate not reported Among children with "normal" body size: **Rapid AGD_{AC} growth: OR: 2.80 (95% CI: 1.12, 6.99)** **Rapid AG growth, dual model for AGD_{AC} and AGD_{AF}: OR: 3.80 (95% CI: 1.50, 9.64)** Similar results when models were adjusted for maternal urinary creatinine (Table S11) BKMR models: In girls, BPS was associated with longer AGD_{AF} at 6 and 48 months when other bisphenols were held at their 25th and 75th percentiles (PIP for BPS: 0.77)	Models adjusted for: mother's pre-pregnancy body mass index, age at delivery, gestational age at delivery, education, parity, and passive smoking before conception, and children's weight-for-length z-scores at each time point. Effect modification examined: infant sex (via stratification). Other bisphenols measured: BPA, BPF, BPAF, TBBPA, TCBPA BKMR models used to estimate effects of BPS as part of a mixture of bisphenols.	BPA and BPF associated with AGD distances for boys and girls at various timepoints. Correlations between BPS and other bisphenols not reported.

*Studies ordered by outcomes then alphabetical by first author
† Concentrations reported as ng/mL or µg/L unless otherwise noted. Studies with concentrations converted from nmol/L to ng/mL will be noted in Comments section
¥ IQR = interquartile range calculated as 75th minus 25th percentile.
Statistically significant results (α = 0.05) are shown in bold.

4.2 Studies in Animals

OEHHA identified 88 studies that examined the developmental effects of BPS in mammalian and non-mammalian animal models. These include 17 studies in mice, 13 in rats, three in sheep, 43 in *Danio rerio* (zebrafish), one in *Oryzias sinensis* (Chinese medaka fish), six in *Caenorhabditis elegans (a type of nematode)*, three in chick embryos, and two in *Drosophila melanogaster* (fruit flies).

4.2.1 Overview

Development involves a tightly regulated spatiotemporal sequence of cell proliferation, differentiation, coordination, and organization. Environmental exposures can affect the instructions, tools, and/or construction required for development, especially during the sensitive period of organogenesis. However, exposures to toxicants at any point from the zygotic stage to birth/hatching, or shortly thereafter, can have adverse developmental effects manifested in the developing, maturing, and/or adult organism.

OEHHA reviewed studies that evaluated BPS-mediated developmental outcomes at life stages ranging from early-stage embryos to adults in both mammalian and non-mammalian organisms. Mammalian-specific developmental outcomes assessed in these studies included implantation and placental effects; and non-mammalian-specific developmental outcomes assessed included hatching, ocular, and cardiac and vascular effects. Many of the outcomes discussed in this section can result from direct effects on the embryo or extraembryonic structures (e.g., the placenta), direct effects on the reproductive system of either parent, or some combination of these. Thus, some of the studies reviewed in this section have been discussed, as appropriate, in other OEHHA documents describing the evidence on the female (OEHHA 2023) and male (OEHHA 2024) reproductive toxicity of BPS. Several other studies reviewed in this section that assess reproductive toxicity outcomes associated with gestational or pre-conceptional exposure may have also been discussed in (OEHHA 2023) or (OEHHA 2024).

All results presented in this section were reported as statistically significant by pairwise comparison with controls ($p \leq 0.05$) unless otherwise noted (e.g., $p \leq 0.5$ by trend test).

The studies varied in design, some with exposure occurring only during gestation, and others with perinatal or early postnatal exposure (e.g., neurodevelopmental studies). Several studies also utilized *ex vivo* or *in vitro* model systems to evaluate effects on early embryo development and implantation, and/or later stages of embryo and fetal development. Most studies were conducted in mice, rats, and zebrafish, of which multiple strains were used. The majority of studies in mammals administered BPS orally by gavage, diet, or in drinking water, although some studies used subcutaneous (SC) or

intraperitoneal (IP) injections. If the route is not specified in the text, the reader should assume BPS exposure occurred in mammals via oral administration to the dams during pregnancy and/or lactation. Fish were generally exposed in container water, and *C. elegans* were exposed directly via the nematode growth medium. Administered doses/concentrations ranged from 0.025 µg/kg to 300 mg/kg [and 3.33 to 50 µg/L as reported when exposed in drinking water] in rodents, 0.004 to 0.5 mg/kg in sheep, 0.001 to 400 mg/L in zebrafish, 250 to 1000 mg/L in Chinese medaka fish, 0.27 to 207 µg/g, or 0.00075 to 7.5 mg/L in chick embryos, 0.6 µg/L to 125 mg/L in *C. elegans*, and 62.6 to 250.27 mg/L in *Drosophila*.

4.2.2 Studies in Mammals

Early Embryo Development and Implantation

Embryonic development and successful implantation are dependent upon many factors, including maternal and paternal gamete parameters, the maternal reproductive system, the placenta, and the embryo. Two studies in mice, four studies in rats, and one study in sheep assessed early embryo development and implantation. These studies were also discussed in OEHHA (2023).

Mice

In an *in vitro* fertilization (IVF) study using adult female mice treated by IP injection for 21 days at doses of 1, 5, 10, 50, or 100 µg/kg-day BPS, there was inhibited embryo development as indicated by developmental arrest of pre-implantation embryos at 50 and 100 µg/kg-day and decreased IVF rate in mouse oocytes harvested from treated females with a dose-dependent decrease in the percentages of two-cell embryos and blastocysts at 10, 50, and 100 µg/kg-day (Nourian et al. 2017).

In F1 oocytes obtained from F0 mice treated orally with 2 or 10 µg/kg-day BPS from gestational day (GD) 12.5 – 15.5 and used for IVF with sperm from untreated males, adverse developmental outcomes included a decrease in the proportion of two- and four-cell embryos and a decreased proportion of blastocysts (MY Zhang et al. 2020).

Rats

In Wistar rats treated with 30, 100, or 300 mg/kg-day BPS via gavage from GD 6 – 19, there was a nonsignificant (NS) 34% increase in post-implantation loss at 300 mg/kg-day with no effect on the number of implantation sites (BASF 2014).

In a modified extended one-generation reproductive study in SD rats, male and female parents (F0) and offspring (F1) were administered BPS via gavage at 20, 60, or 180 mg/kg-day from 10 weeks pre-mating through weaning at postnatal day (PND) 21.

In F0 and F1 dams, there were increases in percent post-implantation loss at 60 (NS for F1;+73%) and 180 mg/kg-day. In F1 dams, there was a 10% decrease (NS) in the number of implantation sites at 180 mg/kg-day (BASF 2019).

As reviewed in a 2019 ECHA report, two anonymous studies observed effects of BPS treatment on implantation. Both studies administered BPS via oral gavage to F0 male and female SD rats. In Anonymous Study 12, both male and female F0 rats were administered 10, 60, or 300 mg/kg-day BPS. F0 males were treated for a total of 45 days including 14 days of premating through mating and thereafter. F0 females were treated for 40 to 46 days from premating, mating, gestation, and up to lactation day (LD) 3. In Anonymous Study 14, both male and female F0 rats were administered 30, 100, or 300 mg/kg-day BPS. F0 males were treated for six weeks during premating and two to four weeks during mating and post-mating. F0 females were treated for six weeks during premating and through gestation and up to LD 21. Both studies reported effects on implantation at 300 mg/kg-day. There were decreases in the number of implantation sites and implantation index in Anonymous Study 12 and a decreased number of implantation sites and an increased percentage of post-implantation loss in Anonymous Study 14 (ECHA 2019).

Sheep

In ewes on restricted or well-fed diets administered 4, or 50 µg/kg-day BPS for three months prior to superovulation and oocyte collection, there was a diet and BPS dose interaction for the number and rate of cleaved embryos, number of >4-cell embryos, number of blastocysts, and number of early blastocysts as well as decreases (NS) in the numbers of cleaved embryos, >4-cell embryos, early blastocysts, and blastocysts in the restricted diet group and increases in these parameters in the well-fed group at 4 µg/kg-day (Desmarchais et al. 2022).

Placental Effects

Proper placental formation and function are critical for embryonic and fetal development. This includes hormone/neurotransmitter production such as progesterone, estradiol (E2), serotonin, dopamine, and norepinephrine. The placenta adapts to support the changing embryo/fetal needs and signals during normal and/or perturbed development. Toxicant-mediated responses in the placenta could arise from either direct effects on the placenta, the conceptus, the mother, the paternal epigenome, or some combination. Placental effects were assessed in one mouse, one rat, and one sheep study; the mouse and sheep studies were also discussed in OEHHA 2023.

Mice

In female C57BL/6J mice orally administered 200 µg/kg-day BPS on a wafer for two weeks prior to mating with an untreated male, placenta histopathology findings were observed in mice for 2 weeks pre-mating and sacrificed on GD 12.5, including decreased ratio of spongiotrophoblast zone to giant cell area. Additionally, there was an increase in placental dopamine concentrations and percentage of dopamine-positive trophoblast giant cells, and a decrease in placental serotonin concentrations and percentage of serotonin-positive giant cells. A substantial increase in the ratio of the primary serotonin metabolite, 5-hydroxyindoleacetic acid, to serotonin was also reported (Mao et al. 2020).

Rats

In female Wistar rats orally administered 0.025 or 4 µg/kg-day BPS on a wafer from one week prior to mating until GD 18, female and male placental weights were increased at 4 µg/kg-day (Fudvoye et al. 2025).

Sheep

In pregnant sheep administered SC injections of 0.5 mg/kg-day BPS from GD 30 – 100, there was an increase (NS) in placental weight and a decrease in trophoblast-derived binucleate cells, with no effects on placental stereology or number of placentomes per placenta at GD 120. There were decreases in serum concentrations of two pregnancy-associated glycoproteins involved in placental endocrine function, E-cadherin expression in placentomes, expression of fusogenic genes, and maternal serum progesterone (NS) at time points ranging from GD 60 – 120 (Gingrich et al. 2018). See Mechanistic Considerations and Other Data Relevant to Developmental Toxicity for more information.

Birth Outcomes

Studies of the effects of gestational (or gestational and lactational) BPS exposure on litter size, fetal viability, birth weight, and birth length were assessed in six mouse studies and five rat studies.

Mice

In mice orally administered 4 µg/kg-day BPS from GD 0 through weaning (LD 28), there was an increased percentage of dead male and female pups during the first postnatal week, with a higher mortality in males. Mortality was highest during or just after parturition. In addition, five out of 15 (33.3%) BPS-treated dams lost their entire litter (Bonaldo et al. 2022).

In the 9-month-old F1 female offspring of F0 mice administered 0.5, 20, or 50 µg/kg-day BPS orally via pipette from GD 11 to birth, there were decreased number of F2 pups per litter at 20 µg/kg-day and parturition and nursing issues at all doses (Shi et al. 2019a).

Exposure of mice *in utero* and during lactation by treating dams with 2 or 200 µg/kg-day BPS orally on a wafer did not result in effects on litter size, litter weight, or pup birthweight in either F1 or F2 litters. However, infanticide and maternal neglect were observed behaviors of F1 dams that were exposed during gestation and lactation, demonstrating adverse effects on maternal behavior (see Neurodevelopment and Behavior for further detail) (Catanese and Vandenberg 2017).

Mice exposed *in utero* from dams treated with 3.33 µg/L BPS in drinking water (author estimated 500 µg/kg-day) from GD 8.5 to PND 3 had slightly decreased body length (-2%) at birth, with no effect on birthweight (Gao et al. 2024).

No effects were reported on litter size or birthweight in F1 male offspring of F0 mice administered 0.2 mg/kg-day BPS orally via pipette from GD 8 (Kim et al. 2015) or in the F2 grand-offspring of F0 ICR female mice orally administered 2 or 10 µg/kg-day BPS from GD 12.5 to GD 15.5 (MY Zhang et al. 2020).

Rats

In the progeny of female rats orally administered 0.025 or 4 µg/kg-day BPS from one week pre-mating to GD 18, fetal weight at GD 18 was decreased in males at 0.025 µg/kg-day and increased in females and males at 4 µg/kg-day. No effects on litter size were reported (Fudvoye et al. 2025).

In BASF (2019), there were decreases in the numbers of pups per litter in F1 progeny at 60 and 180 mg/kg-day (NS both doses; -9% and -16%, respectively) and F2 progeny at 180 mg/kg-day, in total F2 pups at 180 mg/kg-day, in liveborn F1 pups at 180 mg/kg-day, and an increase in stillborn F1 pups at 180 mg/kg-day. There was no effect on the fertility index in F1 dams. In F1 dams, there were two complete litter losses at 180 mg/kg-day (BASF 2019).

Two anonymous studies reviewed in ECHA (2019) reported effects of BPS treatment on birth outcomes. At delivery, there was a decreased number in the F1 offspring of F0 parental rats gavaged with 300 mg/kg-day BPS in Anonymous Studies 12 and 14. No effect on viability index (PND 4 vs. PND 1 survival) or birthweight was reported in Anonymous Study 12 (ECHA 2019).

No effects on litter size or birthweight were reported in the F1 offspring of SD rats treated with 5, 25, or 50 µg/L BPS via drinking water from GD 1 – GD 20 (Ullah et al. 2019).

Structural Malformations and Variations

Skeletal and visceral variations and/or malformations were reported in one rat study and a skeletal variation was reported in one sheep study. Here, there is an important distinction between fetal variation and fetal malformation. Fetal variations are defined by a change that is unlikely to negatively impact the survival or health of the animal and may or may not also occur in control animals. Fetal malformations are defined by a permanent structural change that is likely to negatively impact the survival or health of the animal. Thus, all fetal malformations found have been included in this summary regardless of statistical significance.

Rats

In Wistar rat dams gavaged with 30, 100, or 300 mg/kg-day BPS from GD 6 – 19, there were increases in the incidence (fetuses/litter) of total visceral variations at 100 (NS; +49%) and 300 (NS; +39%) mg/kg-day and individual visceral variations including renal dilation at 100 and 300 mg/kg-day and dilated ureter at 300 mg/kg-day. There was a dose-dependent increase in total skeletal malformations at 100 (NS; +300%) and 300 (+514%) mg/kg-day, including shortened scapula (1/140) and one fetus with multiple skeletal malformations at 100 mg/kg-day, and misshapen basisphenoid (1/127), malpositioned and bipartite sternebra with unchanged cartilage (2/127 fetuses; 2/24 litters), and misshapen tuberositas deltoidea (1/127) at 300 mg/kg-day, with no skeletal malformations observed in the control. Several skeletal variations were present in all groups including controls, however, “total” skeletal variations had no relationship to dose and were not significantly increased in treatment groups relative to control (BASF 2014).

Sheep

In pregnant sheep administered an SC dose of 0.5 mg/kg-day BPS from GD 30 – 100, there was a decrease in biparietal diameter (variation) in male fetuses on GD 120 (Pu et al. 2017).

Sex Ratio

The effects of developmental BPS exposure on sex ratio were assessed in six studies in mice, four studies in rats, and one study in sheep. Several of these studies were also discussed in (OEHHA 2023).

Mice

There was a decrease (NS) in the F1 male:female sex ratio in offspring of F0 female mice orally administered 4 µg/kg-day BPS from GD 0 through weaning (LD 28), but this was likely due to an increase in offspring mortality with a higher mortality in males,

suggesting that male pups may be more sensitive to BPS treatment (Bonaldo et al. 2022).

There were no effects on sex ratio in F1 mice of C57BL6/J F0 females administered 200 µg/kg-day BPS on a wafer for two weeks prior to mating with untreated F0 males (Mao et al. 2020), F1 mice exposed *in utero* from dams treated with 3.33 µg/L BPS in drinking water from GD 8.5 to PND 3 (Gao et al. 2024), F2 grand-offspring of F0 mice orally administered 2 or 10 µg/kg-day BPS from GD 12.5 to GD 15.5 (MY Zhang et al. 2020), F2 grand-offspring of CD-1 F0 mice orally administered 0.5, 20, or 50 µg/kg-day BPS from GD 11 until birth (Shi et al. 2019a), and F1 and F2 offspring of CD-1 dams administered via wafer 2 or 200 µg/kg-day BPS from GD 9 to PND 20 (Catanese and Vandenberg 2017).

Rats

There were no effects on sex ratio in F1 rats exposed *in utero* from dams treated with 5, 25, or 50 µg/L BPS in drinking water from GD 1 to GD 20 (Ullah et al. 2019), in the F1 offspring of rats treated with 0.025 or 4 µg/kg-day from one week pre-mating to GD 18 (Fudvoye et al. 2025), in F1 rats exposed *in utero* from dams treated with 30, 100, or 300 mg/kg-day from GD 6 to GD 19 (BASF 2014), or in the F1 and F2 offspring of F0 and F1 rats treated with 20, 60, or 180 mg/kg-day from 10 weeks pre-mating through weaning at PND 21 (BASF 2019).

Sheep

One sheep study assessed sex ratio and found no effects at 0.5 mg/kg-day (Gingrich et al. 2018).

Neurodevelopment and Behavior

Neurodevelopment during the pre-, peri-, and post-natal periods is especially sensitive to chemical exposures. Effects of BPS on cognitive, motor, and behavioral function have been assessed and observed in several studies that included a postnatal component of exposure. These studies may be directly relevant to human prenatal exposures because the developmental stage of neurological structures affected by postnatal exposure in rodents may correspond to the developmental stage occurring during gestation in humans (Translating Time – Across Developing Mammalian Brains) (Clancy et al. 2007; Workman et al. 2013). Neurodevelopment and behavior were assessed in four mouse and two rat studies.

Mice

In 10-week old male offspring of mice administered 0.2 mg/kg-day BPS via oral pipetting from GD 8 through lactation (PND 21), social behavior was altered with increased anxiety and decreased interest in social interactions, with no effects on sociability or novelty preference indices (Kim et al. 2015).

One study reported alterations in maternal behavior that were generation- and dose-dependent. In this study, F0 dams were orally administered 2 or 200 µg/kg-day BPS via wafer from GD 9 to lactation day (LD) 20, and F0 and F1 maternal behavior was assessed. In F1 dams, there was a higher incidence of infanticide and a decreased latency to interact with and retrieve pups at 2 µg/kg-day and altered nesting time and pup neglect at 2 and 200 µg/kg-day. Effects on maternal behavior were more severe in F1 dams compared to F0 dams. These findings suggest that exposure to BPS as adults (F0) resulted in modest changes to traditional measures of maternal behavior while female offspring exposed to BPS during development (F1) had more detrimental changes (Catanese and Vandenberg 2017).

In pregnant Non-Obese Diabetic Excluded Flora (NODEF) mice, a model for type 1 diabetes, administered 3 µg/kg-day BPS during gestation, female offspring had decreased working and short-term memories and male offspring had increased depression- and anxiety-like (NS) behaviors at 12 weeks (McDonough et al. 2021a).

In both female and male offspring of dams (n = 2) pre- and post-natally administered 50 µg/kg-day BPS via SC injection from GD 9.5 to PND 28, there was a decreased preference for social novelty with no change in sociability. There were no effects on anxiety- and depression-like behaviors, memory, locomotion, or cognition (Moon et al. 2023).

Rats

Decreased learning and memory function were reported in rat offspring of dams administered 40 µg/kg-day BPS via oral gavage from GD 6 to LD 21. There was decreased proliferation in the granular cell layer and hilus, stemness, and self-renewal of neural stem cells in the dentate gyrus region of the hippocampus. There was decreased differentiation of neural stem cells into neurons and number of mature neurons, and increased apoptosis. In hippocampal neurons, there was myelin sheath decompaction and loosening, decreased number of axons, and increased percentages of damaged synapses and mitochondria (Tiwari et al. 2024).

There were no effects on neuronal development and function indicated by the Morris water maze, Functional Observational Battery, or motor activity tests in the F1 offspring of a modified extended one-generation reproductive study in SD rats where male and

female parents (F0) and offspring (F1) were administered BPS via gavage at 20, 60, or 180 mg/kg-day from 10 weeks pre-mating through weaning at PND 21 (BASF 2019).

Endocrine and Metabolic Effects

The endocrine system regulates and connects many physiological functions including metabolism, reproduction, and overall development. Dysregulated endocrine and metabolic programming during development can increase susceptibility to metabolic conditions including obesity, diabetes mellitus, and nonalcoholic fatty liver disease (Heindel et al. 2017).

Endocrine effects on the developing female and male reproductive systems (e.g., ovaries and testes) are discussed later in the document. This section focuses on the developmental effects of BPS on adipose tissue and the liver, two endocrine/metabolic-related organs (Garruti et al. 2023; Scheja and Heeren 2019), and other endocrine and metabolic effects. Key metabolism-associated outcomes at the organ, tissue, and cellular levels are summarized below.

Molecular effects, including the levels of biomarkers (e.g., hormones) and the expression of genes and proteins related to endocrine function in reproduction, metabolism, and developmental processes, are discussed in detail in Section 4.3 Mechanistic Considerations and Other Data Relevant to Developmental Toxicity.

Body composition and adipose tissue

Adipose tissue is a key metabolic organ that regulates energy homeostasis, storage, and utilization (Tseng 2023). Dysregulated adipose function can contribute to metabolic conditions including dyslipidemia, diabetes mellitus, and obesity. The effects of gestational BPS exposure on body composition, adipose tissue and/or adipocytes were assessed in seven studies, including two in mice, four in rats, and one in sheep.

Mice

In 10-week old male offspring of mice administered 0.05, 0.5, 5, or 50 mg/kg-day BPS from GD 9 – 18 and fed either a high-fat diet (HFD) or a standard diet, there was an increase in body weight and gonadal white adipose tissue weight relative to body weight at 5 and 50 mg/kg-day in the HFD group, with no effects in the standard diet group. Food intake, energy expenditure, and gonadal white adipose tissue histology were assessed only in the HFD group. Adipocyte hypertrophy at all doses and no effects on food intake or energy expenditure were reported. There was upregulation of adipogenesis-related genes in the HFD groups at 5 and 50 mg/kg, with no effects of BPS observed in the standard diet groups (Ahn et al. 2020).

In 12-week-old male offspring of mice gavaged with 5, 50, or 500 µg/kg-day from GD 0.5 – 18.5, there was an increase in body weight gain measured over a 12-week period at 50 µg/kg-day BPS without changes to terminal body weight or weekly food intake. There were increases in abdominal white adipose tissue weight relative to body weight and in white adipose tissue adipocyte area (NS) at 50 µg/kg-day (Zhang et al. 2023).

Rats

In male offspring of rats gavaged with 0.4, or 4 µg/kg-day BPS from GD 4 – 21, there were increases in body weight at PND 45, 59, and 73 at both doses and increased body mass and lean mass on PND 30 and fat mass and fat percentage on PNDs 30 and 90 at 0.4 µg/kg; and adipocyte hypertrophy in the visceral adipose tissue on PND 90 at both doses (Molangiri et al. 2023).

In offspring of Wistar rat dams gavaged with 0.4 µg/kg-day BPS from GD 4 – 21, there were increases in body weight and surface area as well as bone mineral content and bone mineral density at PND 30 and 90 (Varma et al. 2024).

In offspring of rats administered 5 µg/kg-day BPS via oral pipetting from GD 6 – 21, there were decreases in epididymal and abdominal adipose tissue weights relative to body weight in males. There were no effects on ovarian adipose tissue weight relative to body weight in females (Kaimal et al. 2021).

There were no effects on retroperitoneal fat pad weight in PND 16 or 80 male rat offspring of dams administered 5, 25, or 50 µg/L BPS from GD 1 – 20. Body weight was increased at 50 µg/L at PND 80 (Ullah et al. 2019).

Sheep

Smaller peri-renal adipocytes and altered gene expression of adipogenic markers in both adipose tissue and primary adipocytes were observed in GD 120 male fetuses of pregnant sheep administered an SC dose of 0.5 mg/kg-day BPS from GD 30 – 100 (Pu et al. 2017).

Liver

The liver is also essential for regulating energy homeostasis. Perturbations to this balance can lead to inflammation, hepatic fat accumulation, and metabolic dysfunction (Azzu et al. 2020). One study each in mice and rats evaluated the effects of developmental BPS exposure on liver function.

Mice

In 12-week-old male offspring of mice gavaged with 50 µg/kg-day BPS from GD 0.5 – 18.5, increased liver triglycerides and lipid deposition without changes in liver weight relative to body weight was observed, indicating excessive hepatic lipid accumulation (Zhang et al. 2023).

Rats

In PND 90 male offspring of rats gavaged with 0.4 and 4 µg/kg-day BPS from GD 4 – 21, increased absolute liver weight, microvesicular steatosis, and increased lipogenesis- and inflammation-related hepatic protein and gene expression was observed (Molangiri et al. 2023).

Other endocrine and metabolic effects

The effects of developmental BPS exposure on levels of metabolic markers in plasma, serum, or tissues were assessed in three studies in mice and two studies in rats.

Mice

In 12-week-old male offspring of mice gavaged with 50 µg/kg-day BPS from GD 0.5 – 18.5, there were increased levels of serum non-esterified fatty acids and triglycerides (Zhang et al. 2023).

In the GD 12.5 placentae of female C57BL/6J mice orally administered 200 µg/kg-day BPS on a wafer for two weeks prior to mating with an untreated male, there were decreased levels of the fatty acids stearic, palmitic, docosahexaenoic, and octadecenoic acid, and no effects on steroid hormone levels (Mao et al. 2020).

At both PND 21 and 12 weeks of age, male offspring of NODEF mice administered 3 µg/kg-day BPS during gestation, there were decreases in non-fasted blood glucose levels, but no effects on glucose or insulin tolerance (McDonough et al. 2021a).

Rats

In PND 90 male offspring of rats gavaged with 0.4 µg/kg-day BPS from GD 4 – 21, there was an increase in corticosterone levels, but no effects on fasting glucose, triacylglycerol, or cholesterol levels (Molangiri et al. 2023).

In the offspring of rats administered BPS by gavage at 0.4, 4, or 40 µg/kg-day from GD 4 – 21, there was an increase in plasma levels of the fatty acid docosahexaenoic acid on PND 90 at 0.4 µg/kg-day with no effects on testicular fatty acid composition in PND 90 males (Varma et al. 2023).

Developing Reproductive System

Female reproductive system

Studies that assessed the effects of gestational and lactational exposure to BPS on the developing female reproductive system are discussed in detail in OEHHA (2023), available here: Evidence on the Female Reproductive Toxicity of Bisphenol S (ca.gov).

Since the publication of OEHHA (2023), two new studies (Gao et al. 2024 and Fudvoye et al. 2025) were identified and included in this document. This section highlights and summarizes the findings from Gao et al. (2024) and Fudvoye et al. (2025) and from the relevant studies reviewed in OEHHA (2023). Results from Gao et al. (2024) and Fudvoye et al. (2025), where applicable, are presented first. Ten studies, Seven in mice and three in rats, assessed the effects of gestational and/or lactational BPS on the developing female reproductive system.

Effects on the ovary

Primordial follicles are the building blocks of follicular development and establish the ovarian reserve. Primordial follicles are formed during gestation and are quiescent until puberty in humans and are formed during the perinatal period in mice and rats. Thus, findings from perinatal exposure studies in mice and rats that assessed effects on primordial follicles are included here.

In Gao et al. (2024), F0 ICR female mice were administered 3.33 µg/L BPS (author estimated 500 µg/kg-day) in drinking water from GD 8.5 to LD (PND) 3. In PND 4 female offspring, there were fewer cysts (nests) and more primordial follicles, decreased ovarian reserves, and increased number of oocytes found in primordial follicles instead of oocyte cysts (Gao et al. 2024).In the ovaries of F1 female offspring of ICR mice orally administered 2 and 10 µg/kg-day BPS from GD 12.5 to GD 15.5, there was accelerated meiotic progression defined by a smaller percentage of oocytes at earlier stages of meiosis prophase I, damaged oocyte structure, increased incidence of spindle malformations, and accelerated cyst breakdown (MY Zhang et al. 2020).

In the ovaries of PND 4 offspring of CD-1 mice orally administered 0.5, 20, and 50 µg/kg-day BPS from GD 11 until birth, germ cell cyst breakdown was inhibited at 0.5 and 20 µg/kg-day and the ratio of primary follicles to total oocytes was decreased at all doses (Shi et al. 2019a).

In the offspring of SD rats orally administered 5 µg/kg-day BPS from GD 6 to GD 21, there was a decrease in the number of *corpora lutea* (Kaimal et al. 2021).

Uterine weight

No effects on uterine weight were observed in the PND 31 offspring of CD-1 mice administered 2, 200, or 2000 µg/kg-day BPS via oral pipetting from GD 8 to PND 2 with and without estrogen challenge to the pups (Kolla and Vandenberg 2019) or in the adult offspring of SD rats administered 5 µg/kg-day BPS via oral pipetting from GD 6 – 21 (Kaimal et al. 2021).

Mammary gland development

Mammary gland development begins during gestation and continues in puberty when production of ovarian E2 and pituitary growth hormone stimulate the growth of terminal end buds. Terminal end buds regress and alveolar buds are formed in adulthood and, in pregnancy, prolactin secreted from the pituitary gland stimulates development of lobuloalveolar units in preparation for lactation. The effects of BPS exposure on mammary gland development varied by timing of outcome assessment.

There was accelerated development of terminal end buds, including a dose-dependent increase in length and count, increased branching at 0.05 and 5 mg/kg-dose, and accelerated glandular development at 5 mg/kg-day in PND 20 female offspring of CD-1 mice gavaged twice per day with 0.05, 0.5, or 5 mg/kg-dose BPS from GD 10.5 – 17.5 (Tucker et al. 2018). Mammary gland ductal area was decreased at 2 µg/kg-day with no effect on number or total area of terminal end buds and estrogen receptor (ER) gene expression was increased in mammary tissue at 200 µg/kg-day in PND 31 female offspring of CD1 mice orally administered 2, 200, or 2000 µg/kg-day BPS from GD 8 to LD 2 (Kolla and Vandenberg 2019).

Mammary neoplastic lesions

There were multiple findings (NS) of mammary neoplastic lesions, including one each of carcinoma, histiocytic sarcoma, papillary carcinoma, and squamous cell carcinoma at 0.5 mg/kg-dose and two adenocarcinomas and one benign fibroadenoma at 5 mg/kg-dose BPS in 11 to 16 month-old female offspring of mice gavaged twice per day with 0.05, 0.5, or 5 mg/kg-dose BPS from GD 10.5 – 17.5 (Tucker et al. 2018).

Puberty onset

In Gao et al. (2024), vaginal opening occurred earlier in the female offspring (26–28 days treated vs. 30–33 days control) of F0 ICR female mice treated with 3.33 µg/L BPS in drinking water from GD 8.5 to LD (PND) 3 (Gao et al. 2024).

In female offspring of CD-1 mice treated with 0.5, 20, and 50 µg/kg-day BPS from GD 11 until birth, varied timing of pubertal onset, measured by age at vaginal opening, was reported with a 1–2 day earlier onset at 0.5 µg/kg-day, 2.5-day later onset at 20 µg/kg-day, and no effect at 50 µg/kg-day (Shi et al. 2019a).

In Fudvoye et al. (2025), there was an NS increase in days to vaginal opening in the female offspring of Wistar rats orally administered 0.025 µg/kg-day BPS from one week premating until GD 18 (Fudvoye et al. 2025).

In F1 female offspring of SD rats gavaged with 20, 60, or 180 mg/kg-day BPS from 10 weeks pre-mating through weaning with continued treatment through production of the F2 generation, vaginal opening was slightly but significantly delayed (PND 33.2 treated vs. PND 32.3 control) at the low dose only (BASF 2019).

Other studies found no effects on pubertal onset including in the offspring of treated mice (BASF 2019; Kolla and Vandenberg 2019; Tucker et al. 2018).

Effects on estrous cycle

In Gao et al. (2024), there was an increased average cycle length with a shortened metestrus phase and prolonged diestrus phase, and earlier first estrus (27–31 days treated vs. 30–37 days control) in the female offspring of ICR female mice treated with 3.33 µg/L BPS in drinking water from GD 8.5 to LD (PND) 3 (Gao et al. 2024).

There was estrous cycle irregularity with several days stalled in estrus and diestrus in the female offspring of CD-1 mice treated with 0.5, 20, and 50 µg/kg-day from GD 11 until birth (Shi et al. 2019a).

One study found no effect on the day of first estrus or estrous cycle length in CD-1 mice (Tucker et al. 2018).

In Fudvoye et al. (2025), there was a NS increase in the percentage of cycle regularity in the female offspring of Wistar rats orally administered 0.025 µg/kg-day BPS from one week premating until GD 18 (Fudvoye et al. 2025).

Reproductive performance

In Gao et al. (2024), there were adverse effects on fertility including decreased litter size by the third, fourth, and fifth mating; increased abortion incidence by the fourth mating; and increased infertility by the fifth mating in the female offspring of ICR female mice treated with 3.33 µg/L BPS in drinking water from GD 8.5 to LD (PND) 3 (Gao et al. 2024).

In the female offspring of CD-1 mice treated with 0.5, 20, and 50 µg/kg-day BPS from GD 11 until birth, there was no effect on reproductive performance at 3 months, but there were decreased successful mating and pregnancy rates at 6 months at 0.5 and 20 µg/kg-day and at 9 months at all doses. (Shi et al. 2019a).

There were no effects on litter size in the F1 offspring or birthweight in the F2 grand-offspring of F0 ICR female mice orally administered 2 or 10 µg/kg-day BPS from GD 12.5 to GD 15.5. There were decreases in the proportion of two- and four-cell embryos and the proportion of blastocysts in F1 oocytes of offspring of F0 ICR mice at 2 or 10 µg/kg-day and used for IVF with sperm from untreated males (MY Zhang et al. 2020).

In a modified extended one-generation reproductive study in SD rats there was increased post-implantation loss in F1 parental SD rats at 60 (NS; +73%) and 180 mg/kg-day BPS (BASF 2019).

Male reproductive system

Studies that assessed the effects of gestational exposure to BPS on the developing male reproductive system are discussed in detail in OEHHA (2024), available here: Evidence on the Male Reproductive Toxicity of Bisphenol S (ca.gov)

One additional relevant study (Fudvoye et al. 2025) was identified since the publication of OEHHA (2024). This section highlights and summarizes the findings from Fudvoye et al. 2025 and from the eight studies reviewed in OEHHA (2024) that assessed effects of gestational BPS on the developing male reproductive system. Three of these studies were in mice and six were in rats.

Reproductive organ weights and histology

Relative to body weight testis weight was increased at 0.5 µg/kg-day in PND 60 F3 male great-grand offspring of F0 mice administered 0.5, or 50 µg/kg-day BPS from GD 7 to birth. There was abnormal distribution of spermatogenesis staging with an increased number of tubules in stages I-VI and a decreased number in stage IX at the same dose (Shi et al. 2019b). In the male offspring of CD-1 mice administered 0.5, 20, or 50 µg/kg-day BPS via oral pipetting from GD 11 to birth, spermatogenesis stage distribution was altered with a decreased percentage of stage VII tubules and increased percentage of stage VIII tubules at 50 µg/kg-day on PND 60. There were no effects on absolute or relative (to body weight) testis weights (Shi et al. 2018).

In PND 90 male offspring of Wistar rats gavaged with 0.4, 4, or 40 µg/kg-day from GD 4 – 21, absolute testis weight was increased at all doses. Histopathology findings in the testes included decreased seminiferous tubule diameter and epithelial height (NS) at 0.4 and 4 µg/kg-day (Molangiri et al. 2022). Absolute seminal vesicle weight was decreased in PND 80 male offspring of SD female rats orally administered 50 µg/L BPS from GD 1 to GD 20. Histopathology findings at PND 80 included decreased seminiferous tubule area at 25 and 50 µg/L and increased seminiferous tubule height and decreased interstitial space, lumen, and diameter at 50 µg/L (Ullah et al. 2019).

Two other studies found no effect on male offspring reproductive organ weights (BASF 2019; Kaimal et al. 2021).

Sperm parameters

Gestational BPS treatment decreased sperm count, motility, and/or daily sperm production.

In the male offspring of CD-1 mice administered 0.5, 20, or 50 µg/kg-day from GD 11 to birth, there were decreases in sperm concentration at 0.5 and 20 µg/kg-day and motility at 0.5 µg/kg-day at PND 60 (Shi et al. 2018). The F3 male grand-offspring of F0 CD-1 mice administered 0.5 or 50 µg/kg-day from GD 7 to birth showed decreased sperm count at 0.5 and 50 µg/kg-day and motility at 0.5 µg/kg-day at PND 60 (Shi et al. 2019b). There was decreased number of sperm in the caput/corpus epididymis and decreased sperm motility at 25 and 50 µg/L, and fewer spermatogonia, spermatocytes, and spermatids and decreased daily sperm production at 50 µg/L in the PND 80 male offspring of SD rats orally administered BPS in drinking water from GD 1 to GD 20 (Ullah et al. 2019).

Anogenital distance

Anogenital distance (AGD) is a marker of developmental endocrine disruption and can be influenced by androgen or anti-androgen factors. AGD was decreased in PND 1 male offspring of SD rats orally administered 5 µg/kg-day from GD 6 to GD 21 (Kaimal et al. 2021).

Several studies found no effect on AGD and/or anogenital index (AGI) at birth in SD rats (BASF 2019; ECHA 2019 [Anonymous Study 12]; Ullah et al, 2019) or Wistar rats (Molangiri et al. 2022).

Mammary gland effects

There was a NS increase in the size of epithelial anlagen and increased spacing between cells in the mammary glands of GD 16 male offspring of CD-1 mice administered 200 µg/kg-day BPS on wafers from GD 9 to GD 16 (Kolla et al. 2019).

Two studies in SD rats did not find effects on male offspring mammary glands, specifically, no effects were observed on nipple retention at birth at 5, 25, or 50 µg/L (Ullah et al. 2019b), and no effects were observed on male nipple or areola anlagen at 20, 60, or 180 mg/kg-day BPS (BASF 2019).

Puberty onset

Gestational BPS exposure did not alter the onset of male puberty, as determined by preputial separation, in male offspring of Wistar rats orally administered 0.025 µg/kg-day

BPS from one week premating until GD 18 (Fudvoye et al. 2025), or in F1 offspring of SD rats at 20, 60, or 180 mg/kg-day (BASF 2019) or 5, 25, or 50 µg/L (Ullah et al. 2019b).

4.2.3 Studies in Non-Mammalian Organisms

Studies investigating the developmental effects of BPS have also been conducted in the following non-mammalian species: zebrafish, Chinese medaka, chickens, *C. elegans*, and *Drosophila*. These non-mammalian models are well-studied and widely used in developmental toxicology research. While maternal and/or placental interactions and effects are not available for evaluation, these animal models share many conserved developmental processes with mammals, and as whole organisms, retain physiological and system-level relevance. Other advantages include their rapid development, amenability to genetic manipulation, and external (visually accessible) development.

Studies in Fish

While zebrafish may appear to be an unlikely translative model for evaluating chemical effects on human health, approximately 70% of human genes have at least one zebrafish orthologue, supporting the use of zebrafish to elucidate molecular mechanisms underlying chemical-mediated toxicity (Howe et al. 2013). The zebrafish genome can also be manipulated with relative ease; thus, the use of transgenic zebrafish lines can facilitate the toxicological evaluation of tissue- and cell-specific assessments on processes such as cardiovascular, neuronal, and ocular development.

Several studies have assessed the effects of BPS on zebrafish development, including studies that treated the parental generation and evaluated effects in subsequent generations, and/or utilized transgenic fluorescent reporter lines to visualize, how BPS may affect processes at multiple levels of biological organization, including hormone receptor activity, brain development, and vascular function. Similarly, Chinese medaka fish have been used as a model organism for development. For example, like zebrafish, the embryos and eggs are transparent and facilitate visualization of early developmental processes in a short period of time (Wittbrodt et al. 2002).

Major developmental processes occur by 5 days post fertilization (dpf) (120 hours post fertilization (hpf)) in zebrafish, which is also when zebrafish larvae begin to free-feed (Licitra 2024). This document includes studies where BPS is administered up to 7 dpf (i.e., around the free-feeding stage). Additionally, this document will define the end of the embryonic stage and the start of the larval stage at 72 hpf (Kimmel et al. 1995; Parichy et al. 2009), the larval period from 72 hpf to ~29 dpf, and the juvenile period from ~30 dpf to ~89 dpf (Bradford et al. 2022; Parichy et al. 2009). Where BPS exposure spans embryonic and larval stages, zebrafish are designated as

embryo/larvae. When available, zebrafish strains will be specified. In Chinese Medaka, hatching occurs around 7 dpf and fish emerge as feeding young adults (Wittbrodt et al. 2002). In total, 44 fish studies assessed the developmental effects of BPS treatment, including 43 studies in zebrafish and one study in Chinese medaka.

Embryo hatchability

Many studies assessed the embryo hatching period ~48-72 hpf (Bradford et al. 2022) and reported outcomes such as time-to-hatching, hatching success, and hatching rate at concentrations that did not impact embryo survival. Some studies reported effects, often at similar BPS concentrations. However, the plasticity of hatching may limit its use as a staging index for zebrafish as compared to other species since hatching may occur sporadically at standard temperature and does not reflect advances in development *per se* (Kimmel et al. 1995; Wisenden et al. 2022).

Accelerated hatching rates were observed in two zebrafish studies:

- Wild-type (WT) embryo/larvae treated with 1 or 100 µg/L BPS from 2 hpf to 120 hpf, hatching rate was accelerated at 48 hpf with 100 µg/L BPS (Qiu et al. 2021).
- WT AB strain zebrafish embryo/larvae treated with 0.1 or 1 µM BPS (OEHHA calculated 25.03 and 250.27 µg/L, respectively) from 2 to 144 hpf, there were accelerated hatching rates in embryo/larvae at 55 hpf (Coumailleau et al. 2020).

Decreased hatching rates or delayed hatching times were observed in nine zebrafish studies and one study in Chinese medaka fish:

- WT WIK strain embryo/larvae treated with 10, 20, 50, 100, 200, or 300 mg/L BPS from 1 hpf to 96 hpf, hatching rate was decreased at 72 hpf with an EC_{50} of 155.47 mg/L BPS (Moreman et al. 2017).
- WT embryo/larvae treated with 0.1, 1, 10, 100, or 1000 µg/L BPS from 4 hpf to 120 hpf, decreased hatching rates were reported with 1, 10, and 100 µg/L BPS exposure at 48 hpf and with 10 and 100 µg/L BPS exposure at 54 hpf (Qiu et al. 2018).
- WT embryo/larvae treated with 0.4, 2, 10, or 50 mg/L BPS from 4 hpf to 120 hpf, there was a delayed hatching time in the 0.4 mg/L treatment group, but no effect on hatching rate overall (Lee et al. 2019).
- WT embryo/larvae treated with 4, 8, or 12 mg/L BPS from 6-10 hpf to 96 hpf, there was a decreased hatching rate in the 12 mg/L group when assessed at 96 hpf with NS decreases in the other two treatment groups (Neighmond et al. 2023).

- F1 offspring of WT zebrafish treated with 0.1, 1, 10, or 100 µg/L BPS from 2 to 75 dpf, there were decreased hatching rates and delayed hatching times at 10 and 100 µg/L (timing not specified) (Naderi et al. 2014).
- Untreated F1 generation of WT Tu strain F0 embryo/larvae treated with 1, 10, or 100 µg/L BPS from 2 to 120 hpf, decreased hatching rates were reported at all BPS concentrations at 48 hpf and 60 hpf, and in the 10 and 100 groups at 72 hpf (Wei et al. 2018).
- F1 offspring of WT AB strain adult F0 zebrafish treated with 0.5, 5, or 50 µg/L BPS for 21 days with or without subsequent F1 exposure from 0 to 6 dpf at the same concentrations of BPS as their parents (F0), decreased hatching rates in untreated F1 offspring were observed with 5 and 50 µg/L BPS treatment in F0, and in treated F1 offspring at all BPS concentrations. Delayed hatching times were observed in untreated F1 offspring with 50 µg/L BPS treatment in F0 and in treated F1 offspring at all BPS concentrations (Ji et al. 2013).
- Chinese medaka fish were treated with 20, 200, or 2000 ng/L BPS from the blastocyst stage (approximately 6.5 to 10 hpf) to 15 dpf, the hatching rate was decreased at 20 ng/L BPS (B Li et al. 2024).

Two multi-generational zebrafish studies reported variable hatching rates based on the generation assessed:

- WT AB strain F0 embryos treated with 1 or 100 µg/L BPS from 3 hpf to 120 dpf hatching rate was assessed in the untreated F1, F2, and F3 generations. A decreased hatching rate was observed at 60 hpf and 72 hpf in F3 offspring at 100 µg/L (Hao et al. 2022).
- WT AB strain F0 embryo/larvae exposed to 10 µg/L BPS from 24 hpf to 180 dpf with and without subsequent F1 exposure from 24 to 96 hpf, there was no effect on hatching in the F0 generation. There was a decreased hatching rate with or without continued BPS treatment in the F1 generation (Dong et al. 2018).

No effects of BPS on hatching rates were reported in eight zebrafish studies:

- Transgenic (*tg*) (*cyp19a1b*:GFP) embryo/larvae treated with 25, 50, 100, 200, or 400 mg/L BPS from 0 dpf to 4 dpf (Christophe et al. 2023).
- WT AB strain embryo/larvae treated with 1 or 100 µg/L BPS from 2 hpf to 96 hpf (Qin et al. 2023).
- WT AB strain embryo/larvae treated with 1, 10, or 100 µg/L BPS from 2 hpf to 72 hpf (Wang et al. 2020).
- WT AB strain embryo/larvae treated with 1, 10, or 100 µg/L BPS from 2 to 48 hpf (Wang et al. 2023).

- WT AB strain embryo/larvae treated with 200 µg/L BPS from 4 hpf to 72 hpf (Gu et al. 2022).
- WT AB strain embryo/larvae treated with 0.01, 0.03, 0.1, 0.3, or 1 µM (OEHHA calculated 2.50 µg/L, 7.51 µg/L, 25.03 µg/L, 75.08 µg/L and 250.27 µg/L, respectively) BPS from 4 hpf to 120 hpf (Gyimah et al. 2021b).
- WT embryo/larvae treated with 0.5, 1, 10, or 50 µM (OEHHA calculated 125.14 µg/L, 250.27 µg/L, 2.50 mg/L, and 12.51 mg/L, respectively) BPS from 0.5 hpf to 120 hpf (Huang et al. 2023).
- Hatch ratio of WT AB strain embryo/larvae treated with 2.5, 12.5, or 25 mg/L BPS from 1.5 hpf to 4 dpf (Mu et al. 2018).

Somatic effects

Body length and weight

Changes to body length with BPS treatment were assessed in 13 zebrafish studies and the Chinese medaka study.

Decreased body length was observed in the following fish studies:

- WT AB zebrafish treated from 2 to 96 hpf, 1 µg/L BPS decreased body length at 96 hpf (Qin et al. 2023).
- WT zebrafish treated from 2 to 120 hpf, decreased body length was reported at 120 hpf with 100 µg/L (Qiu et al. 2021).
- Three studies that treated from 4 to 120 hpf, decreased body length was reported in WT zebrafish at 100 and 1000 µg/L BPS (Qiu et al. 2018; Yang et al. 2018), and in WT AB strain zebrafish at 1 µM at 72, 96, and 120 hpf (250.27 µg/L, calculated by OEHHA) (Gyimah et al. 2021b).
- A transgenerational study, WT AB strain F0 zebrafish were treated with 1 and 100 µg/L BPS from 3 hpf to 120 dpf, and decreased body lengths were reported in untreated F2 and F3 progeny at 120 hpf and 96 hpf, respectively (Hao et al. 2022).
- WT AB strain embryo/larvae from 2 hpf to up to 120 hpf, body length was decreased at 24 and 48 hpf at 1, 10, and 100 µg/L (Wang et al. 2020)
- Decreased body length was observed at 2 µg/L in Chinese medaka exposed from the blastocyst stage to 15 dpf (B Li et al. 2024).

Two studies that treated WT AB strain embryo/larvae from 2 hpf to up to 120 hpf, body length was increased at 72 hpf at 1 µg/L (Wang et al. 2020) and 120 hpf at 1, 10, and 100 µg/L BPS (Wang et al. 2020; Wang et al. 2023).

No effects on body length were observed in the following zebrafish studies:

- WT AB strain embryo/larvae treated with 200 µg/L BPS from 4 hpf to 6 dpf (Jie Gu et al. 2022)
- WT embryo/larvae treated with up to 12 mg/L BPS from 6-10 hpf to 96 hpf (Neighmond et al. 2023).
- WT embryo/larvae treated with up to 50 mg/L BPS from 4 hpf to 120 hpf (Lee et al. 2019).
- Untreated F1 generation of WT Tu strain larvae at 5 dpf following parental exposure to 1, 10, 100, or 1000 µg/L BPS from 2 hpf to 120 dpf (Wang et al. 2019).
- In 4.5 dpf WT AB strain larvae treated from 8 hpf to 4.5 dpf with up to 100 µM BPS (25.03 mg/L BPS, calculated by OEHHA) (Bai et al. 2023).

Changes to body weight with BPS treatment were observed in two zebrafish studies.

Increased body weight was observed in embryo/larvae treated with 1, 10, and/or 100 µg/L BPS from 2 hpf to up to 5 dpf (Wang et al. 2020) and in untreated F1 larvae at 5 dpf from F0 zebrafish treated with 1, 10, or 100 µg/L BPS from 2 hpf to 120 dpf (Wang et al. 2019).

No effects of BPS on body weight were reported in WT AB zebrafish treated with up to 100 µg/L BPS from 2 to 120 hpf (Wang et al. 2023).

Somatic indices

Somatic indices provide a means to transform morphometric analyses into information about physiological processes. Gonadosomatic index (GSI), the ratio of gonadal tissue weight to total body weight, measures relative sexual maturity through gonadal development. Hepatosomatic index (HSI), the proportion of liver tissue weight to total body weight, may represent energy reserves and metabolic health in fish. One transgenerational study assessed BPS-mediated effects on GSI and HSI. Increased GSI was reported in untreated WT AB strain F2 females descended from F0 zebrafish treated with 1 µg/L BPS from 3 hpf to 120 dpf, while decreased GSI was reported in untreated F2 females descended from F0 zebrafish treated with 100 µg/L and in untreated F2 males descended from F0 zebrafish treated with 1 and 100 µg/L BPS. HSI was decreased in the untreated F1 and F2 female descendants of F0 zebrafish treated with 1 (F1 only) and 100 (NS for F1) µg/L BPS (Hao et al. 2022).

Morphological effects

Zebrafish are extensively used in evaluating the embryotoxicity or developmental toxicity of chemicals. Their rapid development and transparency as embryos facilitates

the assessment of morphological effects, including craniofacial, spinal, tail, yolk sac, pericardial, and swim bladder abnormalities (Truong et al. 2011). These observations are often grouped together to determine a “malformation rate” or “rate of deformity.” This section summarizes the effects of BPS on specific malformations. Pericardial effects are discussed in the “Circulatory System Effects” section.

Skeletal and yolk sac effects

Craniofacial and spinal abnormalities were observed in five zebrafish studies and the Chinese medaka study; yolk sac effects were observed in two zebrafish studies and in Chinese medaka (NS).

Increased head size, as indicated by increased intraocular distance, increased lower jaw length, and increased ceratohyal cartilage length was reported at 1 and 100 µM BPS in 4.5 dpf WT AB strain larvae treated from 8 hpf to 4.5 dpf with 1, 10, or 100 µM BPS (0.25, 2.50, and 25.03 mg/L BPS, calculated by OEHHA) (Bai et al. 2023).

Decreased head, ceratohyal cartilage, and palatoquadrate cartilage lengths with 1 µM BPS and decreased interocular distance with 50 µM BPS were observed in 5 dpf WT larvae treated from 0.5 hpf to 5 dpf (Huang et al. 2023).

There was an increased incidence (NS +2-3%), compared to no abnormalities observed in controls, of craniofacial and tail abnormalities and cardiac edema at 20 and 100 mg/L BPS, and yolk sac deformity at 20 mg/L in 96 hpf WT WIK strain embryo/larvae treated from 1 to 96 hpf. In zebrafish treated with 200 mg/L BPS (96-hour LC_{50} = 198.76 mg/L), these effects increased to a 96% and 82% incidence of craniofacial and tail abnormalities, respectively, and a 94% incidence of cardiac edema (Moreman et al. 2017).

Increased malformation rate, including kyphosis, shortened tails, and cardiac edema, was observed in the WT AB strain F1 offspring treated until 6 dpf and descended from F0 zebrafish treated for 21 days during adulthood with 0.5 or 50 µg/L BPS with an NS increase in untreated offspring of treated parents at 50 µg/L (Ji et al. 2013). Increased otic vesicle length and decreased head-trunk angle was observed in 30 hpf WT Tu strain F1 embryos with F0 parental exposure from 2 hpf to 120 dpf to 1, 10, or 100 µg/L BPS (Wei et al. 2018).

In transgenic *cyp19a1b*:GFP embryo/larvae treated from 0 hpf to 4 dpf with 25, 50, 100, 200, or 400 mg/L BPS, yolk deformity was observed at 96 hpf with 400 mg/L BPS. No other morphological effects were observed (Christophe et al. 2023).

In Chinese medaka treated with 200 or 2000 ng/L BPS from the blastocyst stage to 15 dpf, there were non-significant increases in defect rate, including pericardial edema, spinal curvature, enlarged yolk sac, and decreased head-trunk angle (B Li et al. 2024).

No effects on malformations or abnormalities were observed in four zebrafish studies:

- WT embryo/larvae treated from 4 to 120 hpf with up to 50 mg/L BPS (Lee et al. 2019).
- WT AB strain embryo/larvae treated from 1.5 hpf to 4 dpf with up to 25 mg/L BPS (Mu et al. 2018).
- WT AB strain embryo/larvae treated from 2 to 144 hpf with up to 1 µM (250.27 µg/L, calculated by OEHHA) (Coumailleau et al. 2020).
- WT embryo/larvae treated from 0-1 dpf to 7 dpf with 1 µM BPS (Cano-Nicolau et al. 2016).

Swim bladder

The swim bladder, which shares similarities to the lungs, is a gas-filled organ that functions to maintain and regulate buoyancy and may also be involved in acoustic resonance (https://zfin.org). Its developmental phases, including budding, growth/elongation, and inflation of the posterior chamber, occur between 36 to 120 hpf. Complete development, defined by the inflation of the anterior chamber, takes place around 21 dpf.

Decreased percentage of fully inflated swim bladders and increased percentages of partially or not inflated swim bladders were observed in the untreated 96 hpf F1 offspring of F0 WT Tu strain treated with 1, 10, or 100 µg/L BPS from 2 hpf to 120 dpf (Wei et al. 2018).

No effects on the swim bladder were observed at 96 hpf in WT AB strain embryo/larvae treated with 1 or 100 µg/L BPS from 2 hpf to 96 hpf (Qin et al. 2023).

Neurodevelopmental and ocular effects

Neurogenesis

BPS-mediated effects on developmental neurogenesis were reported in five zebrafish studies. Several of these studies utilized transgenic lines to visualize neuronal processes using fluorescent reporters.

There was a 240% increase in neurogenesis in the rostral hypothalamus in 24 hpf WT TL strain zebrafish treated with 6.8 nM BPS (1.70 µg/L, calculated by OEHHA), from 0 to 5 dpf (Kinch et al. 2015).

In one study, transgenic zebrafish expressing the gonadotrophin-releasing hormone 3 (*gnrh3*) promoter linked to green fluorescent protein (GFP) were administered 100 µg/L BPS beginning at 2 hpf. At 25 hpf, there was an increased number of GnRH3 positive neurons in the hypothalamus, with no changes observed in the terminal nerve (Qiu et al. 2016).

In another study, *HuC*-GFP and *hb9*-GFP transgenic zebrafish, generated to assess central nervous system neurogenesis and motor neuron axon length, respectively, were treated with 200 µg/L BPS beginning at 4 hpf. BPS treatment decreased central nervous system neurogenesis and motor neuron axon length at 36 hpf, but not at 72 hpf (Gu et al. 2022).

Accelerated neurogenesis was reported in 5 dpf larvae, as indicated by increases in the ratio of newborn to mature neurons and the number of proliferating neuronal stem cells in WT AB strain zebrafish treated with 1 µM BPS from 8 hpf to 5 dpf (Bai et al. 2023).

Non-significant increases in proliferation in the caudal hypothalamus were observed in WT AB strain larvae treated with 1 µM BPS from 2 hpf to 6 dpf (Coumailleau et al. 2020).

Spontaneous movement, locomotor activity and behavior

BPS-mediated effects on spontaneous movement, locomotor activity, or behavior were assessed in 15 zebrafish studies, with nine reporting effects of treatment.

Decreased spontaneous movement and touch-evoked swim response at 48 hpf and swimming speed and swirl escape rate at 96 hpf in the F1 offspring of WT Tu strain F0 zebrafish treated with 1, 10, or 100 µg/L BPS starting at 2 hpf (Wei et al. 2018).

Increases in spontaneous movements were reported at 24 hpf in WT AB strain embryo/larvae treated with 1, 10 or 100 µM BPS (0.25, 2.50, or 25.03 mg/L, calculated by OEHHA) from 8 hpf to 4.5 dpf (Bai et al. 2023).

No effects on spontaneous movements were observed in two studies in 24 hpf WT AB strain zebrafish treated with either 200 µg/L BPS from 4 hpf (Gu et al. 2022) or with up to 25 mg/L BPS from 1.5 hpf (Mu et al. 2018).

Increased swimming speed was observed at 118 hpf in the 10 µM BPS group with no effects on distance traveled or time active in WT AB strain embryo/larvae treated with 0.01, 0.1, 1, or 10 µM BPS (2.50 µg/L, 25.03 µg/L, 250.27 µg/L, or 2.50 mg/L, calculated by OEHHA) from ~6-7 hpf to 118 hpf (Fraser et al. 2017).

Altered locomotor behavior including abnormal back-and-forth movements was reported at 120 hpf in WT AB strain embryo/larvae treated with 1, 10, or 100 µg/L BPS from 2 to 120 hpf (Wang et al. 2023).

Increases in distance travelled (1 µM), average speed (0.3 and 1 µM), and activity frequency (0.01 and 1 µM) were observed in 120 hpf WT AB strain embryo/larvae treated with 0.01, 0.03, 0.1, 0.3, or 1 µM BPS (2.50, 7.51, 25.03, 75.08, and 250.27 µg/L, calculated by OEHHA) from 4 to 120 hpf (Gyimah et al. 2021b).

An increase in locomotor burst activity was observed in 5 dpf WT TL strain embryo/larvae treated with 0.0068 µM BPS (1.70 µg/L, calculated by OEHHA) from 0 to 5 dpf (Kinch et al. 2015).

Decreases in locomotor activity, including distance traveled, and swim speed were observed in 6 dpf WT AB strain larvae treated with 0.3 and 3 mg/L BPS from 2 hpf to 6 dpf (Gu et al. 2019), while no effects on locomotor activity were observed with 1 µM BPS (250.27 µg/L, calculated by OEHHA) (Coumailleau et al. 2020).

There were no effects on motor behavior reported in WT larvae at 120 hpf with 1 or 100 µg/L BPS exposure from 2 to 120 hpf (Qiu et al. 2021), or at 4 dpf in WT embryo/larvae treated with 100 nM or 100 µM BPS (25.03 µg/L or 25.03 mg/L, calculated by OEHHA) from 2 to 120 hpf (Björnsdotter et al. 2017). No effects on motility were reported in WT larvae at 7 dpf with 1 µM (250.27 µg/L, calculated by OEHHA) BPS (Cano-Nicolau et al. 2016).

Decreased thigmotaxis, or “wall-hugging” neurobehavior was observed in 6 dpf WT AB strain larvae treated with 1, 10, and 100 µg/L BPS from 2 hpf to 6 dpf (Wang et al. 2024).

Maternal exposure to 1, 10, or 30 µg/L BPS for 60 days prior to mating to an untreated male altered behavior but not locomotor activity in untreated 6-month-old adult male offspring. Behavioral effects included altered social anxiety responses, where there was decreased novel group preference at 1 µg/L BPS, decreased shoal cohesion at 30 µg/L BPS, and increased novel tank stress at 1 and 30 µg/L BPS. Arginine-vasotocin levels in the brain increased with 1 µg/L BPS (Salahinejad et al. 2022).

Altered shoaling behavior was observed in 11 dpf WT AB strain embryo/larvae treated with 10 or 100 µM BPS (2.50, and 25.03 mg/L, calculated by OEHHA) from 8 to 120 hpf. Specifically, there were increases in nearest neighbor distance at 10 µM and interindividual distance at 10 and 100 µM (Bai et al. 2023).

Ocular development and behavior

Zebrafish and human eye development share anatomical and functional similarities. BPS-mediated effects on visual development and behavior were reported in four zebrafish studies.

Increases in empty retinal pigmented epithelium areas were reported at all concentrations, with decreased retinal expression of the growth-associated protein GAP43 at 0.3 and 3 mg/L in WT AB strain embryo/larvae treated with 0.03, 0.3, or 3 mg/L BPS from 2 hpf to 6 dpf (Gu et al. 2019).

Relative eye length was decreased at 24 hpf at 4 and 400 nM BPS and increased at 96 hpf with 4 nM BPS in WT AB strain embryo/larvae treated with 4 or 400 nM BPS (1.00 and 100.11 µg/L, calculated by OEHHA) from 2 to 120 hpf. There were decreases in the thickness of all retinal layers at 4 and 400 nM and increased expression of thyroid hormone receptor beta (THRB) protein in retinal tissues with 400 nM BPS at 120 hpf. There were effects on visual behavior such as phototaxis, body color adaptation, and hyperactivity at 120 hpf with 4 (hyperactivity only) and 400 nM BPS (Wei et al. 2023).

BPS damaged perception to long- and short-wave type light signals via decreased ribbon synapse development with altered mosaic arrays and DNA damage in both red cone cells and ultraviolet (UV) cone cells in 5 dpf larvae with 10 and 100 µg/L BPS. In addition, precocious neurogenesis of the hypothalamus, spinal nerves, optic nerve (all at 48 hpf), and retinal ganglion cells (72 hpf) was reported with upregulated mRNA expression of oxidative stress-related genes and cone opsin genes at 120 hpf in WT Tu strain and UV and red cone cell-labeling transgenic *sws1*; thrb zebrafish treated with 1, 10, or 100 µg/L BPS from 2 hpf to 5 dpf (Qiu et al. 2023b). In another study in WT Tu strain zebrafish with the same exposure parameters, there was altered expression of all-trans-retinoic acid and its metabolites in 5 dpf eyes at 10 and 100 µg/L BPS and decreased slow phase gain optokinetic response at all concentrations (Qiu et al. 2023a).

Circulatory system effects

Many aspects of zebrafish circulatory system development and function are similar to humans and can be readily visualized in zebrafish using fluorescent transgenic lines. In zebrafish, 12 studies evaluated the effects of BPS on cardiac and vascular function.

Heart

BPS-mediated effects on heart rate, size, edema, and/or related circulatory outcomes were reported in nine zebrafish studies, and pericardial edema was reported in the Chinese medaka study.

Increased atrial size and atrial to ventricle area (+35.1%) along with decreased heart rate (-8.9%) at 100 µg/L were observed in 120 hpf WT AB strain embryo/larvae treated with 0.1, 1, 10, or 100 µg/L BPS from < 4 hpf to 120 hpf (Qiu et al. 2020). In WT zebrafish treated with 4, 8, or 12 mg/L BPS from 6-10 hpf to 96 hpf, a decrease in circulatory score was observed with 12 mg/L BPS with NS decreases with 4 and 8 mg/L (Neighmond et al. 2023).

Decreased heart rate was observed in untreated 48 hpf F2 embryos descended from F0 zebrafish treated with 1 or 100 µg/L BPS from 3 hpf to 120 dpf, and increased with 100 µg/L in F2 zebrafish at 72, 96 and 120 hpf and in F3 at 48 and 72 hpf (Hao et al. 2022).

Increased heart rate was observed at 72 and 84 hpf with 50 µM BPS and at 96 hpf with 10 and 50 µM BPS in WT embryo/larvae treated with 10 or 50 µM BPS from 0.5 hpf to 120 hpf (Huang et al. 2023). Similarly, in WT AB strain embryo/larvae treated with 1 or 100 µg/L BPS from 2 to 96 hpf, heart rate was increased at 36 and 72 hpf with both BPS concentrations, and at 96 hpf with 100 µg/L BPS, while stroke volume was decreased with 100 µg/L BPS (Qin et al. 2023). In WT AB strain zebrafish treated with 1, 10, or 100 µg/L BPS from 2 hpf up to 72 hpf, heart rate was increased at 72 hpf (but not at 24 or 48 hpf) with 10 and 100 µg/L BPS exposure (Zhang et al. 2022).

Three studies reported no effects of BPS treatment on heartbeat and/or rate in zebrafish embryo/larvae including WT AB strain zebrafish treated with 2.5, 12.5, or 25 mg/L BPS from 1.5 hpf to 4 dpf (Mu et al. 2018); WT zebrafish treated with 100 nM or 100 µM BPS (25.03 µg/L or 25.03 mg/L, calculated by OEHHA) from 2 hpf (Björnsdotter et al. 2017); and WT AB strain zebrafish treated with 200 µg/L BPS from 4 hpf to 6 dpf *(Gu et al. 2022)*.

Cardiac edema was observed in two zebrafish studies and the Chinese medaka study: in 120 hpf F1 offspring of WT AB strain F0 adults treated with 50 µg/L BPS for 21 days (Ji et al. 2013); increased incidence (94% vs. 0% in controls) at 96 hpf with 200 mg/L (calculated LC_{50}) BPS in WT WIK strain embryo/larvae treated with up to 300 mg/L BPS from 1 to 96 hpf (Moreman et al. 2017).

In Chinese medaka treated from the blastocyst stage to 15 dpf, there was an NS increase in pericardial edema with 200 and 2000 ng/L BPS (B Li et al. 2024).

No effects on cardiac edema were observed in three studies, including in WT AB strain zebrafish treated from 2 to 72 hpf with up to 100 µg/L BPS (Zhang et al. 2022), in WT AB strain embryo/larvae treated from 1.5 hpf to 4 dpf with up to 25 mg/L BPS (Mu et al. 2018), and in WT AB strain embryo/larvae treated from 2 to 144 hpf with up to 1 µM (250.27 µg/L BPS, calculated by OEHHA) (Coumailleau et al. 2020).

Vascular development

Vascular development in zebrafish can be easily visualized; this facilitates more nuanced insights into the early events underlying the formation of vessels. Five zebrafish studies observed effects on vessel development and expansion.

In the transgenic *fli*1:EGFP reporter line for vascular development evaluation, zebrafish embryos were treated with 30 mg/L BPS from 2 to 72 hpf. There was a decrease in the percentage of intersegmental vessel development and an increase in intersegmental vessel angle at 30 hpf, and an increase in the area of the common cardinal vein at 48 hpf (Ji et al. 2022).

Increased common cardinal vein growth rate from 24-48 hpf with all concentrations, and a decreased number of endothelial cells within the common cardinal vein was observed at 24 hpf with 10 and 100 µg/L in WT AB strain zebrafish treated with 1, 10, and 100 µg/L BPS from 2 hpf up to 72 hpf (Zhang et al. 2022).

There was a decrease in sinus venous-bulb arteriosus at 1 and 100 µg/L BPS in 72 hpf WT AB strain embryo/larvae treated with up to 100 µg/L BPS from 2 to 96 hpf (Qin et al. 2023).

Increased numbers of red blood cells (RBCs) in the caudal vein were observed in 72 hpf larvae at 1 and 100 µg/L in WT AB strain zebrafish and increased numbers of retained/adhered RBCs in the caudal vein were observed at all concentrations at 72 hpf in a transgenic zebrafish line, *Tg gata1a:DsRed*, a model used to visualize RBCs. Both strains were treated with 1, 10, or 100 µg/L BPS from 2 hpf to 72 hpf. Using the same treatment paradigm, this study also assessed the effects of BPS on the distribution and aggregation of RBCs in the vessels of apolipoprotein Eb-knockout zebrafish, a proposed model to study lipid metabolism disorders. Increased aggregation of RBCs in the caudal vein, intersegmental vessels, and dorsal longitudinal anastomotic vessels were observed at all concentrations (J Li et al. 2023).

In WT AB strain embryo/larvae treated with up to 100 µg/L BPS from 2 hpf up to 120 hpf, temporal effects on vascular development were observed. There was an increase in total angiogenesis at 24 and 48 hpf with 1, 10, and 100 µg/L BPS, and decreases in blood flow velocity at 72 hpf with 100 µg/L BPS and at 96 hpf with 1 and 100 µg/L BPS. At 24 hpf, there was a decrease in the percentage of intersegmental vessel formation at all concentrations and an increased number of intersegmental vessel branches was observed with 100 µg/L BPS. At 48 hpf, increased superficial ocular vessel sprouting malformation rates were observed at all concentrations and increased common cardinal vein area was observed with 1 and 100 µg/L BPS. At 72 hpf, there were increases in the percentages of larvae with ectopic sprouting and

vessel growth at all concentrations, and an increased number and length of ectopic sprouts with 100 µg/L BPS. At 96 hpf, an increased proportion of larvae had lipid accumulation in blood vessels at 1, 10, and 100 µg/L BPS (Wang et al. 2020).

Endocrine effects

The endocrine effects of developmental BPS exposure in zebrafish are detailed in the Mechanisms and Other Supportive Evidence section (see Section 4.3 below). In short, several studies observed BPS-mediated endocrine effects including altered levels or gene/protein expression of sex hormones, altered neuroendocrine function, and altered thyroid function.

Metabolic effects

Effects of developmental BPS exposure on metabolism, including glucose and lipid metabolism, were observed in five zebrafish studies.

Increased glucose levels at 0.3 µM and 1 µM, and altered mRNA expression of insulin and pancreatic genes were observed in 120 hpf WT AB strain larvae treated with 0.01, 0.03, 0.1, 0.3, or 1 µM BPS (2.50, 7.51, 25.03, 75.08, or 250.27 µg/L, calculated by OEHHA) from 4 to 120 hpf (Gyimah et al. 2021a).

In WT zebrafish treated with 50 µM BPS from 0.5 hpf to 120 hpf, bulk RNA-seq of pooled 120 hpf whole larvae identified, through enrichment analysis, terms related to cellular energy (i.e., Krebs cycle) and glucose metabolism (Huang et al. 2023).

Decreased brain glucose uptake with no effect on the protein expression of the glucose transporter glut1 was observed at 6 dpf in WT AB strain larvae treated with 10 or 100 µg/L BPS from 2 hpf to 6 dpf (Wang et al. 2024).

Decreases in total cholesterol and low density lipoprotein C levels were observed with 1, 10, and 100 µg/L BPS treatment in F0 in the 5 dpf F1 progeny of WT Tu strain F0 zebrafish treated with 1, 10, 100, or 1000 µg/L BPS from 2 hpf to 120 dpf. The presence of residual yolk lipids in the viscera or yolk area was also observed with 1, 10, 100, and 1000 µg/L BPS treatment in these 5 dpf F1 progeny (Wang et al. 2019).

Lipid consumption was increased at all concentrations at 6 and 24 hpf in WT AB strain embryos treated with 1, 10, or 100 µg/L BPS from 2 hpf to 90 dpf. This study also observed increased lipid distribution in the yolk area at 24 hpf with 10 and 100 µg/L and at 48 hpf with 1 and100 µg/L BPS. Total cholesterol was decreased at 24 hpf with 1 and 100 µg/L BPS, increased at 48 hpf with 1 and 100 µg/L BPS, and decreased at 120 hpf with all BPS concentrations. Triacylglycerol levels were decreased at 120 hpf with 10

and 100 µg/L BPS, and brain lipid distribution was decreased at 120 hpf with all BPS concentrations (Wang et al. 2023).

Immune effects

BPS-mediated developmental immunotoxicity was observed in two zebrafish studies. WT AB strain F0 zebrafish were treated with 10 µg/L BPS from 24 hpf to 180 dpf and in their F1 progeny either treated or untreated with 10 µg/L BPS from 24 to 96 hpf had increased lysozyme activity and altered immune-related gene expression (Dong et al. 2018). In 120 hpf WT AB strain embryo/larvae treated with up to 100 µg/L BPS from < 4 hpf to 120 hpf, there was a NS induction (+137.5%) of neutrophil count with 100 µg/L, and increased inducible nitric oxide synthase (iNOS or NOS2) activity with 10 and 100 µg/L and IL-12 levels with 100 µg/L BPS (Qiu et al. 2020).

Reproductive performance

Reproductive performance was assessed in one transgenerational study. WT AB strain F0 embryos were treated with 1 or 100 µg/L BPS from 3 hpf to 120 dpf and fecundity or fertility were assessed in the untreated F1, F2, and F3 generations. Decreased fecundity was reported at 100 µg/L BPS in the F1 generation, and increased fertility was reported at 1 µg/L BPS in the F2 generation, while fertilization rates in F3 were not affected by F0 exposure to BPS. BPS effects on hatchability are discussed in a previous section (Hao et al. 2022).

Sex ratio

BPS-mediated effects on sex ratios in zebrafish were reported in four studies with results depending on dose timing and duration. Treatment with 1 µg/L BPS for 60 days in F0 females immediately prior to mating resulted in predominantly male offspring at approximately 90% (Salahinejad et al. 2022; Salahinejad et al. 2023). In WT AB strain F0 males and females treated with 1 or 100 µg/L BPS from 3 hpf to 120 dpf, there were increased percentages of females in the F0 generation at 100 µg/L BPS and in the F1 and F2 generation at 1 and 100 µg/L BPS (Hao et al. 2022).

Studies in Nematodes (*C. elegans*)

Similar to zebrafish, the nematode, *C. elegans*, is a model organism that is widely used in developmental toxicology studies due to its short lifespan, conserved developmental processes, ease of visualization due to its transparency, and due to whole organism assessments, retention of metabolic and other physiological system functions. BPS-mediated effects on nematode development and reproduction were reported in six studies and are grouped by study.

In a three-generation developmental toxicity study, the F0 was exposed starting as eggs to BPS at concentrations of 0.1, 1, 5, or 10 µM for 48 hours, where the subsequent F1 and F2 generations were either not exposed to BPS or exposed to the same concentrations and duration of BPS as their F0 progenitors (McDonough et al. 2021a).

In F0 worms, there was decreased lifespan at all BPS concentrations; decreased number of egg-laying days at 1, 5, and 10 µM; decreased number of worms hatched at 1, 5, and 10 µM; and decreased body bend behavior at 5 and 10 µM. There was a lessening of these effects in F1 and F2 generations that were not exposed to BPS, with improvements in lifespan at all concentrations in the F1 and F2 generations. However, lifespan was still significantly decreased compared to control in the F1 generation at 5 µM and F1 and F2 at 10 µM. The effect on number of worms hatched was recovered at 1 and 5 µM in the F1 generation and 1, 5, and 10 µM in the F2 generation.

When the F1 and F2 generations were also exposed to BPS, there was decreased lifespan and decreased number of worms hatched at all concentrations in both the F1 and F2 generations that were equal to or more pronounced than in the F0 generation, and delayed age of egg laying at 0.1 µM in F1 and 5 µM in F1 and F2 generations. Accumulative effects were present across all three generations at 5 and 10 µM, but only across the first two generations at 0.1 and 1 µM (McDonough et al. 2021a).

In a four-generation study, accumulative effects were only observed in head thrashing behavior. In this study, L4 larvae, the fourth and final larval stage before adulthood, were treated with 0.001, 0.01, 0.1, 1, 10 or 100 µM BPS (0.25, 2.50, 25.03, and 250.27 µg/L and 2.50 and 25.03 mg/L, calculated by OEHHA) and marked effects on locomotion behavior, growth, reproduction, and lifespan, with decreased number of head thrashes and body bends, decreased body length, decreased brood size, and decreased life span were observed at concentrations at or above 0.1 µM in the F0 generation. In subsequent generations with the same treatment paradigm, there was a weakened effect of treatment on body length and body bend behavior, increased brood size in the fourth generation compared to the first generation at 1 µM, and no differences in magnitude of decreased brood size between the fourth and first generations at 0.01, 0.1, 10, and 100 µM. However, brood sizes were decreased when compared to control (Xiao et al. 2019).

In wildtype and abnormal cuticle-forming *bli-1* mutant *C. elegans* embryos exposed to 0.1, 0.5, 1, or 5 µM BPS for 4 hours, there were concentration-dependent decreases in hatching rate and decreased body length at all concentrations in both strains. BPS embryonic exposure also affected the neural functionality of *C. elegans* larvae in both wildtype and *bli-1* mutant strains as demonstrated by the touch habituation response,

with an increased number of anterior touches applied prior to habituation in 0.5, 1, and 5 µM BPS groups (Kucharíková et al. 2023).

In a study exposing L1 larval stage to 24 hours post L4 larval stage worms with 125, 250, or 500 µM BPS (31.28, 63.57, or 125.14 mg/L, calculated by OEHHA), there was a concentration-dependent increase in embryonic lethality with a corresponding decrease in brood size. Worms demonstrated severe reproductive defects including irregular distribution of germline nuclei, concentration-dependent germline nuclear loss, and increased apoptosis. (Chen et al. 2016).

In worms treated with 0.6, 6, or 60 µg/L BPS from L1 larval stage to adult day 3, there was decreased lifespan and number of eggs laid at 60 µg/L and decreased egg hatchability at 6 and 60 µg/L. Additionally, at 60 µg/L BPS, there was decreased body bend frequency, decreased pharyngeal pumping feeding behavior, and increased accumulation of health and aging marker lipofuscin when assessed at 8- and 11-days old (He. W et al. 2024).

One study exposed worms to 1 mM BPS starting from the L1 larval stage up to the five-day-old adult stage. No effects on lifespan were reported. In 1-day-old adults, there was increased neurite beading, indicative of neuronal aging, and decreased oxidative stress tolerance measured by percent survival after culture with hydrogen peroxide. In 3-day-old adults, there were decreases in body length and width, crawling speed and body-bending, and thermal stress tolerance. There was no effect on oxygen consumption rate. In 5-day-old adults, there were increases in protruded vulval structures. In worms treated for 24 hours from the L4 larval stage, brood size was decreased. The progeny of worms treated for 24 hours from the L4 larval stage were treated from the L1 larval stage for three days. There were no effects on development rates (Hyun et al. 2021).

Studies in Chickens

The chick embryo model is also used extensively in developmental biology and toxicology, notably in studies of chemical-mediated teratogenic effects including neural tube defects and other congenital anomalies (Wachholz et al. 2021).

The effects of BPS on embryotoxicity were evaluated in three studies in chick embryos and are grouped by study. All studies administered BPS via *in ovo* injections.

Reduced growth and developmental delay with, heart, eye, craniofacial, limb, and body pigmentation defects were observed in chick embryos treated with 0.03, 0.3, 3 or 30 µM BPS and increased gastrointestinal defects at 3 µM BPS from embryonic day (E)5 to E12. Survival rates was were decreased at 3 µM (40% survival) and 30 µM (0% survival) compared to 100% survival in the control group (Harnett et al. 2021).

Increased embryo mortality with a 57% mortality rate and increased gallbladder-somatic index with no effect on body weight or hepatosomatic index were observed in chick embryos exposed *in ovo* to 210 nmol/g BPS per egg from E4 to E19. Two out of nine female chicks exposed to BPS had effects on gonad morphology with thin and atrophic ovaries, however this evaluation could not be determined in male chicks due to low numbers of male embryos (n = 3 dissected males vs. 9 dissected females) at assessment (Mentor et al. 2020).

Unincubated, fertilized chick embryos were exposed *in ovo* to 0.27, 0.91, 10.6, 52.8, or 207 µg/g BPS. After treatment, eggs were incubated and brought to pipping (E20-21). There was decreased pipping success, embryo mass, and tarsus length at 207 µg/g BPS, and increased gallbladder size at or above 52.8 µg/g. There was an upregulation of genes affecting xenobiotic metabolism, lipid homeostasis, bile acid synthesis, and the thyroid hormone pathway. There were no effects on circulating free T4 in plasma or bile acid concentrations (Crump et al. 2016).

Studies in Fruit Flies (*D. melanogaster*)

The developmental and behavioral effects of BPS on *Drosophila melanogaster* were investigated in two studies that treated parental flies and offspring until pupal formation with 0.25, 0.5, or 1 mM BPS (Santos Musachio et al. 2023; Santos Musachio et al. 2024).

In the first study, parental (F0) flies were exposed for seven days during breeding and the resulting offspring (F1) were exposed until the third instar stage of development. There was a decreased F1 hatching rate at 0.5 and 1 mM BPS, decreased larval body width with a melanotic mass present at 1 mM BPS, and decreased number of pupae formed at 1 mM BPS (Santos Musachio et al. 2023).

In the second study, F0 flies were exposed for five days during breeding and the F1 offspring were exposed until pupae formation. In one- to two-day old F1 flies, increased locomotion exploratory capacity, decreased vertical climbing, increased number of repetitive grooming events, increased number of male combats, and decreased learning ability was observed with 1 mM BPS. Flies also showed decreased social interaction between same-sex flies exposed to 0.5 or 1 mM BPS. Brain size was increased in female offspring at 0.5 and 1 mM (males were not assessed) (Santos Musachio et al. 2024).

The tables below summarize the evidence of BPS on developmental toxicity in animal studies: In mammals (Table 4.2.1), and in non-mammalian species (Table 4.2.2).

Mammalian studies are summarized in Table 4.2.1. Where assessed, maternal-specific effects are noted in the “Maternal effects” column of the table. Outcomes that may be mediated by effects on the conceptus, the placenta, and/or the mother (e.g., resorptions, number of implantations, post-implantation loss, and offspring viability) are tabulated in the “Developmental effects” column.

Mammalian studies with peri- or early post-natal BPS exposure are considered and included here when the outcomes assessed involve developmental processes that occur postnatally in animals, but prenatally in humans. For example, studies with peri- or early post-natal BPS exposure that assess brain or ovarian developmental outcomes would be included. In addition, two studies that assessed the effects of pre- and post-natal BPS exposure on maternal outcomes in female offspring (i.e., F1) are included (BASF 2019; Catanese and Vandenberg 2017). BASF (2019) evaluated body weight and body weight gain, organ weights, food consumption, and water intake in F1 females exposed from their gestational, lactational, and postnatal periods, through weaning of their F2 pups; and Catanese and Vandenberg (2017) assessed F1 maternal behavior toward their F2 progeny following F1 gestational and lactational exposure.

Non-mammalian studies are summarized in Table 4.2.2. When applicable, for studies reporting BPS exposure in molar concentrations in zebrafish, OEHHA calculated equivalent concentrations in µg/L or mg/L for ease of comparison across studies. Zebrafish studies that treated up to 7 dpf were considered and included, with the majority of studies treating up to 5 dpf (120 hpf). The Chinese medaka study treated fish up to 15 dpf. For nematodes, studies treated worms up to the five-day-old adult stage. BPS treatment in chickens was administered *in ovo*, and in fruit flies, administered up to the third larval instar, or just prior to the pupal stage. Several studies considered the effects of parental BPS exposure on offspring development, and others evaluated the effects of multi-generational exposures.

Table 4.2.1 BPS: Evidence on the developmental toxicity in mammals

Study design	Outcomes assessed	Maternal effects	Developmental effects
Ahn et al. 2020 Pregnant C57BL/6N mice, 14 to 16 weeks old, n = 4 to 17 dams per group. Treatment: BPS (purity not stated) in 0.5% ethanol v/v in water (vehicle control), orally in drinking water at 0, 0.2, 2.1, 21.4, and 214.3 µg/mL corresponding to 0, 0.05, 0.5, 5, and 50 milligrams per kilogram per day (mg/kg-day) from gestational day (GD) 9 to GD 18. Offspring fed either standard diet from 3 to 8 weeks of age; or high fat diet from 6 to 10 weeks of age. Male offspring assessed in this study: Outcomes evaluated at ~8 weeks of age for standard diet group and ~10 weeks of age for high fat diet group.	**Maternal:** Body weight. **Developmental:** Body weight in standard and high fat diet groups: Ratio of gonadal (epididymal) white adipose tissue (gWAT) weight to % body weight. Standard and high fat diet groups: mRNA expression of adipogenesis genes in epididymal fat pad tissues. High fat diet group only: Food intake and energy expenditure (heat production based on the respiratory exchange rate = carbon dioxide production / oxygen consumption) adjusted to metabolic body size (total lean mass + 0.2 total fat mass) diet group. gWAT histology.	No effects on body weight.	Body weight and ratio of gWAT weight to % body weight: Increased body weight at 5 (+13%) and 50 (+8%) mg/kg-day and gWAT to % body weight at 5 (+31%) and 50 (+35%) mg/kg-day in high fat diet group. No effects in standard diet group. mRNA expression: Up-regulated *Pparg, Lpl,* and *Adipoq* at 5 and 50 mg/kg; and *Cebpa* and *Fabp4* at 50 mg/kg-day in high fat diet group. No effects in standard diet group. High fat diet group only: Food intake and energy expenditure: No effects. gWAT histology: Adipocyte hypertrophy (increased adipocyte area and diameter) at all doses.
BASF 2014 Female Wistar rats, time-mated, 42 days old at the start of treatment, n = 24–25 dams per group. Treatment: BPS (99.3-99.5% purity) carboxymethyl cellulose (CMC; 1% in potable tap water) at a final volume of 10 ml/kg, administered via daily oral gavage at doses of 0, 30, 100, or 300 mg/kg-day from GD 6 to 19. Animals were sacrificed on GD 20.	**Maternal:** Mortality and moribundity. Clinical signs of toxicity. Food consumption. Body weight and body weight gain (gravid uterus-adjusted and -unadjusted). Gravid uterus weight. **Developmental:** Number of implantations, live and dead fetuses, and early and late resorptions. Reproductive indices (conception rate, post-implantation loss). Fetal weight. Sex ratio. Necropsy (viability; condition of placenta, umbilical cord, membrane, and fluids; and placental weight). Examination of malformations and variations (gross, visceral, and skeletal).	No relevant effects of treatment on mortality and moribundity, clinical signs of toxicity, food consumption, body weight, gravid uterus-adjusted terminal body weight or GD 6-20 body weight gain, or gravid uterus weight.	No effects on number of implantations, live and dead fetuses, or early and late resorptions. Post-implantation loss: Increased at 300 mg/kg-day (NS; +34%). No relevant effects on fetal weight, sex ratio, or necropsy observations. Gross malformations and variations: One fetus with multiple gross malformations including misshapen head and missing face at 100 mg/kg-day; incidence (1/265 fetuses in 1/25 litters) No variations and no relevant unclassified observations. Visceral malformations and variations: No malformations. Variations: Increased renal dilation at 100 (10/125 fetuses; 8/25 litters) and 300 (9/116 fetuses; 8/24 litters) mg/kg-day vs. control (6/127 fetuses; 6/25 litters); and increased dilated ureter at 300 mg/kg-day (3/116 fetuses; 3/24 litters) vs. control (1/127 fetuses; 1/25 litters).

Study design	Outcomes assessed	Maternal effects	Developmental effects
			Total visceral variations: Non-dose dependent increase (NS) in mean% of affected fetuses/litter at 100 (+49%) and 300 (+39%) mg/kg-day. Skeletal malformations and variations: Malformations: One fetus with multiple skeletal malformations including of the skull, vertebral column, ribs, pelvic girdle, and forelimbs associated with multiple gross malformations; and one fetus with shortened scapula at 100 mg/kg-day (vs. zero in control). One fetus with misshapen basisphenoid; one fetus with misshapen tuberositas deltoidei; and two fetuses (2/127 fetuses; 2/24 litters) with malpositioned and bipartite sternebrae (unchanged cartilage) at 300 mg/kg-day (vs. zero in control). Total skeletal malformations: Dose-dependent increase in mean% affected fetuses/litter at 100 (NS; +300%) and 300 (+514%) mg/kg-day Variations: Several skeletal variations present in all groups including controls; the following skeletal variations were significantly increased but fell within the range of historical controls: Incomplete ossification of pubis (2% treated vs. 0% control); and incomplete ossification of ischium (2% treated vs. 0% control) at 100 mg/kg-day (reported as mean% affected fetuses/litter). Incomplete ossification of supraoccipital (45.2% treated vs. 34.1% control); dumbbell ossification of thoracic centrum (5.6% treated vs. 0.7% control); and unossified sternebrae (11% treated vs. 1.5% control) at 300 mg/kg-day (reported as mean% of affected fetuses/litter). No relevant effects on total malformations or variations (sum of gross, visceral, and skeletal).
BASF 2019 Adult SD (Crl:CD) rats, n = 24 rats/sex/dose. Treatment: BPS (99.9% purity) in 0.5% CMC suspension at doses of 0, 20, 60 or 180 mg/kg-day by gavage for 10 weeks premating, up to 2 weeks	**Maternal**: **F0 and F1, with F1 presented in Developmental effects column.** Mortality and moribundity; clinical signs of toxicity; water and food consumption; body weight and body weight gain; clinical pathology (F0 only; hematology, clinical chemistry, thyroid	**F0 maternal:** Increased liver weight (relative to body weight) at 180 mg/kg-day (+7%). No relevant effects on mortality, moribundity, clinical signs of toxicity,	**Pregnancy (F0/F1) and birth (F1):** Increased % post-implantation loss per litter of F1 progeny at 60 (+203%) and 180 mg/kg-day (+239%). No effects on gestation index or number of implantation sites. Decreased number of liveborn pups at 180 mg/kg-day (-16%). Increased stillborn at 180 mg/kg-day (+300%).

Study design	Outcomes assessed	Maternal effects	Developmental effects
mating, and a maximum of 6 weeks post-mating (3 weeks lactation until weaning). F1 offspring were culled on postnatal day (PND) 4 to 10 pups/dose (5/sex when possible) and weaned on PND 21 F1 males and females (n=24 rats/sex/dose) were selected to generate F2 pups; F1 adults were kept within the same treatment groups they were born into. F1 parents were treated by gavage for 10 weeks post-weaning/premating, up to 2 weeks mating, and through lactation for females and 3-4 weeks post-mating for males. F1 parents were sacrificed at 19-25 weeks old and F2 pups were sacrificed on PND 21.	hormone analysis, and urinalysis); pathology (full gross necropsy, absolute and relative organ weights including relevant reproductive organs, microscopic examination of control and high-dose groups unless findings occurred) **Developmental:** **Pregnancy and birth outcomes:** Fertility index, gestation index, live birth index, number of implantations, and post-implantation loss. Pup number. Sex ratio. Liveborn number and index. Stillborn number. Litter size. Macroscopic examination. Viability/mortality (PND 4, 7, 14, and 21). **F1 and F2 progeny:** Clinical signs of toxicity. Male nipple/areola anlagen on PND 13 (F1 and F2), PND 20 (F1), PND 21 (F2). Body weight (PNDs 1, 4, 7, 14, and 21). Anogenital distance (AGD) on PND 1 and anogenital index (AGI). Blood TSH and T4 concentrations; PND 4 and 22 (pooled by sex and litter when needed). Full gross necropsy. **F1 progeny:** Sexual maturation (preputial separation beginning PND 38 and vaginal opening beginning PND 27). Pathology (full gross necropsy and histopathology [right mammary glands (control and high dose) and left mammary fat pads]). F1 Male sperm analysis: Motility, testis and epididymis counts, and abnormality at sacrifice. F1 Neuronal development and function: Auditory startle (PND 24). Learning and memory (≥PND 60).	food or water consumption, body weight or body weight gain, gestation index, implantation sites, clinical pathology, gross pathology, or histopathology.	Decreased (NS) mean number of pups per litter at 60 (-9%) and 180 (-16%) mg/kg-day. There were no relevant effects on sex ratio, live born index, or viability/mortality. **F1 progeny:** There were no relevant effects on nipple/areola anlagen (males), body weight/body weight gain, AGD or AGI, gross necropsy, preputial separation, thyroid hormone levels, or pathology. Vaginal opening: Slightly increased at 20 mg/kg-day only (PND 33.2 treated vs 32.3 control; +3%). F1 Male sperm analysis: No effects. **F1 females (exposed up to 12 weeks pre-conception, and through gestation and lactation of F2 progeny):** Vaginal hemorrhage in one female during weeks 4-5 after pre-mating and one female on GD 23 at 180 mg/kg-day. No relevant effects on food or water consumption, or body weight. Increased relative (to body weight) adrenal weights at 60 (+11%) and 180 (+13%) mg/kg-day. Increased absolute kidney weight at 180 mg/kg-day (+7%). F1 Neuronal development and function: No effects. **Pregnancy (F1/F2) and birth (F2):** No effects on fertility or gestation indices. Increased % post-implantation loss at 60 (NS; +73%) and 180 (+284%) mg/kg-day. Decreased (NS) implantation sites at 180 mg/kg-day (-10%). Increases in terminal body weight at 60 (+4%) and 180 (NS; +6%) mg/kg-day. Decreased number of pups/litter and total pups at 180 mg/kg-day (-20% and -30%, respectively). Two females had complete litter loss at 180 mg/kg-day. There were no relevant effects on sex ratio, live born index, number of stillbirths, or viability/mortality. **F2 progeny:** There were no relevant effects on male nipple/areola anlagen, body weight/body weight gain, AGD or AGI, gross necropsy, or organ weights.

Study design	Outcomes assessed	Maternal effects	Developmental effects
	Functional Observational Battery (PND 75). Motor activity (PND 75). **F2 progeny:** Absolute and relative organ weights (brain, spleen, and thymus; n=1 pup/sex/litter).		
Bonaldo et al. 2022 Adult female C57BL/6J mice, 3 months old, n ≥ 10 animals per group. Treatment: BPS (purity not reported) in corn oil (vehicle control), oral exposure via pipette at doses of 0 (n = 10) or 4 µg/kg-day (n = 15) from mating to offspring weaning (PND28). Dams sacrificed at weaning. The oxytocin system within the paraventricular nuclei (PVN) and supraoptic nuclei (SON) was evaluated due to its role in the regulation of maternal care behavior and because it is a target of endocrine-disrupting chemicals.	**Maternal**: Body weight and food intake throughout pregnancy and lactation. Spontaneous maternal behavior during the first postnatal week (PND1 to PND 7). Oxytocin immunohistochemistry analysis of the PVN and SON. **Developmental**: Offspring measures: Number of pups at birth, sex ratio, percentage of dead pups/litter.	No effects on body weight and food intake. Spontaneous Maternal Behavior: BPS dams spent more time outside the nest compared to control dams with significant decrease in the average time spent in pup-related behavior. Oxytocin immunohistochemistry: No significant effect in the PVN or SON.	No effect on total number of pups per litter at birth. There were more female pups than males with more male dead pups at PND 0. Lost the entire litter in 5 of the 15 treated dams during the first postnatal week.
Castro et al. 2015 Pregnant Wistar rats, n = 6 per group. Treatment: BPS (98% purity) in 0.1% DMSO/99.9% olive oil, subcutaneously exposed to 0 or 10 µg/kg-day from GD 12 to parturition. Litters were culled to 8 pups with 4 males and 4 females. Female pups were exposed via subcutaneous injection from PND 1-21. Pups were sacrificed 30 min after last injection and brains saved for neuro-steroidogenesis analysis. Data derived from n ≥ 6 animals from 6 litters in each group.	**Developmental**: Female offspring assessed. Effects on 5α-reductase (*5α-R, Srd5a*) isozymes (1, 2, and 3), dopamine, and serotonin (5-HT) related genes in the prefrontal cortex. RT-PCR, western blot, and quantitative PCR array. Analysis of BPS effects on 84 key genes associated with dopamine and serotonin in the prefrontal cortex of juvenile female rats.	Not assessed.	Decreased *5α-R3* mRNA levels; no effect on protein levels No effect on *5α-R1* or *5α-R2* mRNA levels (no data on protein expression for these two isozymes). The covariate, male/female ratio at birth was not related to the number of mRNA molecules of *5α-R1, 5α-R2* or *5α-R3*. Genes associated with the dopamine and serotonin systems: 5-HT: Upregulation of 5 genes, including *Cyp2d4* (involved in 5-HT synthesis) and downregulation of 1 gene involved in metabolism and 2 genes involved in signal transduction. NS downregulation of two dopamine receptor genes: *Drd1* and *Drd3*.
Catanese and Vandenberg 2017 Adult female CD-1 mice, n = 10 to 17 per group. Treatment: BPS (99% purity) in 70% ethanol on a wafer at a dose of 0 (vehicle), 2, or 200 µg/kg-day,	**Maternal (F0)**: Body weight. Maternal behavior toward F1 progeny: Infanticide, maternal neglect, nest size, pup retrieval, and general behavior assessed on LD 2, LD 7, and LD 14.	F0: Body weight not reported. Maternal behavior: No effect on the time spent on grooming pups. Increased time spent on the	Birth outcomes: No effects on litter size, litter weight, and average pup weight in F1 and F2 litters. No effect on sex ratio of litters born to either generation. F1 maternal behavior toward F2 progeny: Increased (13% vs. 0% control) % of litters with infanticide or

Study design	Outcomes assessed	Maternal effects	Developmental effects
daily from GD 9 to PND 20 (F0); F1 were bred for another generation to result in F2. Litters were culled to 10 pups on lactation day (LD) 1. F0 dams were directly exposed; F1 pups were exposed via the mother (placental transfer *in utero* and lactational transfer during the perinatal period). Two F1 female offspring from each F0 dam were raised to adulthood, mated with unexposed CD-1 males, and tested for maternal behavior. Brain immunohistochemistry in F0 and F1 dams of the medial preoptic area (MPOA) and the ventral tegmental area (VTA), two brain regions critical for maternal care.	Brain immunohistochemistry in MPOA and VTA: LD21 **Developmental**: Birth outcomes: Litter size, litter weight, and average pup weight on LD 1. Sex ratio Open-field behavioral assay: on GD 16 and LD 10/11. Maternal behavior on F2 progeny: Infanticide, maternal neglect, nest size, pup retrieval, and general behavior assessed on LD 2, LD 7, and LD 14. Brain immunohistochemistry in MPOA and VTA in F1 dams on LD21: Assessed the number of cells expressing Erα and tyrosine hydroxylase	nest on LD 14 at 200 µg/kg-day. Decreased nest internal volume at 2 µg/kg-day on LD 2. Increased latency to interact with and retrieve pups at 200 µg/kg-day on LD 14 and 2 µg/kg-day on LD 2. No effects on open-field behavior. ERα expression in MPOA or tyrosine hydroxylase immunoreactivity in VTA: Increased ERα in caudal subregion of the central MPOA at 200 µg/kg-day. No effect on tyrosine hydroxylase immunoreactivity in the VTA.	severe maternal neglect at 2 µg/kg-day Increased (17% vs. 4% control) % of litters with moderate maternal neglect at 200 µg/kg-day. Decreased time spent on the nest at 2 µg/kg-day and 200 µg/kg-day on LD 2 and LD 7. Increased time building and repairing the nest on LD 14 at 200 µg/kg-day. Decreased latency to interact with and retrieve pups at 2 µg/kg-day on LD 7. No effects on open-field behavior. No effects on ERα expression in MPOA or tyrosine hydroxylase immunoreactivity in VTA.
Chouchene et al. 2024 Adult female Wistar rats, 3 months old, n = 7 control and n=6 BPS-treated dams. Treatment: BPS (99% purity), vehicle not reported, via oral gavage at 0.2 mg/kg-day from GD 9 until PND 21. Controls are indicated as untreated; administration of vehicle via gavage was not reported. AGD measured in 2-4 females per dam per group. Some dams were sacrificed on GD 20 and the rest of the dams and female pups were sacrificed on PND 21. This study has serious limitations, due to the apparent absence of vehicle control, and inclusion of only untreated controls. Therefore, this study is not discussed in the narrative text of this document.	**Maternal:** Body weight every five days. T3 levels on GD 20 and LD 21 Thyroid histopathology on GD 20 and LD 21. **Developmental:** Birth outcomes: Gestational length. Litter size. Sex ratio. PND 21 survival index. Live birth index. In female offspring: Body weight every five days. Cranio-caudal length. Absolute ovary weight and GSI. Nipple count (unclear day assessed, presume	BW: Not reported. BWG (GD 9 until LD 21): Decreased (NS; -40%). Serum hormone levels: Decreased T3 on GD 20 with no effects on LD 21. Thyroid histopathology: Damage to follicle structure, including epithelium hypertrophy and resorption vacuoles; increased percentage of active follicles and decrease percentage of inactive follicles on GD 20 and LD 21, with increased total	Birth outcomes: Gestational length: No effect. Litter size: Increased (NS; -27%). Sex ratio (M/F): Study narrative reports no effect; however, the table reports a NS increase (+115%).in M/F sex ratio (1.58 in controls and 3.39 in treated) PND 21 survival index: No deaths. Live birth index: No effect; 100% in both groups. Female offspring: BW: Decreased (-12%). Cranio-caudal length: No effect. Absolute ovary weight: Decreased (NS; -25%). GSI: No effect. Nipple count: No effect. AGD: No effect.

Study design	Outcomes assessed	Maternal effects	Developmental effects
	PND 4) AGD on PND 4 and 21. Serum T3 levels on PND 21. Thyroid histopathology on PND 21. Ovarian histopathology on PND 21: Percentage of ovarian follicles. Ovarian cytoskeletal protein expression: DAAM-1 and alpha-tubulin on PND 21. Oocyte development-related gene expression: *Figla* and *H1foo* on PND 21. E2, FSH, and LH on PND 21. Oxidative stress: SOD and CAT activities. Lipid peroxidation (MDA). Protein sulfhydryl group levels.	number of thyroid follicles on GD 20 (+56%) and PND 21 (+31%).	Serum T3 levels: No effect. Thyroid histopathology: Evidence of damage, including epithelium hypotrophy, resorption vacuoles, and invagination of the follicular cells. Increased percent active follicles and decreased percent inactive follicles, with no effect on total number of thyroid follicles. Ovarian histopathology: Altered percentage of follicles in different stages of folliculogenesis, including increased antral and atretic follicles and decreased primordial and primary follicles. Ovarian cytoskeletal protein expression: Decreased DAAM1 and alpha tubulin. Oocyte development-related gene expression: Decreased *Figla* and increased *H1foo* (NS). Serum hormone levels: Decreased E2, FSH, and LH (NS). Oxidative stress: Increased SOD and CAT activities and MDA levels. Decreased protein sulfhydryl group levels.
Desmarchais et al. 2022 Female Ile-de-France sheep, 2.5-year-old, n = 10 animals per dose per diet. Treatment: BPS (purity not reported), daily in the diet (vehicle not reported) at doses of 0, 4 or 50 µg/kg-day for at least three months. BPS and diet interaction with two diet groups: restricted (R) and well fed (WF). Animals were estrous synchronized and stimulated for superovulation with FSH. Then, mature follicles were aspirated under anesthesia from all 60 ewes at 7-day intervals during the breeding season (September to December). BPS treatment had no effect on the total number of follicles available for aspiration. The recovered cumulus–oocyte complexes (COCs) were used for *in vitro* maturation, *in vitro* fertilization	**Developmental:** Embryo production data.	Not assessed.	IVF: No significant effects on any of the parameters in terms of number of embryos and developmental rates. NS decreases (approximately 40%) at 4 µg/kg-day in the numbers of cleaved embryos, >4-cell embryos, blastocysts, and early blastocysts in the R diet group. NS increases (approximately 200%) at 4 µg/kg-day in these parameters in the WF diet group. Significant diet and BPS dose interaction for the number and rate of cleaved embryos, the number of >4-cell embryos, the number of blastocysts and the number of early blastocysts.

Study design	Outcomes assessed	Maternal effects	Developmental effects
(IVF), and embryo culture procedures. Oocytes were fertilized with sperm from untreated ram donors. BPS levels measured in plasma, urine, and follicular fluid of ewes. BPS-glucuronide (BPS-g) was measured in plasma prior to BPS exposure: five out of 60 ewes had detectable plasma BPS-g levels with a mean concentration of 1.16 ng/mL Plasma BPS was higher in both restricted and well-fed diet groups treated with 50 vs 4 µg/kg-day but quantitative data were not provided. Urinary BPS measured in six ewes, three from 0 and three from 50 µg/kg-day groups, one month after ovum pickup: ~0.8 nM and ~1.6 nM with 0 and 50 µg/kg-day, respectively. BPS-glucuronide levels were undetected at 0 and ~108.6 nM at 50 µg/kg-day. Follicular fluid BPS measured in 26 ewes undergoing same treatment as the 60 ewes in main study, with pre-ovulatory follicles punctured after 6 months of exposure: BPS not detected in 24 of 26 ewes, but BPS-g detected in 18 of 26 ewes exposed to 4 or 50 µg/kg-day (mean of 8.7 and 5.5 nM in restricted and well-fed ewes at 4 µg/kg-day, respectively; mean of 102.5 and 43.6 nM in restricted and well-fed ewes at 50 µg/kg-day, respectively).			
ECHA 2019 - Anonymous Study 12, 2000 (OECD TG 421 protocol). Adult SD rats, n = 12 rats per sex per group (F0). Treatment: BPS (purity >99%) in 0.5 % aqueous sodium CMC solution with 0.1 % Tween 80 administered by oral gavage at 0, 10, 60 or 300 mg/kg-day. Males treated for a total of 45 days including 14 days of premating through mating, and until the day before necropsy. Females treated for 40 to 46 days from premating, mating, and gestation up to LD 3.	**Maternal**: Body weight. **Developmental**: Implantation sites and implantation index. Mean number of offspring. Offspring birth weight. Viability index. AGD.	Decreased body weight at the end of the gestation period at 300 mg/kg-day.	Reduced mean number of implantation sites and implantation index at 300 mg/kg-day. Decreased mean number of offspring at birth at 300 mg/kg-day (9.1 vs 14.3 in control group). No effect on offspring birth weight, viability index or AGD.

Study design	Outcomes assessed	Maternal effects	Developmental effects
ECHA 2019 - Anonymous Study 14, 2017 Adult SD rats, n = 10 rats per sex per group. Treatment: BPS (>99% purity) in 0.5 % aqueous sodium carboxymethyl cellulose (CMC) solution with 0.1 % Tween 80 administered via oral gavage at doses of 0, 30, 100 or 300 mg/kg-day. Males treated for approximately 10 weeks (6 weeks premating, 2-4 weeks mating and post mating). Females treated from 6 weeks premating, through gestation and lactation until PND 21.	**Maternal**: Clinical signs. Body weight. Mortality. **Developmental**: Implantation sites. Post-implantation loss. Mean number of offspring. Offspring body weight (PND 21). Gross pathological findings.	Clinical signs: Excessive salivation at 300 mg/kg-day. Body weight: Reduced body weight (-6%) at 300 mg/kg-day. Mortality: No effects.	Reduced mean number of implantation sites (2 females without implantation) at 300 mg/kg-day. Increased percentage of post-implantation loss at 300 mg/kg-day. Reduced number of pups delivered at 300 mg/kg-day. No gross pathological findings in F1.
Fudvoye et al. 2025 Female Wistar rats, n = 15-25 per group. Treatment: BPS (purity not reported) in corn oil on a wafer at a dose of 0 (vehicle), 0.025, or 4 µg/kg-day from one week premating until GD 18. Cesarean sections were performed on GD 18. A subgroup of dams at 0 and 0.025 µg/kg-day treated until PND 21 (n=4). **Experiment 1:** Placental transcriptomic analyses. All groups, n = 10. **Experiment 2:** Fetal and postnatal growth. Vehicle control and BPS low dose group, n = 15. BPS high dose group, n = 5. Results appeared to include a combination of offspring exposed gestationally only as well as those exposed throughout gestation and lactation.	**Maternal:** Pregnancy rate. Body weight gain (time period not reported). **Placental:** Placental weight. Placental tissue from female fetuses: Transcriptomics: log fold change threshold > |0.5| and $p < 0.05$. mRNA expression using RT-qPCR of DNA methylation-associated enzymes: *Dnmt1, Dnmt3a, Dnmt3b, Tet1,* and *Tet2* and the steroid receptor coactivator 2 gene (*Src2*). DNA methylation analyses of 24 CpG sites in the *Src2* promoter. **Developmental:** Birthweight. Litter size. Sex ratio. Female offspring (0.025 µg/kg-day): Vaginal opening mean age. Number of females showing vaginal opening. Estrous cycle regularity. Male offspring (0.025 µg/kg-day): Balano-preputial separation in male offspring.	Pregnancy rate: Decreased at 0.025 µg/kg-day: (-32%); unclear if statistical analysis was performed. Body weight gain: No effects.	**Placental:** Placental weight: Increased at 4 µg/kg-day in both female and male offspring. DEGs: 5 with 0.025 and 3 with 4 µg/kg-day. 0.025 and 4 µg/kg-day: *LOC103689945*, *Fut2*, *Nxpe1*. 0.025 µg/kg-day only: *Wnt7b*, *AABR07002659.1*. No effects on DNA methylation-associated gene expression or *Src2*. DNA methylation-associated enzyme expression: No effect. DNA methylation analysis of *Src2*: decreased percentage methylation in 6 out of 24 CpG sites at 0.025 µg/kg-day. **Developmental:** Birthweight: Decreased in males at 0.025 µg/kg-day and increased in females and males at 4 µg/kg-day. Litter size: No effect. Sex ratio: No effect. Female offspring: Vaginal opening mean age: Increased (NS) days to vaginal opening at 0.025 µg/kg-day. Number of females showing vaginal opening: No effect. Estrous cycle regularity: Increased (NS; unclear if statistical analysis was performed) percent showing regularity (~+35%). Male offspring: Balano-preputial separation: No effect.

Study design	Outcomes assessed	Maternal effects	Developmental effects
Gao et al. 2024 Pregnant ICR mice, 8-weeks old, n = 30 per group. Treatment: BPS (purity not reported) in 0.067% ethanol v/v at concentrations of 0 or 3.33 µg/L (estimated equivalent of 500 µg/kg-day based on a daily water intake of 1.5 mL/10 g body weight; actual water intake not measured) via drinking water from GD 8.5 to PND 3. Some neonates in the BPS group were intraperitoneally injected with 2 mg/kg-day rapamycin (autophagy agonist and mTOR inhibitor) from PND 0-3 (control injected with 0.5% ethanol, v/v). At birth, female pups were culled to 6 pups/litter/group. Maternal BPS serum concentration on days 7 and 14 of exposure: Mean serum concentrations of 1.16 ng/mL at day 7 and 1.27 ng/mL at day 14.	**Maternal**: Body weight, gestational duration, and behavior (reported qualitatively only). **Developmental**: Pup birth outcomes obtained within 12 hours of birth: (litter size, birth weight (females), sex ratio, body length and AGD in females. PND 4 female pups: Oocyte cyst breakdown and primordial follicle (PF) assembly (histology and MVH immunofluorescence). Serum AMH concentration. Ovarian ultrastructural analysis (transmission electron microscopy [TEM]). Ovarian gene and protein expression during folliculogenesis (RT-qPCR and immunoblotting). Oxidative stress in ovaries (reactive oxygen species [ROS; DCF fluorescence]; lipid peroxidation [MDA]; glutathione [GSH] peroxidase, catalase [CAT], and superoxide dismutase [SOD] activities; *Glrx2*, *Gpx1*, *Cat*, and *Sod1* gene expression; and GPX1, CAT, and SOD1 protein expression). Apoptosis analysis in ovaries (TUNEL assay; TEM analysis; *Bcl2*, *Bax*, *Caspase-3 [Casp3]*, and *Caspase-9 [Casp9]* gene expression; and cleaved [Cl]-/Pro-Cas-3, Cl-/Pro-Cas-9, BCL2, and BAX protein expression). Autophagy analysis in ovaries (TEM analysis; *p62*, *beclin-2 [Becn2]*, and *Lc3b/Lc3a* gene expression; and phosphorylated [p]-mTOR/mTOR ratio, pULK1/ULK1 ratio, LC3B/LC3A ratio, BECN1, and P62 protein expression). Vaginal opening (female offspring, PND 21 onwards). Estrous cycle analysis of female offspring observed over a 30-day period.	Decreased gestational duration (-2%).	Pup birth outcomes: Decreased pup body length (-2%). No effects on sex ratio, birth weight or AGD. PND 4 female pups: Oocyte cyst breakdown and PF assembly: Fewer cysts and more PFs observed. Decreased number of oocytes/ovarian tissue section (-28%). Decreased % oocytes in cysts (-13%). Increased % oocytes in PFs (+43%). AMH concentration: Decreased serum AMH (-22%). Ovarian ultrastructural analysis: Separation of individual oocytes due to long projections of somatic cells surrounding cysts; plasma membranes not penetrated. Ovarian gene expression during folliculogenesis: Decreased *Kit*, *Nobox*, *Gdf9*, *Sohlh2*, *Kitl*, *Bmp15*, *Lhx8*, *Figla*, and *Tgfb1*. Ovarian protein expression during folliculogenesis: Decreased c-KIT, NOBOX, GDF9, SOHLH2, SCF, BMP15, LHX8, FIGLA, and TGFB1. Oxidative stress in neonatal ovaries: Increased ROS and lipid peroxidation. Decreased GSH peroxidase, CAT, and SOD activities. Decreased *Glrx2*, *Gpx1*, and *Cat* gene expression. Decreased GPX1, CAT, and SOD1 protein expression. Apoptosis analysis in neonatal ovaries: Increased number of TUNEL-positive cells. TEM imaging identified apoptotic characteristics, including chromatin aggregation and oocyte vacuolization. Increased *Casp3*, *Casp9*, and *Bax* gene expression. Decreased *Bcl2* gene expression. Increased Cl-/Pro-Cas-3, Cl-/Pro-Cas-9, and BAX protein expression. Decreased BCL2 protein expression. Autophagy in neonatal ovaries: Fewer autophagosomes in the cytoplasm of oocytes and somatic cells. Decreased gene expression of *Becn2* and ratio of *Lc3b/Lc3a*.

Study design	Outcomes assessed	Maternal effects	Developmental effects
	Fertility (n=8 [each from different mothers]; 8-weeks old mated with wild-type fertile males; produced 5 litters in a 6-month period). mTOR/ULK1 pathway analysis (rapamycin + BPS co-treatment in PND 4 female offspring.		Increased p-mTOR/mTOR ratio and P62 protein expression. Decreased pULK1/ULK1 ratio, LC3B/LC3A ratio, and BECN1 protein expression. Female offspring, PND 21 onwards: Earlier puberty indicated by earlier day of vaginal opening (26-28 days treated vs 30-33 days control). Earlier first estrus (27-31 days treated vs. 30-37 days control) and first regular estrous cycle (33-36 days treated vs 35-38 days control). Shortened metestrus phase (-51%), prolonged diestrus phase (+37%), and increased average cycle length (+23%). Fertility: Decreased litter size with the third, fourth, and fifth mating in F1 female (-24%, 26%, and 51%, respectively). Increased incidence of abortion during fourth mating (2/8 exposed vs. 0/8 control; dams that experienced abortion were infertile in the fifth mating). Increased incidence of infertile mice by fifth mating (3/8 treated vs. 0/8 control). Co-treatment with BPS and rapamycin: Inhibition of mTOR with rapamycin co-treatment led to recovery of BPS-mediated effects on autophagy, oxidative stress, apoptosis, and folliculogenesis except for gene expression of p62 (NS decrease).
Gingrich et al. 2018 Pregnant Polypay and Dorset crossbred sheep, n = 6 to 7 animals per group. Treatment: BPS (purity not reported) in corn oil, daily subcutaneous injection (injection volume not reported), at doses of 0, or 0.5 mg/kg-day from GD 30 to 100. Serum samples were collected once every two weeks from GD 30–120 for hormonal, protein, and biochemical analyses. Animals were sacrificed, and placenta samples were collected on GD 120. Internal fetal dose of unconjugated BPS: 4.9 and 10.6 ng/mL reported in fetal arterial blood on GD 117-118	**Developmental:** Placental endocrine function: Pregnancy-associated glycoprotein 1 and pregnancy-specific protein B. Serum progesterone. Placental morphology. Protein and mRNA expression of factors involved in trophoblast fusion.	Maternal-specific effects not assessed.	Placental endocrine function: Decreased serum maternal pregnancy-associated glycoprotein1 on GD 75 to GD 90 Decreased serum pregnancy-specific protein B on GD 60, 75, and 90 NS decrease in serum progesterone at GD 75-105 (P=0.09) Placenta: NS increase in placental weight (P=0.07) No effect on placental tissue distribution, or number of placentomes per placenta. Decreased (-20%) in trophoblast derived binucleate cells. Protein expression: Lower (-50%) e-cadherin protein expression in GD 120 placentomes.

Study design	Outcomes assessed	Maternal effects	Developmental effects
from two singleton male fetuses; BPS concentrations in two control fetuses were 0.02 ng/mL (LOD).			Increased protein expression of transcription factor glial cell missing factor 1 (GCM1). Fusogenic genes: Downregulated mRNA expression of *enJSRV* and *HYAL2*.
Kaimal et al. 2021 Pregnant SD rats, n ≥ 9 per group. Treatment: BPS (≥ 98% purity) in phosphate buffered saline (10 ml vehicle control), orally via micropipette at a dose of 5 µg/kg-day from GD 6 to GD 21. Female and male offspring (F1) were sacrificed at 16 to 24 weeks of age on the day of diestrus (females).	**Maternal**: Body weight and body weight gain. Spontaneous abortion. **Developmental**: Birth measures (PND 1): Stillborn pups, body weight, head circumference, chest circumference, crown to rump length, AGD. Postnatal measures (PND 7, PND 14, and PND 21): Litter weights. Post-weaning measures (age 3, 6, and 12 weeks): Body weights, food intakes, water intake. Relative organ weights: Adipose tissue (abdominal, epididymal, and ovarian), pituitary gland, testes and epididymis, and ovary and uterus. Ovarian morphometric analysis: Follicle characterization and counts. Oxidative stress in PND 21 testes: DNA oxidation product 8-hydroxy deoxyguanosine (8-OHdG) immunohistochemistry. Serum testosterone levels in males (age 16 to 24 weeks).	No effect on body weight, body weight gain, or spontaneous abortion.	Birth measures: Two stillborn pups (one case per litter in 2/13 litters). Decreased AGD in male offspring. No effect on postnatal measures or post-weaning measures. Relative organ weights: Abdominal adipose tissue weight: Decreased in BPS-treated males. Epididymal adipose tissue weight: Decreased in BPS-treated males No effects: Ovarian adipose tissue, pituitary gland, testes and epididymis, or ovary and uterus weights. Ovarian morphometric analysis: Decreased number of *corpora lutea* with BPS treatment. No effect on number of follicles at any other stage. Oxidative stress in PND 21 testes: Increased accumulation of 8-OHdG in the seminiferous tubules. No effect in serum testosterone levels in adult males.
Kim et al. 2015 Pregnant CD-1 mice, n = 5 per group. Treatment: BPS (99 % purity) in tocopherol stripped corn oil daily (volume: 1 µl/g body weight). Administered orally by pipette at 0 or 0.2 mg/kg-day from GD 8 through PND 21. Study designed to assess interactions between body weight and social behaviors in male mice.	**Maternal**: Body weight. **Developmental:** F1 males assessed: Body weight and litter size. Spontaneous motor activity (PND 21): Open Field Test with 1 male pup per litter. Sociability (week 10): Three-Chamber Social Approach Test with same-litter triad.	No effect on body weight.	F1 males: No effect on body weight at birth or litter size. Lower body weight at week 11 through 16 with BPS exposure. Spontaneous motor activity: No effect in Open Field Test (data not shown). Sociability: Three-Chamber Social Approach Test: Stage I: Increased mean velocity of movement. Stage II: Increased mean velocity of movement (+12.5%) in the chamber with the stranger mouse. Stage III: Decreased time (-35%) spent with the familiar mouse

Study design	Outcomes assessed	Maternal effects	Developmental effects
	Sociability index. Social novelty preference index. Social dominance/subordination: Tube Test (weeks 11 and 15) with cohabited male triads. Urine Marking Test (weeks 12-14) with cohabited male triads.		and stranger mouse. No effect on sociability index or social novelty preference index. Social dominance/subordination: Tube test: Social dominance was NS inversely related to body weight for control and BPS-treated. Consistent rankings between weeks 11 and 15. Urine Marking Test: Supported tube test results (data not shown).
Kolla and Vandenberg 2019 Pregnant CD-1 mice, n ≥ 7 per group. Treatment: BPS (purity not reported) in tocopherol stripped corn oil, daily oral administration with a pipette to the mouth (1 µg oil/g body weight) at doses of 0, 2, 200, or 2000 µg/kg-day from GD 8 to PND 2. Ethynyl estradiol (EE) challenge: following the same treatment protocol of BPS, two female pups per litter were treated with EE at doses of 0, or 1 µg//kg-day, for 10 days (from PND 21 to PND 30). Animals sacrificed on PND 31.	**Developmental**: F1 females assessed. Time to vaginal opening AGI Uterus weight. Mammary gland histology. Steroid receptor mRNA expression: ERα (*Esr1*) and PR (*Pgr*). EE x BPS interaction.	Not assessed.	No effects on vaginal opening, No effects on AGI or uterine weight. Mammary gland histology: Decreased ductal area at 2 µg/kg-day. No effect on the number or total area of terminal end buds. Steroid receptors expression: Increased gene expression of *Esr1* at 200 µg/kg-day. No effect on *Pgr* expression. EE – BPS interaction: No effects of EE challenge on vaginal opening, AGI, uterine weight, ductal area, number or total area of terminal end buds, or *Esr1* and *Pgr* mRNA expression.
Kolla et al. 2019 Pregnant CD-1 mice, n = 6–7 animals per group. Treatment: BPS (purity >99%) at doses 0, 2, or 200, µg/kg-day in 70% ethanol (vehicle control) on wafers from GD 9 to GD 16.	**Developmental:** Histology of male mammary gland. Immunohistochemical analysis of mammary tissues for androgen receptor (AR) and ERα (ESR1).	Not assessed.	Male mammary gland effects on GD 16: NS increases in size of epithelial anlagen and the mammary epithelial area divided by number of epithelial cells with the highest values at 200 µg/kg-day. No effect on epithelial cell size. Increased space between cells (lumen formation). No staining for AR in epithelial cells and dose-dependent decrease in AR expression in the mesenchyme. Inconsistent results for ESR1 in epithelial cells with no difference between treatment groups.
Mao et al. 2020 Female C57BL/6J mice, n > 6 animals per group. Exposure: BPS (> 98% purity) in 70% ethanol (8 to 24 µL/kg) applied and allowed to dry on a small wafer, fed daily at doses of 0, or 200 µg/kg-day for two weeks.	**Maternal:** Maternal weight during gestation. **Developmental:** Pregnancy success, implantation sites, number of fetuses, sex ratio. Placenta morphometric analyses. Measurement of the labyrinth,	No effects on maternal weight.	No effects on pregnancy success, implantation sites, number of fetuses, or sex ratio. Effects in GD 12.5 placenta: Decreased ratio of spongiotrophoblast zone to GC area. Metabolomics: Effect on fatty acids: Decreased stearic acid, hexadecanoic (palmitic) acid, docosahexaenoic acid, and octadecenoic acid.

Study design	Outcomes assessed	Maternal effects	Developmental effects
After treatment, females were paired with untreated males. Sacrificed on GD 12.5; each uterine horn was incised; the uterine position of each conceptus was delineated, and placenta samples were obtained and saved half in liquid nitrogen and the other half was fixed for histological analyses.	spongiotrophoblast, and trophoblast giant cell (GC) areas. Metabolomics. Neurotransmitters: Effects on serotonin (5-HT) and dopamine tissue distribution by immunohistochemistry. Placental steroid hormone levels: Estradiol-17β (E2), estrone, corticosterone, testosterone, and P. Transcriptomic (RNA-seq) analysis of placental tissues on GD 12.5: identification of differentially expressed genes (DEGs).		Neurotransmitters: Increased dopamine concentration and percentage of dopamine-positive GCs. Decreased 5-HT concentration and percentage of 5-HT-positive GCs. Ten-fold increase in the ratio of 5-hydroxyindoleacetic acid (5-HIAA, a primary 5-HT metabolite) to 5-HT. Placental steroid hormone levels: No effects. DEGs: Identification of 11 DEGs in BPS-treated placentae compared to controls. One upregulated gene, *Actn2* with a 2.17-fold change. Ten downregulated genes including *Calm4* with -22.52-fold change and *Guca2a* with -26.72-fold change.
McDonough et al. 2021b Pregnant Non-Obese Diabetic Excluded Flora (NODEF) mice, n = 5–6 per group. Treatment: BPS (purity not stated) dissolved in 100% ethanol and added to corn oil (final ethanol concentration 0.05%) then administered via oral pipette at 0 (n = 5) or 3 (n = 6) µg/kg-day from breeding day 1 to parturition. Assessment of male and female offspring from PND 21 to 12 weeks.	**Developmental:** Body weights. Metabolic analysis: blood glucose, glucose tolerance, and insulin tolerance. Behavioral tests: Working memory (Y-maze test), short-term memory (novel object test), depression-like behavior (tail suspension test), and anxiety-like behavior and locomotion (open field test).	Not assessed.	Body weight: Increased in female offspring at age 18 weeks. Decreased in male offspring at PND 21. Metabolic analysis: No effect on glucose or insulin tolerance tests. Decreased non-fasted blood glucose levels in males at PND 21 and age 12 weeks. PND 21 behavioral tests: No behavioral differences for either sex. 12 weeks behavioral tests: Working memory and short-term memory: Impaired in female offspring. Depression-like behavior: Increased in male offspring. Anxiety-like behavior: Increased (ns, p=0.076) in male offspring.
Molangiri et al. 2022 Pregnant Wistar rats, n = 5–6 dams per group, n= 10–20 pups per group. Treatment: BPS (purity not stated) in olive oil (vehicle control) by gavage at 0, 0.4, 4 or 40 µg/kg-day from D 4 to GD 21. Male offspring were evaluated for male reproductive toxicity on PND 90.	**Maternal**: Body weight at GD 4,18, and 21. **Developmental**: Offspring body weights recorded fortnightly, starting at PND 45. Testis weight. AGD (0.4 µg/kg-day). Testis histopathology (0.4 and 4 µg/kg-day). Plasma testosterone level (0.4 and 4 µg/kg-day).	No effect on body weights.	Increase in offspring body weight at PND 90. Body weight changes independent of the food intake (stated, but data not presented). Testis weight: Increased at all doses. AGD: No effects. Testis effects: Decreased diameter of seminiferous tubules. Decreased (NS) epithelial height. Increased thickening of basal membrane and increased interstitial space between seminiferous tubules at 4 µg/kg-day. Increased plasma testosterone levels at 0.4 µg/kg-day.

Study design	Outcomes assessed	Maternal effects	Developmental effects
	Sperm DNA damage assessed by DNA fragmentation using an acridine orange assay (0.4 and 4 µg/kg-day). Sperm motility assessed indirectly by measuring preserved phosphorylated AKT levels in the testis (0.4 and 4 µg/kg-day). Protein expression of testis-expressed protein TEX11 (0.4 and 4 µg/kg-day). mRNA expression in testis (0.4 and 4 µg/kg-day). Global DNA methylation of sperm (0.4 and 4 µg/kg-day).		Sperm DNA fragmentation: Fragmented, hypermethylated sperm DNA and poor sperm motility in adult rat offspring (PND 90). Decrease in AKT and pAKT protein expression impaired sperm motility via reduced PI3K-AKT mediated energy activation. Decreased mRNA expression of *Ar* in the testis. Increased protein expression of TEX11. Downregulated mRNA expression of *Tex101* and *Spo11* in adult rat testis at 0.4 µg/kg. No effects on the mRNA expression of other spermatogenesis-related genes (*Akap4*, *Catsper1, Catsper2, Gpr56, Ddx4, and Tssk1*) and testis-expressed family genes (*Tex11, Tex12, Tex14*, and *Tex15*). No effects on global DNA methylation of sperm.
Molangiri et al. 2023 Pregnant Wistar rats, n = 40. Treatment: BPS (purity not stated) in olive oil (vehicle control). Oral exposure by gavage at doses of 0, 0.4, or 4 µg/kg from GD 4 to GD 21. Male offspring (F1) evaluated from PND 30 to PND 90.	**Developmental**: F1 male offspring assessed. Body weight. Body composition. PND 90: Plasma biochemical analysis: fasting glucose, triacylglycerol, cholesterol, and corticosterone. Histology: visceral adipose tissue and liver tissue. Adipose gene expression. Adipose protein expression. Hepatic gene expression. Hepatic protein expression. Hepatic inflammation markers.	Not assessed.	F1 males: Body weight: Increased at PND 45, PND 59, and PND 73. Body composition (measured with 0.4 µg/kg only): Increased body mass, lean mass, fat mass, and fat percentage at PND 30. Increased fat mass and fat percentage at PND 90. Plasma biochemical analysis: No effect on fasting glucose, triacylglycerol, and cholesterol. Increased corticosterone concentration with 0.4 µg/kg. Histology: dose-dependent increased adipocyte hypertrophy. Increased liver weight and presence of microvesicular steatosis at 0.4 and 4 µg/kg. Adipose gene expression: Upregulated *Hsd11b1* at 0.4 µg/kg. Adipose protein expression: Increased FABP4, IL1B, COX2, CHOP, and CASP3 at 0.4 and 4 µg/kg. Increased CRP at 0.4 µg/kg. Increased HSD11B1 at 4 µg/kg. Decreased PPARG at 0.4 and 4 µg/kg. Hepatic gene expression: Upregulated *Ppara, Fasn, Srebf1, Acaca, Nampt, Prkaa2*, *Fads2, Er, and Hsd11b2* at 4 µg/kg Upregulated *Hsd11b1* at 0.4 and 4 µg/kg.

Study design	Outcomes assessed	Maternal effects	Developmental effects
			Hepatic protein expression: Increased ADRP lipid droplet-associated protein, FGF21 hepatokine, and PPARA. Hepatic inflammation markers: Increased expression of IL6, CRP, IL1B, TNFA, and COX2 pro-inflammatory cytokines, and Increased lipid peroxidation at 0.4 and 4 µg/kg
Moon et al. 2023 Pregnant C57BL/6J mice, 25–30g, n = 2 per group. Treatment: BPS (purity not stated) in corn oil (vehicle control) at 0 or 50 µg/kg-day via subcutaneous injection from GD 9.5 to PND 28. Female and male offspring (F1) were examined for behavior (n ≥ 15 per group) from PND 42 to PND 84.	**Developmental:** F1 behavior: Social interaction behavior and social novelty: Three-chamber social test with unfamiliar mouse and social interaction test. Anxiety-like behavior: Open-field test and elevated plus-maze test. Depression-like behavior: Tail suspension test and forced swimming test. Motor coordination and learning: Rotarod test. Memory and cognition: Novel object recognition.	Not assessed.	No effect: sociability, anxiety- and depression-like behaviors, motor coordination, learning, memory, and cognition. Social novelty: Lower preference index during social novelty test with BPS exposure.
Nourian et al. 2017 Adult female mice on same cycling stage, strain not specified, n = 70 animals total. Treatment: BPS (99% pure) in ethanol (% not specified), daily IP injections (volume not specified) at doses 0, 1, 5,10, 50 or 100 µg/kg-day for 21 consecutive days. 24 hours after the last treatment, five mice in each group were euthanized and ovaries collected. Oocytes collected for *in vitro* fertilization (IVF) assays were obtained from five super-ovulated female mice randomly selected from each group. Total number of oocytes collected showed a decreasing trend with increasing concentration of BPS.	**Developmental:** IVF outcomes: fertilization rate, 2-cell embryo, blastocyst, and arrested embryo percentages.	Not assessed.	IVF outcomes: Decreased fertilization rate, 2-cell embryo, and blastocyst percentages with 10, 50, and 100 µg/kg-day treatment. Increased embryo arrest with 50 and 100 µg/kg-day treatment.
Pu et al. 2017 Pregnant Polypay Dorset crossbred sheep, n = 7–8 ewes per group.	**Developmental:** GD 120. Body weight. Biparietal diameter. Perirenal adipose tissue histology.	Not assessed.	GD 120: Body weight: No effect. Biparietal diameter: Decreased in male fetuses. Perirenal adipose tissue histology: No gross differences in tissue. No effects on unilocular (white adipocyte) size.

Study design	Outcomes assessed	Maternal effects	Developmental effects
Treatment: BPS (99.7% purity), in corn oil (vehicle control), daily subcutaneous injection of 0 or 0.5 mg/kg from GD 30 to GD 100 (term: ~147 days). Ewes bred with a single fertile ram to reduce paternal confounding factors. Fetal perirenal adipose tissue, which represents the largest adipose store at age assessed, collected on GD 120. Primary cell culture of perirenal adipose tissue, with fetal preadipocytes induced to differentiate for 8 days (terminal differentiation stage) into adipocytes.	*in vitro* (primary culture of fetal perirenal adipose tissue). Preadipocyte differentiation and proliferation via Oil Red O (ORO) and growth curve analysis, respectively. mRNA expression of genes associated with early and late adipogenesis, cell proliferation, and sex-steroid receptors in adipose tissue and cells.		Left shift in the adipocyte perimeter plot (indicating smaller size) in males. *in vitro* (primary culture of fetal perirenal adipose tissue). Preadipocyte differentiation and proliferation: No effects. mRNA expression in adipose tissue. Decreased *ADIPOQ* in males. mRNA expression in primary cells. Undifferentiated preadipocytes: Increased *ESR1, ESR2,* and *GR* in males. Differentiated adipocytes: Increased *FABP4* and *ADIPOQ* in males.
Shi et al. 2018 Pregnant CD-1 mice, n = 5 animals per group to generate 5 litters per group. Treatment: BPS (purity >98%) dissolved in 100% ethanol and then diluted in tocopherol-stripped corn oil. Daily treatment to pregnant dams at 0, 0.5, 20 or 50 µg/kg-day orally via pipette tip from GD 11 until birth. Male pups, 2-3 from each litter evaluated on PND 12 or 60.	**Maternal:** Body weight. **Developmental:** F1 male offspring. Testis weight and testis/body weight ratio. Sperm Parameters: sperm concentration and motility. Testis histopathology. Hormone concentration: serum E2 and testosterone. Steroidogenic protein- and enzyme-related gene expression. Apoptotic gene expression. Oxidative stress gene expression. Methyltransferases gene expression and histone modification. Apoptotic germ cells (TUNEL).	No effect on body weight.	PND 12: No effect on testis weight or testis/body weight ratio. Apoptotic germ cells: Increased proportion of TUNEL-positive tubules and increased number of TUNEL-positive cells per tubule at all doses. PND 60: No effect on testis weight or in the ratio of testis to body weight. Sperm parameters: Decreased sperm concentration with 0.5 (-34%) and 20 µg/kg (-45%). Decreased sperm motility at 0.5 µg/kg (-60%). Histopathology: Decreased percentage of tubules in stage VII and increased percentage of tubules in stage VIII at 50 µg/kg. Hormone concentration: Increased serum E2 at 50 µg/kg. No effect on testosterone. Steroidogenic protein- and enzyme-related gene expression: Increased *Star* at 0.5 and 20 µg/kg-day. Increased *Cyp11a1* at 0.5 and 50 µg/kg-day. Increased *Cyp19a1* at 50 µg/kg. Apoptotic gene expression: Decreased *Bad and Bax* at all doses. Increased *Cycs* at 0.5 µg/kg-day. Oxidative stress gene expression: Decreased *Cat* with 0.5 and 20 µg/kg. Decreased *Gpx4* with 0.5 µg/kg.

Study design	Outcomes assessed	Maternal effects	Developmental effects
			Decreased *Sod2* with 0.5, 20, and 50 µg/kg. Increased *Sod1* with 20µg/kg. DNA methyltransferases expression: Increased *Dnmt1* with 20 µg/kg. Increased *Dnmt3b* with 50 µg/kg. Histone methyltransferases expression: Decreased *Setd1a* with 0.5 µg/kg (NS decrease with 20 and 50 µg/kg). Decreased *Setd1b*, *Kmt2e*, and *Suz12* with 0.5, 20, and 50 µg/kg. Increased *Dot1l* with 20 and 50 µg/kg. Apoptotic germ cells: No change in number of TUNEL positive cells (data not shown).
Shi et al. 2019a Pregnant CD-1 mice, number of animals not specified, analysis performed on 4–5 litters per group. Treatment: BPS (purity not reported) in corn oil. Daily oral treatment by placing a pipette tip in the mouth at doses of 0, 0.5, 20, or 50 µg/kg-day from GD 11 to birth. One female pup from each litter was euthanized on PND 4 and ovaries were fixed for histological analysis. F1 females were mated at 3, 6, and 9 months of age with untreated CD-1 males.	**Maternal**: Body weight gain. **Developmental**: Ovarian histology at PND 4: germ cells and folliculogenesis. Serum E2 and testosterone concentration at age 3, 6, and 9 months. Ovarian steroidogenic protein- and enzyme-related gene expression: *Star, Cyp11a1, Cyp17a1, Hsd3b1, Hsd17b1,* and *Cyp19a1* at age 3, 6 and 9 months. Fertility: Puberty onset; estrous cyclicity; time to vaginal plug; successful mating rate; pregnancy rate; and F2 offspring numbers, body weights, and sex ratio.	Body weight gain not reported.	Ovarian histology: Retention of germ cells in nests at 0.5 and 20 µg/kg-day; no effects in primordial follicles / total oocytes ratio. Decreased primary follicles, total oocytes ratio at all doses; no effects on secondary follicles. Serum hormone concentration: Increased testosterone at 50 µg/kg-day at 9 months. No effect on testosterone at other doses or in E2 levels at any dose or age. Steroidogenic enzymes: Increased on mRNA *Cyp11a1* at 3 months with 0.5 µg/kg-day. Fertility: Vaginal opening earlier with 0.5 µg/kg-day (-1 to -2 days) and delayed with 20 µg/kg-day (+2.5 days). Estrous cyclicity: irregular with stalled estrus and diestrus at all doses. Time to vaginal plug: Increased with all BPS concentrations at ages 6 months and 9 months. Successful mating and pregnancy rates: Decreased at age 6 months with 0.5 µg/kg-day and 20 µg/kg-day treatments, and at age 9 months for all treatments. F2 offspring numbers: Decreased pups/litter at age 9 months with 20 µg/kg-day. F2 pup body weights and sex ratio: No effects. Some BPS-treated (at all concentrations) F1 pregnant females at age 9 months at mating showed parturition or nursing issues.

Study design	Outcomes assessed	Maternal effects	Developmental effects
Shi et al. 2019b Pregnant CD-1 mice, number of animals per group not specified. Treatment: BPS (purity not reported) in corn oil, daily oral exposure at doses of 0, 0.5 or 50 µg/kg-day from GD 7 to birth. F2 generation: F1 offspring at 6–7 weeks bred to other F1 mice from the same treatment group using different litters to avoid inbreeding. F3 generation: F2 mice from the same treatment group that were not siblings or cousins were bred). Examined both testes from one male per litter on PND 6 and PND 60 (n=6 litters/group/age) from F3.	**Maternal**: Body weight gain. **Developmental:** F3 males assessed. PND 6 testis: Histology Gene expression of DNA methyltransferases (Dnmt1, Dnmt3a, and Dnmt3b), cofactors, histone methyltransferases and histone marks (H3K4me3, H3K9me2, H3K9me3, and H3K27ac). DNMT3A, DNMT3B, H3K9me2, and H3K9me3 expression. PND 60: Testis weight, testis/body weight ratio, – sperm count, and sperm motility. Morphometric analyses: Distribution of testis tubule stages of spermatogenesis. Serum hormone concentration: E2 and testosterone. Testicular steroidogenic enzyme gene and protein expression. DNA and histone methyltransferase expression. DNA damage and apoptosis.	Body weight gain not reported.	F3 PND 6: Increased DNA methyltransferases and histone methyltransferases mRNA in testis at 50 µg/kg-day. Increased expression of methyltransferase cofactor *Dnmt3l* with 50 µg/kg-day. Increased expression and aberrant localization of DNMT3B at 0.5 and 50 µg/kg-day. F3 PND 60: Testis weight: No effect. Testis/body weight ratio: Increased with 0.5 µg/kg-day. Sperm count: Decreased with 0.5 µg/kg-day (-40%) and 50 µg/kg-day (-48%). Sperm motility: Decreased with 0.5 µg/kg-day. Histology: Morphometric analysis: Abnormal distribution of the stages of spermatogenesis showing increased number of tubules in stages I-VI and decreased stage IX tubules with 0.5 µg/kg-day. Serum hormone concentration: Decreased testosterone concentration with 50 µg/kg-day. No effect on E2 Testicular steroidogenic enzyme gene expression: Increased relative mRNA expression of *Star* and *Cyp19a1* at 0.5 and 50 µg/kg-day.
Tiwari et al. 2024 Female Wistar rats. ***In vivo:*** Treatment: BPS (purity not reported) in corn oil via oral gavage at 0 (vehicle control) or 40 µg/kg-day from GD 6 to LD (PND) 21. Assessment of hippocampal neural stem cells (NSC): offspring received intraperitoneal injections of the proliferation marker BrdU from PND 17 to PND 21 and sacrificed four hours following last BrdU administration.	***In vivo*:** Body weight on PND 21. Hippocampal (dentate gyrus region) NSC phenotype and quantification: Proliferation (BrdU) on PND 21. Stemness and self-renewal on PND 21. BAX and cleaved CASP3 protein expression on PND 21. Ultrastructure of hippocampal neurons on PND 21.	Not reported.	***In vivo*:** Body weight: No effects (quantitative data not reported). Hippocampal NSC phenotype and quantification: Decreased proliferation in granular cell layer and hilus. Decreased NSC stemness and self-renewal. Apoptosis: increased BAX and cleaved CASP3. Ultrastructure of hippocampal neurons: Myelin sheath decompaction and loosening. Decreased number of axons. Increased percentages of damaged synapses and mitochondria.

Study design	Outcomes assessed	Maternal effects	Developmental effects
NSC fate and survival: subgroup of offspring sacrificed on PND 42, three weeks after last BrdU administration. ***In vitro:*** Primary hippocampal NSC and neuronal culture of GD 14 Wistar rat embryos. Viability: 20, 50, 100, 150, 200, 300, or 400 µM BPS for 24 hours; decreased viability at ≥200 µM. Neurosphere growth kinetics assay on NSC-derived primary neurospheres: 0 or 150 µM BPS for 24 hours. Proliferation assay and dendritic measurement: 0, 0.001, 0.010, 0.100, 1, 10, or 100 µM BPS for 48 (proliferation) and 72 (dendritic) hours. Differentiation assay: 0 or 150 µM BPS for 48 hours.	Differentiation and survival on PND 42: BrdU co-labeled with DCX or NeuN (neuronal differentiation) and cleaved Caspase-3 (apoptosis). Conditioned avoidance response on PND 42. ***In vitro*:** Neurosphere growth kinetics assay to assess NSC self-renewal potency. Primary NSC proliferation. Primary NSC differentiation: co-labeling with MAP-2 (mature neuron marker) and GFAP (astrocyte marker). Dendritic length and number of primary hippocampal neurons.		Decreased differentiation of NSC into neurons. Decreased number of mature neurons. Conditioned avoidance behavior: Decreased learning and memory function. ***In vitro*:** Neurosphere growth kinetics assay: Decreased number and size of neurospheres. Primary NSC proliferation: Decreased proliferation at all concentrations. Primary NSC differentiation: Inhibition of neuronal differentiation (decreased number of MAP-2+ cells) and induction of glial differentiation (increased number of GFAP+ cells). Dendritic length and number: Decreased at all concentrations.
Tucker et al. 2018 Pregnant CD-1 mice, GD 8.5, n ≥ 11 animals per group. Treatment: BPS (purity ≥ 97.5%) in pure sesame oil, twice daily by oral gavage (10 µL/g body weight) at doses of 0, 0.05, 0.5, or 5 mg/kg-dose (assumed to be 0, 0.1, 1.0, or 10 mg/kg-day) from GD 10.5 to GD 17.5. Analysis on female offspring from PND 20 to 14 months (1 or 2 per litter).	**Developmental:** Offspring body weight. Female offspring: Observations on F1 at PND 16, 20, 28, 35, 56, weekly between PND 63-83, and at 3, 8, and 14 months of age. Female pubertal indices: Timing of first estrus and estrous stage at vaginal opening; and estrous cyclicity. Mammary gland development score: By age and level of development, scoring based on lateral and longitudinal epithelial growth (mammary epithelial area), presence or absence of terminal end buds, mammary epithelial branching density, budding, and appearance of ductal ends at PND 20, 28, 35, and 56. Serum hormone levels: E2, P, testosterone, and dehydroepiandrosterone (DHEA) at PND 20, 28, 35, and 56, and at 3, 8, and 14 months of age. Spontaneous occurrence and mammary gland lesion incidences at 3, 8, and 14 months.	Not assessed.	Decreased body weight on PND 56 at 5 mg/kg-day (no effects on body weight at other ages or doses) Female offspring: No differences in age at vaginal opening (PND 25–27); first estrus (PND 27–28) or number of normal estrous cycles (3–4 days). Mammary gland development. PND20: Dose-dependent increase in terminal end buds length and counts. Increased branching density at 0.05 and 5 mg/kg. Increased developmental score (accelerated glandular development) at 5 mg/kg. No effects on mammary epithelial area. PND28: No effects on mammary gland development. PND 35: Increased developmental score at all doses. PND 56: Increased developmental score at 0.5 mg/kg. Serum hormone levels. PND 20: Increased E2 at 0.5 and 5 mg/kg. PND 28: Increased testosterone at 0.05 mg/kg.

Study design	Outcomes assessed	Maternal effects	Developmental effects
	Nuclear receptor gene expression (*Esr1, Pgr, Ar,* and *Gper1*) in mammary gland tissue at 8 and 14 months.		PND 35: Decreased testosterone at 0.5 and 5 mg/kg. PND 56: No effects. 3 months: Decreased progesterone and DHEA at 5 mg/kg. 8 months: Decreased E2 at 0.05 mg/kg-day and DHEA and testosterone at 0.5 mg/kg. 14 months: No effects. Mammary gland lesion incidences. 3 months of age: Higher incidence in diagnosis of mixed cell inflammation or terminal end buds at 0.5 mg/kg. 8 months of age: No differences in mammary gland lesion incidences. 14 months of age: Increased incidence of: perivascular lymphoplasmacytic inflammation; inflammation diagnoses; and non-neoplastic lesions (lobuloalveolar hyperplasia) at 0.5 mg/kg. Decreased E2 at 0.05 mg/kg and testosterone and DHEA at 0.5 mg/kg at 8 months of age. No effects at 14 months of age. Nuclear receptor expression in mammary gland tissue: Decreased *Pgr* at 5 mg/kg at 8 months. While NS at 11-16 months of age, multiple mammary neoplastic lesion types diagnosed: Carcinoma: one at 0.5 mg/kg. Histiocytic sarcoma: one at 0.5 mg/kg. Papillary carcinoma: one at 0.5 mg/kg. Squamous cell carcinoma: one at 0.5 mg/kg. Adenocarcinoma: two at 5 mg/kg. Benign fibroadenoma: one at 5 mg/kg.
Ullah et al. 2019 Pregnant SD rats, 80-90 days old, n = 8 dams per group. Treatment: BPS (purity not stated), in 0.1–0.5% ethanol diluted in water (vehicle control), orally in drinking water at concentrations of 5, 25, and 50 µg/L from GD 1 to GD 20 Male offspring were sacrificed on PND 16 (2 males/litter) and PND 80 (8 males/group).	**Maternal:** Gestational weight gain. **Developmental**: Litter size. Sex ratio. Birthweight (PND 1). AGD (PND 1). Nipple retention (NR; PND 14). Body weight (PND 6, 14, and 16).	No effects on gestational weight gain.	Litter size: No effect. Sex ratio: No effect. Birthweight: No effect. AGD: No effect. NR: No effect. PND 6 and 14 body weight: Not reported. PND 16 body weight: No effect. Organ and tissue weights on PND 16: No effects. Puberty onset: No effect.

Study design	Outcomes assessed	Maternal effects	Developmental effects
Apart from female and male offspring counts at PND1, all other data reported are for male offspring only.	Organ and tissue weights on PND 16. (absolute testes, prostate, epididymis, seminal vesicle, bulbourethral gland, adrenals, bulbocavernosus muscles, fat pad, and liver). Puberty onset determined by preputial skin separation (checked daily from PND 35). Body weight (PND 80). Organ and tissue weights on PND 80. (absolute; left and right testes, left and right epididymides, seminal vesicle, prostate, fat pad, kidney, liver, and adrenals). Histopathology on PND 80 (testes and epididymides). Testis morphology (area % of seminiferous tubule, interstitial space, lumen, and epithelium, and diameter and height of seminiferous tubule). Epididymis (caput and cauda regions) morphology (tubular and lumen diameter, epithelial height, epithelium %, and lumen %). Number of spermatogonia, spermatocytes, and spermatids in seminiferous tubules. Sperm parameters on PND 80 (Daily sperm production (DSP), count in different regions of epididymis, and transit time). Oxidative stress status in testes on PND 80 (lipid peroxidation (LPO) [TBARS] and total ROS levels, and CAT, POD, and SOD activities). Plasma hormone concentrations on PND 80 (testosterone, E2, LH, and FSH).		PND 80 body weight: Increased at 50 µg/L. Organ and tissue weights on PND 80: Decreased absolute seminal vesicle weight at 50 µg/L. Histopathology and morphology of testes and epididymides on PND 80: Testis: Decreased area % of seminiferous tubule at 25 and 50 µg/L. Increased seminiferous tubule epithelial height; and decreased area % of seminiferous tubule, interstitial space, lumen, and seminiferous tubule diameter at 50 µg/L. No effects on caput or cauda epididymis. Number of spermatogonia, spermatocytes, and spermatids in seminiferous tubules: Decreased % motile sperm at 25 and 50 µg/L. Decreased numbers of spermatogonia, spermatocytes, and spermatids at 50 µg/L. Sperm parameters: Decreased number of sperm in caput/corpus epididymis at 25 and 50 µg/L; and decreased DSP at 50 µg/L. Oxidative stress in testes on PND 80: Decreased POD activity at 25 and 50 µg/L. Increased LPO and total ROS at 50 µg/L. Decreased CAT and SOD activities at 50 µg/L. Plasma hormone concentrations on PND 80: Increased E2 at 50 µg/L. Decreased testosterone, LH, and FSH at 50 µg/L.
Varma et al. 2023 Pregnant Wistar rats, 3 months old, number of dams in each group not reported. Treatment: BPS (purity not reported) in extra virgin olive oil (vehicle control) via oral gavage at doses of 0, 0.4, 4, or 40 µg/kg-day from GD 4 to GD 21. Plasma from female and male offspring at PND 90 (n = 3 animals per group).	**Developmental**: Plasma total fatty acid composition on PND 90. Testis total fatty acid composition on PND 90.	Not assessed.	Plasma total fatty acid composition on PND 90: Increased C22:6 n-3 (docosahexaenoic acid) at 0.4 µg/kg. Testis total fatty acid composition on PND 90: No effects.

Study design	Outcomes assessed	Maternal effects	Developmental effects
Testis from male offspring sacrificed at PND 90 (n = 4 males per group).			
Varma et al. 2024 Pregnant Wistar rats, n = 40. Treatment: BPS (purity not reported) in olive oil (vehicle control) at concentrations of 0 or 0.4 µg/kg-day via oral gavage from GD 4-21. Offspring were evaluated at PND 30 and PND 90.	**Developmental:** F1 Whole body composition (Dual-energy X-ray absorptiometry [DEXA]). F1 Bone density (DEXA). F1 Plasma analysis (PND 90): insulin-like growth factor 1 (IGF1), alkaline phosphatase activity, Gla-type osteocalcin, and calcium.	Not assessed.	F1 whole body composition: Increased body weight at 30 (+68%) and 90 (+32%) days old Increased body surface area at 30 (+53%) and 90 (+22%) days old. F1 bone composition: Increased bone mineral content (+63% and +31%, respectively) and bone mineral density (+6% and +7%, respectively) at 30 and 90 days old. F1 plasma analysis: Increased alkaline phosphatase and Gla-type osteocalcin, Decreased calcium, No effect on IGF1.
MY Zhang et al. 2020 Pregnant ICR mice, 8 weeks old, number of dams in each group not reported. Total number of mice used in study was 174.Treatment: BPS (purity not reported) in 1% DMSO diluted in normal saline, daily oral administration at doses of 0, 2, or 10 µg/kg-day for 4 days from GD 12.5 to GD 15.5. Note: In a dose finding study, 18 pregnant mice across the six dose groups were treated with BPS at doses of 0, 2, 10, 50, 100, or 200 µg/kg-day for 4 days from GD 12.5 to GD 15.5. All doses had effects on meiotic progression, of the lower doses of 2 or 10 µg/kg-day were used for subsequent studies. Culture of complete oocytes isolated from F1 female mice (5 weeks old). Metaphase II (MII) oocytes from cumulus-oocyte complexes (COCs) of 5-week-old F1 females used for *in vitro* fertilization (IVF) and blastocyst culture.	**Maternal**: Body weight gain. **Developmental**: F1 generation. GD 15.5 ovaries: Meiotic prophase I (MPI) progression. Gene expression and protein levels (*gene*/protein) for germ cell and meiosis-related genes: *Dazl*/DAZL, *Stra8*/STRA8, *Scp3*/SCP3, and *Dmc1(*gene expression only). PND 3 ovaries: Cyst breakdown. PND 21 ovaries: Folliculogenesis. Oocyte percentages in follicles. Gene expression and protein levels (*gene*/protein) for oocyte-related genes: *Bmp15*/BMP15 and *Gdf9*/GDF9. 5 weeks of age: Complete oocyte culture: Germinal vesicle breakdown (GVBD). First polar body extrusion (PBE). Spindle assembly and chromosomal arrangement. IVF:	No effect on body weight gain.	Effects on F1 females: GD 15.5 ovaries. Accelerated MPI progression at both doses: Decreased percentage of zygotene stage and increased percentages of pachytene and diplotene stage oocytes. Germ cell and meiosis-related *gene* and protein expression. Increased *Stra8*, *Scp3*, and *Dmc1* at both doses and *Dazl* at 10 µg/kg-day. Increased DAZL and STRA8 at both doses and SCP3 at 10 µg/kg-day. PND 3 ovaries: Accelerated cyst breakdown. Higher proportion of mouse vasa homolog (MVH) positive oocytes in primordial follicles at both doses. PND 21 ovaries: Oocyte percentages in follicles: Increased primordial and decreased antral follicles at both doses; and decreased secondary follicles at 10 µg/kg-day. No effects on total oocyte numbers. Oocyte-related gene and protein expression: Decreased *Bmp15* and *Gdf9* and BMP15 and GDF9 at both doses. 5 weeks of age: Cultured complete oocytes: Decreased % GVBD and PBE at both doses. Increased % of aberrant spindles and misaligned

Study design	Outcomes assessed	Maternal effects	Developmental effects
	Cleavage and blastocyst rate. Rates of 4- cell embryos. Epigenetic effects: Histone methylation levels. Nuclear staining of oocytes for H3K4me3 and H3K9me3. F2 generation. Litter size. Sex ratio. Birthweight. PND 3 ovaries: Cyst breakdown. PND 21 ovaries: Folliculogenesis.		chromosomes at both doses. IVF: Decreased rates of cleavage and blastocyst at both doses. Decreased rate of 4-cell embryos at both doses. Histone methylation levels: Decreased H3K4me3 and increased H3K9me3 at both doses. Effects on F2 generation: No effects on F2 litter size, sex ratio, or birthweight. PND 3 ovaries: Accelerated cyst breakdown without change to total number of oocytes PND 21 ovaries: No effects.
Zhang et al. 2023 Pregnant ICR mice, number of animals not reported. Treatment: BPS (purity not stated) in vehicle (not stated) exposed daily to 0, 5, 50, and 500 µg/kg-day by oral gavage from GD 0.5–18.5. Male offspring were assessed in this study. Food intake and body weights measured for all dose groups. All other outcomes assessed in 50 µg/kg group. Authors note weekly measurements of body weight and food intake in male offspring up to 12 weeks of age. Animals were sacrificed for tissue collection at 12 weeks of age.	**Developmental:** Weekly measurements of body weight and food intake up to 12 weeks of age. All following outcomes assessed at 50 µg/kg. Relative (to body weight) abdominal white adipose tissue (WAT) and liver weights. WAT and liver histopathology: Adipocyte area in WAT. Liver lipid content: Triglyceride levels (TG) and fat deposition. Serum levels of total cholesterol (CHOL), non-esterified fatty acids (NEFA), and TG. miRNA sequencing of serum exosomes and WAT. qRT-PCR validation of miR-29a-3p.	Not assessed.	No effects on body weight. Increased body weight gain at 50 µg/kg. No effects on food intake. All following outcomes assessed at 50 µg/kg. Increased relative WAT weight. No effects on relative liver weight. WAT and liver histopathology: WAT: NS increase in adipocyte area. Increased liver TG and hepatic lipid deposition. Increased serum NEFA and TG. miRNA sequencing of serum exosomes and WAT: Differentially expressed miRNAs identified for both exosomes and WAT: miR-29a-3p expression decreased in both exosomes and WAT. Validated with qRT-PCR in adipose tissue.

Table 4.2.2 BPS: Evidence on the developmental toxicity in non-mammalian species

Study Design	Outcomes assessed	Major Findings
Bai et al. 2023 Zebrafish (wild-type [WT], AB strain). Treatment: BPS (> 98% purity) in 0.1% DMSO (vehicle control) at 1, 10, or 100 (= EC_{25}) µM (equivalent to 0.25, 2.50, and 25.03 mg/L, calculated by OEHHA), or 5 µM Valproic acid (VPA, positive control) from 8 hours post-fertilization (hpf) to 120 hpf. For neurobehavioral assays, embryos/larvae were exposed from 8 hpf to 4.5 days post-fertilization (dpf) (corresponds to 108 hpf). For immunocytochemistry (ICC) of neuronal markers and qRT-PCR assays on genes encoding ion channels and acetylcholine receptor, only one BPS concentration was used (1 µM). Endpoints assessed from 5 dpf (120 hpf) to 13 dpf. Note: Initial screening for mortality and malformations: embryos were exposed to a "wide range of concentrations." Concentrations used in main experiment were selected based on computed effective concentration for malformation (EC_{25}).	Larval mortality at 120 hpf (n = 20 larvae, 3 biological replicates); LC_{50} calculated. Malformations at 120 hpf (n = 20 larvae, 3 biological replicates); 25% effective concentration (EC_{25}) and half-maximal effective concentration (EC_{50}) calculated. Body measurements: body length (BL), intraocular distance (ID), lower jaw length (LJL), and ceratohyal cartilage length (CCL) at 4.5 dpf (n = 30 larvae). Shoaling behavior: nearest neighbor distance (NND, mm) and interindividual distance (IID, mm) at 11 dpf (n = 10 larvae). Motor and social behaviors: spontaneous movement (tail bends/min) at 24 hpf, larval locomotion at 5 dpf, light/dark exploration at 10 dpf, and social contact at 13 dpf (n = 22-44 larvae). ICC and gene expression analyses at single concentration of 1 µM BPS ICC: number of mature newborn neurons and number of neural stem cells in proliferation at 5 dpf (n = 4-10 larvae). qRT-PCR gene expression analysis at 120 hpf (n = 3, 20 larvae pooled as one replicate).	Mortality: LC_{50} = 224 µM. Malformations: EC_{25} = 100 µM, EC_{50} =144 µM; Bent spine, malformed tail, and yolk sac edema observed at 250 µM. Body measurements: Increased ID, LJL, and CCL (i.e., macrocephaly) at 1 and 100 µM. No effect on body length. Positive control (valproic acid) reported similar effects of increased ID, LJL, and CCL and no effect on body length. Shoaling behavior: increased NND at 10 µM, increased IID at ≥ 10 µM, i.e., reduced prosocial behavior. Motor and social behaviors: 24 hpf: Increased spontaneous movement at ≥ 1 µM BPS. 5 dpf: Hyperactivity during both light and dark periods at ≥ 1 µM BPS. 10 dpf: Increased anxiety-like behavior in light/dark exploration at ≥ 1 µM BPS. 13 dpf: Decreased social contact at ≥ 1 µM BPS. Neurogenesis: Accelerated neurogenesis as indicated by increased number of newborn neurons and proliferating neural stem cells. Gene expression: Upregulated expression of several genes associated with potassium and calcium ion channels; and downregulated expression of calcium ion channel gene *tnnc-2* and acetylcholine receptor gene *chrna1.*
Björnsdotter et al. 2017 Zebrafish (WT), n = 5-10 eggs per well, ≥ four replicates/concentration. Treatment: BPS (purity 98%) at 100 nM or 100 µM in 0.1% or 0.001% DMSO (vehicle control), respectively (equivalent to 25.03 µg/L and 25.03 mg/L, calculated by OEHHA) from 2 hpf to 120 hpf, solution not refreshed	Developmental abnormalities scored at 24, 48, 72, 96 and 120 hpf. Behavioral test (locomotor) - exposed embryos without any visual malformations transferred for observation at 4 dpf.	Developmental abnormalities: No visual, heartbeat, or behavior effects at either concentration.

Study Design	Outcomes assessed	Major Findings
Cano-Nicolau et al. 2016 Zebrafish (WT, strain not specified); 80 embryo/larvae per concentration, n = 6 independent spawns. Tg *cyp19a1b*-GFP, 20 embryo/larvae per concentration. Treatment: BPS (98% purity) in ≤ 0.1% (v/v) DMSO (vehicle control) at 0 or 1 µM (equivalent to 250.27 µg/L, calculated by OEHHA) from 0-1 dpf to 4 (tg) or 7 (WT) dpf. 100% of exposure medium was renewed daily. 1 nM EE2 used as a positive control.	Survival rate. Motility. Teratogenicity. *cyp19a1b* gene expression in 7 dpf WT larvae whole brain using RT-qPCR and brain sections using *in situ* hybridization. Estrogenic activity in live 4 dpf (Tg) *cyp19a1b*-GFP larvae in radial glial cells. Competitive binding assay: Estrogen receptor-binding affinity for zebrafish estrogen receptors Esr1, Esr2a, and Esr2b: incubated with 1 nM [^{3}H]-E2 with or without 0.01, 0.1, 1, 10, or 100 nM radio-inert E2 or 0.1, 1, 10, 100, 1000, and 10,000 nM BPS.	Survival rate: No effect. Motility: No effect. Teratogenicity: No effect. *cyp19a1b* gene expression: Increased in whole brain with both BPS (~40-fold induction) and EE2 (~65-fold induction). Strong expression in the caudal hypothalamus with both BPS and EE2 treatments. Estrogenic activity: Induction (NS; 6-fold) of *cyp19a1b* promoter activity with BPS and EE2 (~30-fold). Competitive binding assay: Weak binding affinities for zebrafish estrogen receptors.
Chen et al. 2016 *Caenorhabditis elegans* (*C. elegans*) hermaphrodite worms (N2 Bristol strain [WT]) cultured on nematode growth medium (NGM) plates without cholesterol, n = 3 to 20 worms per trial, in triplicate or quadruplicate. Treatment: BPS (purity not stated) in 0.1% ethanol (vehicle control) at 0, 125, 250 or 500 µM (equivalent to 31.28, 62.57, and 125.14 mg/L, calculated by OEHHA) for four days from the first larval stage (L1) to the end of the first day of adulthood (24 hours post-L4). Internal BPS concentrations measured post-exposure: <LOD (0.1), 0.21, and 0.39 µg/g, respectively.	Fertility: viable egg number, embryonic lethality (%), and number of adult offspring (i.e., brood size). Germline effects. Germ line nuclear loss and apoptosis. Outcomes assessed at 500 µM BPS only: Germline effects: Germline morphology. Diameter of mitotic nuclei. Nuclear gap frequency. Cell division effects. Checkpoint protein (CHK-1) activation: phosphorylated CHK-1 (pCHK-1). Meiotic recombination kinetics (RAD-51 levels). Synaptonemal Complex (SC) assembly and maintenance (SC component [SYP-1] immunostaining). Gene expression: RNA-seq (whole worms). RT-qPCR (whole worms or germlines) of genes involved in double-strand break repair (DSBR) and DNA damage response (DDR) checkpoint activation as well as validation of RNA-seq results.	Fertility: No effects on the number of fertilized eggs. Concentration-dependent increase in embryonic lethality ≥ 125 µM. Decreased brood size at 125, 250 (NS), and 500 µM (associated with increased embryonic lethality). Germline effects: No effects on overall germline size. Irregular distribution of germline nuclei. Concentration-dependent increases in germline nuclear loss and apoptotic index. No effects on mean nuclear diameter. Germline nuclear gap phenotype observed in 34% of worms treated with 500 µM. Cell division effects: Increased checkpoint activation, indicated by increased worms with pCHK-1. No effects on meiotic recombination kinetics, indicated by no effects on RAD-51 levels. Increased synapsis defects and reduced SYP-1 levels Gene expression: RNA-seq: 878 differentially expressed genes (DEGs) with >1.2-fold up- or down-regulation compared to vehicle control (more up-regulated than down-regulated genes). Top gene ontology terms include embryo development and reproduction. RT-qPCR: decreased expression of DDR and checkpoint activation genes.

Study Design	Outcomes assessed	Major Findings
Christophe et al. 2023 Transgenic (*tg*)(*cyp19a1b:*GFP) zebrafish Treatment: BPS (98% purity) dissolved in 0.1% v/v DMSO at 25, 50, 100, 200 or 400 mg/L from 0 – 96 hpf or 4 dpf. Tested according to OECD TG 236 (Fish Embryo Toxicity [FET] assay) and TG 250 (EASZY assay) protocols to assess acute toxicity, developmental toxicity, and estrogenic activity.	Refined FET assay: Coagulation at 8 hpf. Lack of somite formation and non-detachment of the tail at 48 & 72 hpf. Heartbeat detection at 48, 72, and 96 hpf. Cumulative mortality rate at 96 hpf and LC_{50} derived from the observations above; specific effects not reported. Hatching rates at 48, 72, and 96 hpf. Non-lethal developmental effects: Yolk deformity, growth retardation, no spontaneous movement, edema, no blood tail circulation, no/less pigmentation, head and spinal malformations, and hemorrhage. Cumulative sub-lethal endpoint EC_{50} derived from observations above. EASZY assay: Detection of endocrine active substances acting through estrogen receptors. Estrogenic activity (fluorescence intensity) at 96 hpf.	Refined FET assay: Coagulation: Not reported. Somite formation and tail detachment: Not reported. Heartbeat detection: Not reported. At 96 hpf: LC_{50} > 100mg/L. No effects on hatching rate. Non-lethal developmental effects: Deformity of yolk observed at 400 mg/L. No effects on the other developmental endpoints. 96 hpf EC_{50} of cumulative sub-lethal endpoints = 263 mg/L EASZY assay: Estrogenic activity EC_{50} = 43 mg/L.
Coumailleau et al. 2020 Zebrafish (WT, AB strain) and transgenic Tg (*cyp19a1b:*GFP) zebrafish embryos/larvae, ~80 zebrafish per concentration, five replicates. Treatment: BPS (purity not stated) in 0.01% v/v DMSO (vehicle control) at 0, 0.1 and 1 µM (equivalent to 25.03 µg/L and 250.27 µg/L, calculated by OEHHA), or 1 nM ethinyl estradiol (EE2 positive control) from 2 to 144 hpf. 100% of the medium was renewed daily. For locomotor assays, only 1 µM BPS was used. Endpoints assessed at 144 hpf except for hatching rate, which was assessed from 48 to 72 hpf.	Embryo survival. Hatching rate at 48, 55, and 72 hpf. Abnormalities: spinal aberrations, yolk sac or cardiac edema, aberrations in pigmentation, and loss of equilibrium. Locomotor activity: distance swam, swimming time, and mean speed in one hour (n = 12 zebrafish, 4 biological replicates). Aromatase B (AroB) protein expression in two brain regions: posterior region of the preoptic area (POA) and the caudal hypothalamus at the level of the nuclear recessus posterior (NRP) (n = 10 zebrafish). Number of mitotically active cells in the POA and NRP. Activation of the AroB *cyp19a1b* promoter.	Embryo survival: No effect. Hatching rate: Increased at ≥ 0.1 µM at 55 hpf and in positive control. No effect at 48 hpf (no hatching occurred) or 72 hpf (all embryos hatched). Abnormalities: No effects. No effects on locomotor activity. AroB protein expression: Increased (NS) AroB-positive cells in caudal hypothalamus region at 1 µM. No AroB-positive cells detected in preoptic area. Mitotically active cells: No effect with increased (NS) proliferation in the NRP. AroB *cyp19a1b* promoter activation: Co-localization of GFP expression associated with increased *cyp19a1b* promoter activity and the *de novo* detection of AroB protein was confirmed using double labelling fluorescence.

Study Design	Outcomes assessed	Major Findings
Crump et al. 2016 Chicken embryos *in ovo*, 15-60 eggs per dose, triplicate. Experiments included 3 replicates and 15-60 eggs per dose. Treatment: BPS (98% purity) in DMSO (vehicle control) at 0, 0.01, 1, 10, 50, and 200 mg BPS/mL corresponding to 0, 0.27, 0.91, 10.6, 52.8, and 207 µg/g actual injected mean concentrations. *In ovo* injection into air cell (i.e., air space that forms between the inner and outer membranes) via repeater pipette. Eggs were incubated after treatment and brought to pipping (days 20-21). Hepatic mRNA expression and PCR arrays to compare mRNA profiles of embryonic livers used 52.8 and 207 µg/g egg only. Endpoints assessed on day 22.	Pipping success and time to pip. LD_{50} calculated. Embryo weight. Liver weights: absolute and liver-somatic index (LSI). Morphology: tarsus length, head plus bill length, and gallbladder length. Hepatic mRNA expression (n = 5-6 embryonic livers). PCR arrays to compare mRNA profiles of embryonic livers. Circulating free thyroxine (T4) and bile acid concentration in plasma (n = 8 embryos).	Decreased pipping success at 207 µg/g (58% treated vs 93% in control) No differences in time to pip (data not shown). Calculated LD_{50} = 279 µg/g Decreased embryo weight at 207 µg/g. Liver weights: Not reported. Morphology: Decreased tarsus length at 207 µg/g Increase in gallbladder length at ≥ 52.8 µg/g Effects on head plus bill length not reported. Genes upregulated at 52.8 µg/g in hepatic tissue: *UGT1a9* and *SULT1b1* (associated with xenobiotic metabolism), *ACSL5* and *CYP7B1* (associated with lipid metabolism/homeostasis functional pathway), *HSP90AB1* (Heat-shock protein gene), *DIO1* (associated with the thyroid hormone pathway). Also increased at 207 µg/g though findings were not statistically significant. PCR arrays: Confirmed increases and dose trends observed in the genes described above. Expression levels of 2 estrogen-responsive genes, apolipoprotein II and vitellogenin (VTG), were too low to quantify changes. No effects on circulating free T4 or bile acid concentrations.
Dong et al. 2018 Zebrafish (WT, AB strain). Treatment: BPS (purity not specified) in 0.01% v/v DMSO (solvent control) at 0 or 10 µg/L from 24 hpf until spawning at 180 dpf for parental generation (F0), n=100 per treatment, in triplicate. Offspring (F1) of BPS-treated F0 were either untreated or continued treatment (10 µg/L BPS) from 24 hpf to 96 hpf, bacterial (PAM3CSK4) or viral (Poly I:C) challenge at 72 hpf. The study does not specify whether untreated F1 offspring received the solvent control. BPS content in F1 eggs following 10 µg/L F0 BPS treatment: 18.7 ng/g wet weight BPS.	Hatching and survival rates (F0 and F1). Lysozyme activity. Respiratory burst. Oxidative defense gene expression: *Catalase (cat), copper zinc superoxide dismutase (cu/zn-sod, sod1), manganese superoxide dismutase (mn-sod, sod2), lysozyme (lyz), myeloperoxidase (mpx),* and *glutathione peroxidase 1* (*gpx1).* Immune-related gene expression: *Toll-like receptor (tlr) 3, tlr2, myeloid differentiation factor 88 (myd88), toll/IL-1 receptor domain-containing adaptor inducing IFN-β (trif), tumor necrosis factor α (tnfa), interleukin-1β (il1b), interferon (ifn, ifnphi1), myxovirus-*	Hatching and survival rates: F0: No effects. F1: Decreased hatching rate with (-56%) and without (-39%) continued BPS treatment and survival rate with (-63%) and without (-50%) continued BPS treatment. F1 Lysozyme activity: Increased in F1 with and without continued BPS treatment. Increased with and without Poly I:C or PAM3CSK4 infection. F1 Respiratory burst assay: Inhibited (-35%) PMA-induced ROS production in F1 without continued BPS treatment. F1 Oxidative defense gene expression: *cat, cu/zn-sod,* and *mn-sod:* Decreased with and without continued BPS treatment. Decreased with and without Poly I:C or PAM3CSK4 infection.

Study Design	Outcomes assessed	Major Findings
All assays performed in the F1 generation unless noted.	*resistance gene (mx), matrix metalloproteinases (mmp) 9, mmp13, recombination-activating genes (rag) 1,* and *rag2*.	*lyz:* Increased with and without continued BPS treatment; and Increased with and without Poly I:C or PAM3CSK4 infection. *mpx* and *gpx1:* No effect. F1 Immune-related gene expression: *tlr3, tlr2, trif, tnfa, mx, rag1,* and *rag2*: Decreased with and without continued BPS treatment. *ifn:* Decreased with continued BPS treatment. Decreased with PAM3CK4 infection. *mmp13:* Increased with continued BPS treatment. Increased with Poly I:C or PAM3CSK4 infection. *mmp9:* Increased with continued BPS treatment only. *myd88* and *il1b:* No effect.
Fraser et al. 2017 Zebrafish (WT, AB strain), n = 12-16 zebrafish per concentration, 3-4 replicates. Treatment: BPS (98% purity) in 0.01% DMSO (vehicle control) at 0, 0.01, 0.1, 1, or 10 µM (equivalent to 2.50, 25.03, 250.27 µg/L, and 2.50 mg/L, calculated by OEHHA). from 6-7 hpf until endpoint assessment at 96, 100, and 118 hpf.	Behavior (96, 100, and 118 hpf): Cumulative distance travelled, time spent active per minute, and average swimming speed during 40 min light-dark-light cycle.	Behavior: Cumulative distance traveled and time active: No effect. Swimming speed: Increased at 10 µM at 118 hpf only.
Gu et al. 2019 Zebrafish (WT, AB strain), n = 10-20 zebrafish per concentration, in triplicate. Treatment: BPS (98% purity) in 0.01% v/v DMSO at 0, 0.03, 0.3, and 3 mg/L, or 0.3 mg/L chlorpyrifos (CPF, positive control, for behavioral assays) from 2 hpf to 6 dpf. Endpoints assessed at 6 dpf. Dose range-finding study conducted with 150-450 mg/L BPS to determine 96-hour LC50 = 323 mg/L.	Mortality. Locomotor behavior: Total distance traveled and swimming speed during light/dark paradigm. Retina histopathology. Retina immunohistochemistry with GAP43 protein. Oxidative stress: Superoxide dismutase (SOD) and catalase (CAT) activity. Apoptosis (acridine orange staining assay). Gene expression of target neurodevelopment-related genes: *elavl3, gap43, gfap, mbp, syn2a and a1-tubulin* (*tuba1b*).	Mortality: No mortality. Locomotor behavior: Decreased distance traveled and swimming speed at 0.3 and 3.0 mg/L BPS groups and 0.3 CPF group. Retina histopathology: Increased retinal morphological abnormalities including empty areas in the retinal pigmented epithelium at all concentrations with increased severity with concentration and slightly sparse ganglion cell layer at 3.0 mg/L. Retina immunohistochemistry: Decreased Gap43 expression in 0.3 and 3 mg/L groups. Oxidative Stress: CAT: Increased activity at 0.3 and 3.0 mg/L. SOD: Increased activity at 0.3 mg/L and decreased activity at 3 mg/L. Apoptosis: Observed at 0.3 and 3.0 mg/L in whole body, higher fluorescence intensities in brain (region not specified).

Study Design	Outcomes assessed	Major Findings
		Gene expression: *elavl3*, *mbp, syn2a*, and *gfap:* Downregulated at 3.0 mg/L. *tuba1b* and *gap43:* Downregulated at 0.3 and 3.0 mg/L.
Gu et al. 2022 Zebrafish (WT, AB strain), n = 10-50 zebrafish per concentration in triplicate, Experiment 1. Zebrafish (transgenic lines, *HuC*-GFP and *hb9*-GFP) for neurotoxicity evaluation, n = 10 larvae/concentration in triplicate, Experiment 2. Treatment: BPS (99% purity) in 0.01% v/v DMSO (vehicle control) at 0 and 200 µg/L from 4 hpf to 72 hpf (Experiment 1) or 6 dpf (Experiment 2). 50% of the exposure solution was renewed daily. Endpoints assessed from 24 hpf to 6 dpf (Experiment 1) or 36 and 72 hpf (Experiment 2).	Experiment 1: Survival rate (72 hpf). Hatching rate (48 and 72 hpf). Body length (6 dpf). Heart rate (3 and 6 dpf). Spontaneous movement (24 hpf). Locomotor behavior (6 dpf): Distance, swimming time, swimming behavior track, and speed. Levels of 13 neurotransmitters using LC-MS/MS assay: GABAergic system (glutamate, glutamine and r-Amino-butyric acid [GABA]); dopaminergic system (DOPA, dopamine, norepinephrine, 3-methoxytyramine, tyramine and normetanephrine), serotonergic and kynurenergic system (5-hydroxyindoleacetic acid, serotonin and 5-hydroxy-L-tryptophan) and cholinergic system (acetylcholine). Experiment 2: Central (*HuC*-GFP line) and motor (*hb9*-GFP line) neuronal expression, measured by fluorescent intensity of GFP at 36 and 72 hpf. Motor neuron axon length in *hb9*-GFP line.	Experiment 1: No effects on survival rate, hatching rate, embryo mortality, body length, heart rate, spontaneous movement, or locomotor behavior. Neurotransmitter levels: Decreased norepinephrine and 5-hydroxy-L-tryptophan levels. Increased 3-methoxytyramine and tyramine levels. No significant effects on the other neurotransmitters. Experiment 2: Neuronal expression: Decreased GFP expression in the central nervous system of transgenic *HuC*-GFP zebrafish at 36 hpf. No effect at 72 hpf. Motor neuron ventral axon length: Decreased at 36 hpf. No effect at 72 hpf.
Gyimah et al. 2021a Zebrafish (WT, AB strain), ~100 zebrafish per concentration in triplicate . 100 embryos per group and exposure for each group was set in triplicate. Treatment: BPS (> 99%) in 0.01% v/v DMSO (vehicle control) at 0, 0.01, 0.03, 0.1, 0.3, and 1.0 µM (equivalent to 2.50, 7.51, 25.03, 75.08, and 250.27 µg/L, calculated by OEHHA) from 4 to 120 hpf. Endpoints assessed at 24, 48, 72, 96, and 120 hpf.	Glucose levels in larvae at 120 hpf. Pancreatic-related gene expression: *pdx1, foxa2, ptfla*, and *isl1.* Insulin gene expression: *ins*. DNA methyltransferase gene expression: *dnmts*.	Glucose levels increased at 0.3 (+7%) and 1.0 (+74%) µM. Pancreatic-related gene expression: *pdx1* increased at: 48 hpf at 0.01, 0.03 and 1.0 µM; 96 hpf at ≥ 0.03 µM; and 120 hpf at ≥ 0.01 µM. *foxa2* increased at 48 hpf at ≥ 0.3 µM and 120 hpf at ≥ 0.01 µM); and decreased at 72 hpf at ≥ 0.01 µM and 96 hpf at 1.0 µM. *ptfla1* increased at 24 hpf at 0.1 µM; 48 hpf at 0.01 µM; and 120 hpf at ≥ 0.01 µM. *isl1* decreased at 96 hpf at 0.01 and 0.03 µM and increased at 120 hpf at 0.01, 0.03 (NS), 0.1, 0.3, and 1.0 µM).

Study Design	Outcomes assessed	Major Findings
		Insulin gene expression: Increased at 48 hpf at 1 uM and 96 and 120 hpf at 0.01, 0.03 (NS), 0.1, 0.3, and 1.0 uM; and decreased at 72 hpf at ≥ 0.3 µM. DNA methyltransferase gene expression: *dnmt1*: Decreased at 48 hpf at 0.01 (NS), 0.03, 0.1 (NS), 0.3, and 1.0 uM and 96 hpf at ≥ 0.01 µM; and increased at 72 hpf at 0.1 µM and 120 hpf at 0.01 (NS), 0.03, 0.1, 0.3, and 1.0 uM. *dnmt3*: Decreased at 48 hpf at 0.01 (NS), 0.03 (NS), 0.1 (NS, 0.3 (NS), and 1.0 uM and 96 hpf at ≥ 0.01 µM); and increased at 120 hpf at 0.01, 0.03 (NS), 0.1 (NS), 0.3, and 1.0 uM. *dnmt4*: Increased at 120 hpf at ≥ 0.01 µM. *dnmt5*: Decreased at 24 hpf at ≥ 0.01 µM and 96 hpf at 0.01 and 0.03 µM; and increased at 48 hpf at 0.01 and 0.1 µM and 120 hpf at ≥ 0.01 µM. *dnmt6*: Increased at 72 hpf at 0.01 (NS), 0.03 (NS), 0.1 (NS), 0.3 (NS), and 1.0 uM and 120 hpf at ≥ 0.01 µM; and decreased at 96 hpf at 0.01, 0.03, 0.1 (NS), 0.3 (NS), and 1.0 uM. *dnmt7* decreased at 48 hpf at 0.01, 0.03, 0.3 µM and 96 and 120 hpf at ≥ 0.01 µM. *dnmt8* increased at 48 hpf at ≥ 0.1 µM and 120 hpf (≥ 0.01 µM).
Gyimah et al. 2021b Zebrafish (WT, AB strain). Zebrafish (transgenic, Tg(*HuC*:GFP), for neuronal development analysis. Treatment: BPS (<99%) in 0.01% v/v DMSO (vehicle control) at concentrations 0, 0.01, 0.03, 0.1, 0.3, and 1 µM (equivalent to 2.50, 7.51, 25.03, 75.08, and 250.27 µg/L, calculated by OEHHA) from 4 hpf to 120 hpf. Solutions replaced every 24 hours. Approximately 30 embryos collected every 24 hours from each treatment group. Embryos were snap frozen in liquid nitrogen and maintained at -80°C until analysis. Performed in triplicate.	Mortality. Hatching rate, malformations (curved spine, pericardial edema), body length, and heart rate. Behavior (120 hpf): Total distance moved, average speed, maximum acceleration, mania frequency and time, activity frequency and time, static frequency and time. Neuronal GFP expression in Tg(*HuC*:GFP) zebrafish. Development-related gene expression: *vegfa, wnt8a, and mstn*. Neurodevelopment-related gene expression: *ngn1, elavl3, gfap, a1-tubulin* (*tuba1b*)*, mbp,* and *gap43*.	Mortality: not reported. No effects on hatching rate or malformations. Body length: Decreased at 72 hpf, 96 hpf, and 120 hpf at 1 µM (-8%, -7%, and -5%, respectively). Heart rate: Decreased at 96 hpf at 0.03 µM (-6%). Increased at 96 hpf at 0.1, 0.3 and 1 µM (+6% each). Behavior: Total distance and activity time: Increased with 1 µM. Average speed and maximum acceleration: Increased with 0.3 and 1 µM. Mania frequency: Increased with 0.01, 0.03, and 1 µM. Mania time: Increased with 0.03 µM. Activity frequency: Increased with 0.01 and 1 µM. Static frequency: Increased with 1 µM. Decreased with 0.3 µM. Static time: Decreased with 0.3 µM.

Study Design	Outcomes assessed	Major Findings
		Neuronal GFP expression: Increased at 72 hours at 0.01, 0.1, and 0.3 µM and 120 hpf at ≥0.1 µM hpf. Development-related gene expression: *vegfa:* Increased at 72 hpf at 1 µM and 120 hpf at ≥0.01 µM; and decreased at 96 hpf at 0.01, 0.03, 0.1 (NS), 0.3, and 1 µM. *wnt8a:* Increased at 48 hpf at 0.01, 0.03, and 0.1 µM and 120 hpf at 0.3 and 1 µM; and decreased at 48 hpf at 0.3 and 1 µM and at 96 hpf at ≥0.01 µM. *mstn1:* Increased at 24 hpf at 0.3 and 1 µM and 120 hpf at ≥0.01 µM; and decreased at 72 hpf at ≥0.01 µM and at 96 hpf at ≥0.3 µM. Neurodevelopment-related gene expression: *ngn1:* Increased at 48 hpf at 0.03 and 0.3 µM and 120 hpf at ≥0.01 µM; and decreased at 48 hpf at 0.1 and 1 µM. *elavl3:* Increased at 120 hpf at 0.01 (NS), 0.03, 0.1 (NS), 0.3 (NS), and 1.0 µM. *gfap:* Increased at 72 hpf at 1 µM; 96 hpf at 0.1 and 0.3 µM; and 120 hpf at ≥0.03 µM. *tuba1b:* Increased at 120 hpf at ≥0.03 µM. *mbp:* Increased at 48 hpf at 0.03 and 0.1 µM and 120 hpf at 0.1 µM hpf. *gap43:* Increased at 24 hpf at 0.03 µM and 120 hpf at ≥0.01 µM.
Hao et al. 2022 Zebrafish (WT, AB strain). Treatment: BPS (purity ≥ 98%) in 0.002% DMSO (vehicle control) at 0, 0 (blank control), 1, and 100 µg/L from 3 hpf to 120 dpf, solution renewed every two days. F0 females and males exposed to BPS were mated to produce F1 generation. F1 embryos unexposed for 120 days; F2 and F3 also unexposed. Endpoints assessed in F0, F1, and F2 at 120 dpf. F3 generation was raised to 5 dpf.	Hatch rate, heart rate, body length, gonadosomatic index (GSI), hepatosomatic index (HSI), and sex ratio (female:male). Reproductive performance: Egg number, sperm concentration, and fertility rate. Gonadal histological examination (n >5). Plasma sex steroid levels (estradiol and testosterone) in F1 and F2 (n = 10 fish pooled, 3 replicates). Global methylation levels (5-mC) in F0, F1 and F2 gonads (5 fish gonads, 6 replicates). DNA methyltransferase (*dnmts) and* DNA methylation (*tet1, tet3)* gene expression in F1 and F2 gonads (n = 5 fish gonads, 6 replicates). Expression of genes involved in sex hormone synthesis.	Hatch rate: Decreased hatch rate in F3 100 µg/L group at 60 and 72 hpf. No effect in F2 generation. Heart rate: F2: Increased at 100 µg/L at 72, 96, and 120 hpf and decreased at 1 and 100 µg/L at 48 hpf. F3: Increased at 100 µg/L at 48 and 72 hpf. Body length: Decreased in F2 and F3 at 1 and 100 µg/L at 120 and at 96 hpf, respectively. GSI: Increased in F2 females at 1 µg/L, and decreased in F2 females at 100 µg/L and F2 males at 1 and 100 µg/L. HSI: Decreased in F1 females at 1 µg/L and 100 (NS) and decreased in F2 females at 100 µg/L. Sex ratio: Increased in F1 and F2 at 1 µg/L and F0, F1, and F2 at 100 µg/L. Reproductive performance: Egg number: Decreased in F1 at 100 µg/L. Sperm concentration: Decreased in F1 and F2 at 1 and 100 µg/L. Fertility rate: Increased in F2 at 1 µg/L only.

Study Design	Outcomes assessed	Major Findings
		Ovary histology: F1: Decreased % primary growth stage oocytes, increased % full-grown oocytes, and follicular atresia at 100 µg/L. F2: Decreased % primary growth stage oocytes and increased % full-grown oocytes at 1 and 100 µg/L, and follicular atresia at 100 µg/L. Testis histology: F1: Increased % spermatogonia and spermatocytes at 1 and 100 µg/L. Decreased % spermatozoa at 100 µg/L. F2: Increased % spermatogonia and spermatocytes, sperm pyknosis, and seminiferous tubule gap formation at 1 µg/L. Increased % spermatogonia and spermatids, spermatid leakage, and interstitial cell loss at 100 µg/L. Plasma sex steroid hormones: F1 females: Increased E2/testosterone ratio at 100 µg/L. F2 females: No effects on E2, testosterone, or E2/testosterone ratio. F1 males: Increased E2, decreased testosterone, and increased E2/testosterone ratio at 100 µg/L. F2 males: Increased E2, decreased (NS) testosterone, and increased E2/testosterone ratio at 100 µg/L. DNA methylation levels: F0 testis: Decreased at 100 µg/L. F1 testis: Increased at 100 µg/L. F2 ovaries: Increased at 1 µg/L. DNA methyltransferases and DNA methylation gene expression: F1 ovaries: Increased *dnmt8* at 100 µg/L and *dnmt3, tet1, and tet3* at 1 and 100 µg/L, and decreased *dnmt6* and *dnmt7* at 1 µg/L, *dnmt5* at 100 µg/L, and *dnmt4* at 1 and 100 µg/L. F1 testis: Increased *tet3* at 100 µg/L and *tet1* at 1 and 100 µg/L, and decreased *dnmt6* at 100 µg/L and *dnmt1, dnmt3, dnmt4, dnmt5, dnmt7,* and *dnmt8* at 1 and 100 µg/L. F2 ovaries: Increased *dnmt8* and *tet1* at 100 µg/L, and decreased *dnmt1* at 1 µg/L, *dnmt7* at 100 µg/L, and *dnmt6* at 1 and 100 µg/L. F2 testis: Increased *dnmt8* at 1 µg/L, decreased *tet3* at 1 µg/L and *dnmt3, dnmt7,* and *dnmt8* at 100 µg/L and *dnmt4, dnmt5, dnmt6* at 1 and 100 µg/L. Expression of genes related to sex hormone synthesis: F1 ovaries: Decreased *star, cyp19a,* and *3β-hsd* at 1 µg/L; decreased *cyp11a* increased *17β-hsd* at 100 µg/L; and decreased *cyp17* at 1 and 100 µg/L.

Study Design	Outcomes assessed	Major Findings
		F1 testis: Increased *star* and *17β-hsd* and decreased *cyp11a, cyp17,* and *3β-hsd* at 1 and 100 µg/L. F2 ovaries: Increased *cyp11a* at 1 µg/L and *cyp19a* at 100 µg/L, decreased *star and 17β-hsd*at 100 µg/L, and decreased *cyp17* and *3β-hsd* at 1 and 100 µg/L. F2 testis: Decreased *cyp11a* and increased *17β-hsd* at 1 µg/L, decreased *star* and *cyp19a* at 100 µg/L, and decreased *cyp17* and *3β-hsd* at 1 and 100 µg/L.
Harnett et al. 2021 Chicken embryos *in ovo.* Experiments included at least 3-5 independent trials with approximately 20 embryos per treatment group. Treatment: BPS (> 98% purity) in 0.01% ethanol (vehicle control) at 0, 0.003, 0.03, 0.3, 3 and 30 µM (equivalent to 0.75, 7.51, 75.08, and 750.83 µg/L and 7.51 mg/L, calculated by OEHHA) injected into egg on embryonic day 5. Endpoints assessed on embryonic day 12.	Embryo survival (LC50 calculated) Developmental defects: Body length and weight. Gastrointestinal heart, eye, craniofacial, limb, and body pigmentation.	Survival: Decreased at 3 µM (40%) and 30 µM (0%) versus control (100%). Calculated LC50 = 2.48 µM. Developmental toxicity: Body length: Dose-dependent decrease in 0.03, 0.3, 3, and 30 µM group. Body weight: Dose-dependent growth restriction in 0.3, 3, and 30 µM. Developmental defects: Dose-dependent toxicity. Increased heart, eye, craniofacial, limb, and body pigmentation defects at 0.03, 0.3, 3, and 30 µM. Increased gastrointestinal defects at 3 µM.
He. W et al. 2024 *C. elegans*, N2 wildtype strain, n = 30 worms per experiment per group. Treatment: BPS (99% purity) dissolved in ethanol to a stock concentration of 10 mg/mL, then diluted in K buffer (3 g/L NaCl, 2.4 g/L KCl) at concentrations of 0, 0.6, 6, and 60 µg/L from L1-larvae to adult day-3 (~6.5 days).	Percent survival (survival curve). Mean lifespan. Body bend assessment (adult day 5, 8, and 11). Pharyngeal pumping (adult day 5, 8, and 11). Lipofuscin (aging-related pigment) accumulation (adult day 8 and 11). Reproductive capacity starting at the L4-larval stage. Number of eggs laid. Egg hatchability (ratio of progeny to eggs) where progeny was counted two days after laying.	Percent survival: Decrease indicated at 60 µg/L. Mean lifespan: Decreased at 60 µg/L (-15.91%). Body bend assessment: Decreased body bend frequency at all concentrations on day 5 and at 60 µg/L on days 8 and 11. Pharyngeal pumping: Decreased at 60 µg/L on days 8 and 11. Lipofuscin accumulation: Increased at 60 µg/L on days 8 and 11. Reproductive capacity: Decreased number of eggs laid at 60 µg/L. Decreased egg hatchability at 6 and 60 µg/L.

Study Design	Outcomes assessed	Major Findings
Huang et al. 2023 Zebrafish (WT, strain not specified) Treatment: BPS (purity 98%) in 0.1% DMSO at 0, 0.5, 1, 10, and 50 µM (equivalent to 125.14 and 250.27 µg/L and 2.50 and 12.51 mg/L, calculated by OEHHA), solutions completely replaced every 24 hours Exposure window: zygotic stage (~0.5 hpf to larval stage 120 hpf). At least n = 44 individual larvae for whole-mount cartilage staining and measurement. Pools of n = 15-20 whole zebrafish, three biological replicates at 50 µM for bulk RNA-sequencing. Approximately n = 25 larvae in each replicate for measurements of oxidative stress markers.	Hatching rates: 48, 60, and 72 hpf Heart rate: 72, 84, and 96 hpf ROS detection: 96 hpf Morphometry: 120 hpf Pharyngeal cartilage development: ceratohyal (CH), palatoquadrate (PQ) and Meckel's cartilage lengths and angles. Craniofacial development: Head length, eye diameter and depth, interocular distance Measurement of oxidative stress markers (lipid peroxidation level (MDA), Sod, Cat, Gpx, Gst, and MD): 120 hpf Transcriptome (bulk RNA-seq) of pooled whole larvae at 50 µM: 120 hpf mRNA expression (qRT-PCR) of 30 target genes in tricarboxylic acid (TCA) or Krebs cycle to examine dose-response effects: 120 hpf.	Hatching rates: no observed effects at any timepoints. Heart rate: 72 hpf: increased heart rate at 50 µM 84 hpf: increased heart rate at 50 µM 96 hpf: increased heart rate at 10 and 50 µM. ROS detection at 96 hpf: no observed effects. Pharyngeal cartilage development: Decreased CH and PQ cartilage lengths at 1 µM Decreased CH-PQ angle at 0.5, 1, and 10 µM Decreased CH-CH, PQ-Meckel's, and Meckel's-angles at 10 µM. Craniofacial development: Decreased head length, eye diameter, and eye depth at 1 µM Decreased interocular distance at 50 µM Decreased body length stated in text, data not shown. Oxidative stress markers: Decreased Gpx levels at 1 µM Decreased *cat* expression at 50 µM. Transcriptome: DEGs: 2,685 upregulated and 2,998 downregulated genes at 50 µM, with enrichment analysis terms predominantly related to cellular energy metabolism (fatty acid, amino acid, and glucose metabolism pathways). RT-qPCR: Altered mRNA expression of cellular energy metabolism (enzymes in TCA cycle).
Hyun et al. 2021 *In vivo*: *C. elegans* strains: WT: N2. TJ536: *zcIs356 [daf-16p::daf-16a/b::GFP + rol-6(su1006)].* CF1553: *muIs84 [(pAD76) sod-3p::GFP + rol-6(su1006)].* CL2166: *dvIs19 [(pAF15) gst-4p::GFP::NLS]* III. CZ13799: *juIs76 [unc-25p::GFP + lin-15 (+)]* II. Treatment: BPS (purity 98%) in DMSO at 0 or 1 mM starting from the L1 larval stage and up to the 5-day-old adult stage unless otherwise noted.	*C. elegans:* Development rates assessed in progeny: L4 stage larvae treated for 24 hours, and their progeny treated from L1 larval stage for 3 days. Reproduction assay: number of laid eggs of parental worms treated for 24 hours from L4 stage. Lifespan assay (mortality) assessed daily from L4. Oxidative stress tolerance measured by % survival after culture with 0.5 or 1 mM H_2O_2 in 1-day-old adults.	*C. elegans:* Development rates: No effects. Reproduction: Decreased brood size. Lifespan: No effects. Oxidative stress tolerance: Decreased survival at 1 mM H_2O_2. Appearance of neurite beading: Increased number of beading structures in 1-day-old adults, with no further increase in axonal beads in 9-day-old adults. ATP levels: Increased.

Study Design	Outcomes assessed	Major Findings
All outcomes except for stress response visualization and neuronal morphology assessed in WT: N2 strain. Transgenic lines used to evaluate antioxidant pathway markers expressed GFP under regulation of *sod-3* promoter (CF1553), *gst-4* promoter (CL2166), or DAF-16 (TJ536). CZ13799 strain used to assess neuronal morphology (swelling or beading of commissural neurites) of GABAergic motor neurons (juIs76). Note: Study states neurite beading was assessed in 1-day-old adults in figure caption and the results section. The methods section and supplemental table notes assessment in 2-day-old adults. *In vitro:* Wild-type mouse embryonic fibroblasts (MEF). Treatment: BPS (purity 98%) in 0.5% DMSO at 0, 50, 100, 250, or 500 µM for 24 hours. Cell viability: NS concentration-dependent decrease, significant at 100 µM BPS only. At 500 µM, -20% decrease.	Appearance of swelling or beading in neurites, an indicator of neuronal aging, of GABAergic motor neurons in 1-day-old adults. ATP levels in 2-day-old adults. Antioxidant pathway marker expression in 2-day-old adults. Oxygen consumption rate in 3-day-old adults. Thermal stress tolerance in 3-day-old adults. ROS levels in 3-day-old adults. Mitochondrial membrane potential and mitochondrial mass in 3-day-old adults. Body size in 3-day-old adults. Crawling speed and body-bending in 3-day-old adults. Vulval morphology in 5-day-old adults. *In vitro,* MEF*:* Mitochondrial function: ROS levels, mitochondrial permeability transition pore (mPTP), and ATP levels.	Antioxidant pathway marker expression: Increased expression of Psod-3 (superoxide dismutase) and Pgst-4 (glutathione-S-transferase); and increased nuclear localization of DAF-16. Oxygen consumption rate: No effects. Thermal stress tolerance: Decreased survival. ROS levels: No effects. Mitochondrial membrane potential and mass: Decreased. Body size: Decreased body length and width. Crawling speed and body-bending: Decreased. Vulval morphology: Increased protruded vulva structure. *In vitro,* MEF*:* Mitochondrial function: ROS levels: No effect. mPTP opening: No effect. ATP levels: No effect.
Ji et al. 2013 Zebrafish (WT, AB strain). Age 3 to 4 months. Four male and six female fish (and two replicates) per group. Treatment: BPS (purity not stated) in 0.1% (v/v) methanol (vehicle control) at 0, 0.5, 5, or 50 µg/L for 21 days. Solution replaced every 48 hours. F1 eggs were collected on day 16 of exposure to F0 and raised with or without subsequent BPS exposure until 6 dpf. Adverse effects on F1 generation were examined with or without subsequent exposure to BPS.	Hatching rate (%), time to hatch (day), malformation rate (kyphosis, shortened tails, and cardiac edema; %), phenotypic changes (120 hpf).	Hatching rate: Decreased at 5 and 50 µg/L with only parental BPS treatment. Decreased at 0.5, 5, and 50 µg/L with parental and F1 BPS treatment. Time to hatch: Increased at 50 µg/L with only parental BPS treatment. Increased at 0.5, 5, and 50 µg/L with parental and F1 BPS treatment. Malformation rate: Increased at 0.5 and 50 µg/L with parental and F1 BPS treatment. NS increase at 50 µg/L with only parental BPS treatment.
Ji et al. 2022 Zebrafish (WT, AB strain) for embryo acute toxicity. Zebrafish (transgenic, Tg (*fli*1:EGFP) line) for vascular development evaluation. Tg (*fli*1:EGFP) zebrafish:	Acute toxicity test: 96-hour LC_{50} estimated. Vascular development: intersegmental vessel (ISV) development at 24 hpf, common cardinal vein (CCV) development and endothelial cells at 48 and 72 hpf, growth of subintestinal vessels (SIV) at 72 hpf, ventral CCV diameter of the larvae at 72 hpf (n = 20 embryos, 3 replicates).	Acute toxicity: 96-hour LC_{50} = 300.8 mg/L. Oxidative stress at 72 hpf: Cat: Increased activity (+45%). Sod, ROS, and MDA activity: No effect. Vascular development: No effect on ISV length or interval distance at 30 hpf. Decreased % of completed ISV and increased ISV angle with 30 mg/L treatment at 30 hpf.

Study Design	Outcomes assessed	Major Findings
Treatment: BPS (99% purity) in 0.01% v/v DMSO (vehicle control) at 30 mg/L from 2 to 72 hpf. Endpoints assessed at 24-72 hpf.	Oxidative stress (72 hpf): Sod, Cat, ROS, and MDA concentrations (n = 50 larvae, 3 replicates).	No effect on ISV in vascularized yolk area at 72 hpf. CCV: Increased area with 30 mg/L treatment and no effect on number of endothelial cells at 48 hpf (impaired remodeling process). No effect on area or width at 72 hpf.: Oxidative stress at 72 hpf.
Kinch et al. 2015 Zebrafish (WT, TL strain). Zebrafish (Aromatase B morpholino (AroB-MO), TL strain). Treatment: BPS (purity not stated) in a 1:3 ratio of 0.002% (vol/vol) 1 M NaOH to 95% EtOH (vehicle control) and diluted to a final concentration of 6.8 nM (equivalent to 1.70 µg/L, calculated by OEHHA) in embryo medium from 0 to 5 dpf. Co-exposure with 1 µM of estrogen receptor antagonist ICI 182,780 (ICI) in WT locomotor activity experiment. Outcomes assessed at 5 dpf. Experiment 1: Effects of BPS on neurogenesis in the rostral hypothalamus in WT larvae. Experiment 2: Effects of BPS on locomotor activity/behavior in WT larvae with or without ICI and in AroB-MO larvae.	Hypothalamic neurogenesis via 5-ethynyl-2'-deoxyuridine (EdU) incorporation during cell proliferation (24 hpf). Locomotor behavior: Duration of hyperactivity bursts (anxiety-like behavior). Co-treatment with ICI. AroB-MO.	Hypothalamic neurogenesis: Increased (+240%) with 6.8 nM treatment. Locomotor behavior: Hyperactivity bursts: Increased (+160%) with BPS treatment. Co-treatment with ICI: No effect on BPS-mediated hyperactivity increase. AroB-MO: Attenuated BPS-mediated hyperactivity increase.
Kucharíková et al. 2023 *C. elegans* (WT, N2 strain). *C. elegans* (*bli-1* mutant strain). BLI-1; an epidermal developmental protein. Treatment: BPS (99.7 % purity) in 10% ethanol at concentrations 0, 0.1, 0.5, 1, and 5 µM (equivalent to 25.03, 125.14, and 250.27 µg/L and 1.25 mg/L, calculated by OEHHA) in S-buffer (vehicle control). Embryos were exposed for 4 hours at 20°C with gentle shaking, then transferred to NGM plates. Nematodes examined for changes in reproduction, body length, and neural functionality. All experiments performed at least three times using approximately 50 eggs per concentration.	Hatching rate (%). Body length (18 hours post plate transfer). Neural functionality via touch habituation (48 hours post plate transfer): Larvae administered an anterior touch repeated every 10 seconds until it no longer recoils.	Hatching rate: WT: Dose-dependent decrease at all concentrations. *Bli-1*: Dose-dependent decrease at 0.5, 1, and 5 µM. Increased sensitivity at 1 and 5 µM BPS compared to WT. Body length: Decreased at all concentrations in both WT and *bli-1*. Neural functionality via touch habituation: Increased number of anterior touches until habituated at 0.5, 1, and 5 µM in WT and *bli-1*.
Lee et al. 2019 Zebrafish (WT, strain not specified). Treatment: BPS (purity not reported) in 0.01% v/v DMSO (vehicle control) at concentrations 0, 0.4, 2, 10, and 50 mg/L. Embryos were exposed from 4 hpf to 120 hpf and exposure medium was not renewed for the duration.	Survival rate.: Hatching rate Time to hatch. Malformation rate (bent spine, eye malformation, and yolk sac edema). Body length. Eyeball size/body length ratio. TH levels (120 hpf, 10 and 50 mg/L BPS).	No effects on survival rate, hatching rate, malformation rate, body length, and eyeball size/body length ratio. Time to hatch: Delayed hatching with 0.4 mg/L BPS treatment. TH levels: Triiodothyronine (T3) and thyroxine (T4): Concentration-dependent linear increase, only reaching significance in T3 at 50 mg/L. Gene transcription analysis: *tshr, crh,* and *tshb:* Increased at 2 mg/L.

Study Design	Outcomes assessed	Major Findings
Developmental observation: 6 larvae per replicate with 4 replicates per treatment. Evaluated every 24 hours during exposure. Thyroid hormone (TH) measurements: 120 larvae per replicate with 3 replicates for 10 and 50 mg/L treatments. Transcriptional analysis: 25 larvae per replicate with 5 replicates for 2, 10, and 50 mg/L treatments.	Gene transcription analysis (2, 10, and 50 mg/L BPS): Genes related to TH synthesis - thyroid stimulating hormone receptor (*tshr*), hematopoietically expressed homeobox (*hhex*) and thyroid peroxidase *(tpo)*; TH transporter and metabolism - transthyretin (t*tr*), uridine diphosphate glucuronosyltransferase 1 ab (*ugt1ab*); thyroid stimulation - corticotrophin-releasing hormone *(crh*), thyroid stimulating hormone β (*tshb*).	*ttr*: Increased at 2 and 10 mg/L. *hhex, tpo,* and *ugt1ab:* Increased at 2, 10 and 50 mg/L.
J Li et al. 2023 Zebrafish (WT, AB strain) Apolipoprotein Eb-knockout (*ApoEb*$^{-/-}$) referred to as ApoEb mutants, a proposed model for lipid metabolism disorders. *Tg (gata1a:DsRed)* line, model to visualize red blood cells (RBCs). Treatment: BPS (purity ≥ 98%) in 0.002% DMSO (vehicle control) at 0, 1, 10, or 100 µg/L BPS from 2 hpf to 72 hpf. WT: n = 12 per treatment group. ApoEb mutant zebrafish: n ≥ 40 per treatment group. *Tg (gata1a:DsRed):* n = 11 per treatment group (presumed).	All outcomes assessed at 72 hpf. Blood flow and retention of RBCs (relative percentage of adhered RBCs) over a 10 second interval visualized in the caudal (tail) vein of *Tg (gata1a:DsRed)* zebrafish. Integrated density of RBCs in caudal vein determined by o-phenylamine dye positive staining in WT zebrafish. RBC distribution and aggregation in vessels in ApoEb mutant zebrafish.	Blood flow and retention of RBCs: Increased number of RBCs remaining in caudal vein at all concentrations. Increased RBC numbers in caudal vein at 1 and 100 µg/L. RBC distribution and aggregation in vessels in ApoEb mutant zebrafish: Increased aggregation of RBCs in the caudal vein, intersegmental vessels, and dorsal longitudinal anastomotic vessels at all concentrations.
B Li et al. 2024 Chinese medaka fish (*Oryzias sinensis*) embryos, n = 10 per group, with six replicates. Acute toxicity: Treatment: BPS (98% purity) in 0.1% (v/v) DMSO (vehicle control) at concentrations of 0, 250, 500, 750, or 1000 mg/L from 0 to 24, 48, 72, or 96 hpf. Developmental exposure: Treatment: BPS (98% purity) in 0.0001% (v/v) in DMSO (vehicle control) at concentrations of 0, 20, 200, or 2000 ng/L from blastula stage (unspecified whether early or late blastula, ~6.5 to 10 hpf) to 15 dpf. Solution was replaced every two days.	Survival rate. Hatching rate. Heart rate. Blood circulation. Growth parameters at 15 dpf. Body length. Heart rate. Presence of abnormal phenotypes (pericardial edema, spinal curvature, enlarged yolk sac, and decreased head-trunk angle). Transcriptomic analysis (RNA-seq) at 15 dpf. Gene ontology and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses of DEGs in treated vs. control.	No effects on survival rate. Decreased hatching rate at 20 ng/L. Decreased body length at 2000 ng/L. No effects on heart rate. Abnormal phenotypes: NS increases in defect rate for multiple abnormalities at 200 and 2000 ng/L. Transcriptomic analysis: DEGs: treated vs. controls 3 upregulated and 19 downregulated at 20 ng/L, 26 upregulated and 130 downregulated at 200 ng/L, and 68 upregulated and 41 downregulated at 2000 ng/L. 1 upregulated and 3 downregulated common DEGs across treatment groups: Gene ontology enriched terms: glycogen and lipid metabolism and transformation; energy metabolism. KEGG enrichment analysis: 20 ng/L: steroid biosynthesis, glucagon signaling pathway, and insulin signaling pathway. 200 ng/L: NS enriched pathway. 2000 ng/L: immune-related and disease-related pathways, including

Study Design	Outcomes assessed	Major Findings
		complement and coagulation cascades, phototransduction, pertussis, legionellosis, alcoholic liver disease, and others not listed here.
McDonough et al. 2021a *C. elegans* (N2 strain), cultured and age-synchronized via bleaching; remaining intact eggs (F0) were seeded with BPS and hatched and grown for 48 hours. Experiments performed in triplicate. Treatment: BPS (purity 98%) in ethanol diluted with K (3.04 g/L NaCl, 2.39 g/L KCl) buffer (vehicle control) at 0, 0.1, 1.0, 5.0, and 10.0 µM (equivalent to 25.03 and 250.27 µg/L and 1.25 and 2.50 mg/L, calculated by OEHHA) for 48 hours. Experiment 1: F0 generation. Experiment 2: F0 exposed to BPS were allowed to mature and lay eggs. F1 and F2 generations were unexposed. Experiment 3:F0 exposed to BPS were allowed to mature and lay eggs. F1 and F2 generations were also exposed. In all experiments, endpoints assessed after 48 hours.	Lifespan :(Experiments 1, 2, and 3) Lifespan assay: measurement of viability (alive or dead) 24 hours after BPS treatment and checked daily until all worms were dead. Fertility: (Experiments 1, 2, and 3) Total offspring (number of hatched offspring + number of unhatched eggs); numbers of unhatched eggs, days laying eggs, and hatched offspring; age (in days) at start of egg laying; and lethality rates (number of unhatched eggs/total offspring x 100). Behavior: (Experiment 1) head thrashes, body bends in F0 generation only.	Experiment 1: Lifespan: Decreased at all concentrations. Fertility: Decreased number of worms hatched and number of days laying eggs at 1, 5, and 10 µM. Behavior: Increased head thrashes at 0.1 µM; and decreased body bends at 5 and 10 µM. Experiment 2: F1 lifespan: Decreased compared to control at 5 and 10 µM; and increased compared to F0 at 0.1, 1, 5, and 10 µM. F2 lifespan: Decreased compared to control at 10 µM; and increased compared to F0 at all concentrations and compared to F1 at 1 and 10 µM. Fertility. F1 number of hatched worms: Decreased compared to control at 5 and 10 µM; and increased compared to F0 at 1 and 5 µM. F2 number of hatched worms: No effects compared to control; increased compared to F0 at 1 and 5 µM; and compared to F1 at 5 and 10 µM. F1 and F2 number of days laying eggs: No effects (data not shown). F1 and F2 lethality rate and number of offspring hatched: No effects (data not shown). Experiment 3: F1 lifespan: Decreased compared to control and F0 at all concentrations. F2 lifespan: Decreased compared to control and F0 at all concentrations and compared to F1 at 5 and 10 µM. Fertility. F1 number of hatched worms: Decreased compared to control at all concentrations, and compared to F0 at 0.1 and 5 µM. F2 number of hatched worms: Decreased compared to control and F0 at all concentrations, and compared to F1 at 0.1 and 10 µM. F1 age at start of egg laying: Delayed at 0.1 and 5.0 µM. F2 age at start of egg laying: Delayed at 5 µM. F1 number of days laying eggs: Decreased compared to control at 1 µM. F2 number of days laying eggs: Decreased compared to control at 5 µM.

Study Design	Outcomes assessed	Major Findings
Mentor et al. 2020 Chicken embryos *in ovo, n* = 28 embryos. Treatment: BPS (≥ 98% purity) in DMSO (vehicle control) with 210 nmol/g egg (corresponds to 53 µg/g egg) injected into eggs on embryonic day 4. Endpoints assessed on embryonic day 19.	Embryo mortality. Body weight. Liver weight; liver-somatic index (LSI) calculated as 100 x liver weight/body weight. Gallbladder weight; gallbladder-somatic index calculated as 1000 x gallbladder weight/body weight. Gross morphology, size, and histology of gonads.	Mortality: Increased embryo mortality (57% vs. 24% in control group). Body weight, LSI: No effect. Gallbladder-somatic index: Increased. Gonad morphology, size, and histology: Males: Could not be determined. Only 3 males were alive at endpoint assessment. Females: 2 of 9 BPS-exposed females had thin and possibly atrophic ovaries.
Moreman et al. 2017 Zebrafish (WT, WIK strain), n = 20 embryos per group in triplicate. Zebrafish Tg(ERE:Gal4ff)(UAS:GFP). Treatment: BPS (≥ 97% purity) in 0.01% v/v ethanol (vehicle control) at concentrations 0, 10, 20, 50, 100,200 and 300 mg/L. Treatment duration from 1 hpf to 96 hpf. Larvae assessed on 3, 24, 48, 72, and 96 hpf. Estrogenic potency and tissue targets for estrogenic responses analyzed in the estrogen responsive transgenic zebrafish Tg(ERE:Gal4ff)(UAS:GFP). Fish were co-exposed with 607 µg/L estrogen receptor inhibitor ICI 182 780. Larval uptake of BPS was determined at 120 hpf in 3 replicates, each containing 5 larvae: Nominal external water concentration: 50 mg/L Measured external water concentration: 52.3 mg/L Measured uptake per larvae: 3.34 ng/larvae Estimated bioconcentration factor: 0.067	Mortality: Calculated at 96 hpf. Hatching rate (72 hpf, EC_{50}), and abnormalities (cardiac edema, craniofacial abnormality, tail development, cranial hemorrhage, and yolk sac deformity. GFP expression in ERE-TG zebrafish larvae treated with BPS or co-exposed to ICI 182 780.	Mortality: 96 hour-LC_{50}: 198.76 mg/L Hatching rate: 72 hour-EC_{50}: 155.47 mg/L. Percent of zebrafish with abnormalities: Induced cardiac edema (94%), craniofacial abnormality (96%), and tail abnormality (82%) with 200 mg/L BPS treatment. NS percent of cardiac edema (2%, 3%), craniofacial abnormality (2%, 3%), and tail abnormality (2%, 2%) at 20 and 100 mg/L, respectively, and yolk sac deformity (2%) at 20 mg/L BPS. GFP expression in ERE-TG larvae: Induced GFP in the heart at 20 (+2.7-fold) and 50 (+10.8-fold) mg/L. Induced GFP in the liver (+48-fold) and tail somites (+6-fold) at 50 mg/L. 20 mg/L BPS co-exposed with ICI 182 780 completely attenuated BPS-mediated induction of GFP in the heart and tail somites.
Mu et al. 2018 Zebrafish (WT, AB strain). Treatment: BPS (99% purity) at 0, 2.5, 12.5, or 25 mg/L or at 0.5, 5, or 25 mg/L for estrogenic activity evaluations. Treatments lasted from 1.5 hpf to 4 dpf. 60 hatched larvae were collected for ER protein level estimation and gene expression studies to determine estrogenic activity. A docking study of BPS binding modes to zebrafish estrogen receptors (Erα [Esr1], ERβ1 [Esr2a], and ERβ2 [Esr2b]) was	Mortality. Hatch ratio. Rate of deformity (yolk sac edema, spine deformation, pigmentation inhibition, pericardial edema). Spontaneous movement (systemic twist of embryo, 24 hpf). Heart rate (48 hpf). Estrogen receptor binding: BPS binding potential to Erα (Esr1), ERβ1 (Esr2a), and ERβ2 (Esr2b). Esr1 protein level. Estrogen receptors gene expression (real-time PCR).	No effect on mortality. No effect on hatch ratio, rate of deformity, spontaneous movement, and heart rate. Estrogen receptor binding: BPS binding potential: Esr1 (-10.05 kcal/mol) < Esr2a (-11.23 kcal/mol) < Esr2b (-14.26 kcal/mol). Esr1 protein level: No effect. Estrogen receptors gene expression: No effect.

Study Design	Outcomes assessed	Major Findings
performed using homology modeling, molecular docking, and molecular dynamics simulation methods.		
Naderi et al. 2014 Zebrafish (WT, strain not specified). Treatment: BPS (purity >98%) in 0.01% acetone v/v (vehicle control) with concentrations of 0, 0.1, 1, 10 and 100 µg/L from 2 dpf to 75 dpf. 50% of exposure solution was renewed daily. Adult males and females from the same treatments were then selected to breed and randomly assigned to spawning tanks with 2 males per 2 females.	Hatching rate (%). Time to hatch (hours).	Hatching rate: Decreased in 10 and 100 µg/L groups. Time to hatch: Increased in 10 and 100 µg/L groups.
Neighmond et al. 2023 Zebrafish (WT, strain not specified). Treatment: BPS (purity not stated) at concentrations 0, 4, 8, and 12 mg/L in DMSO (vehicle control). Treated from 6-10 hpf to 96 hpf with solution refreshed every 24 hours. Body length data, n = 31 to 43 per group. Heart rate and circulatory score, n = 23 per group. Gene expression analysis: 20 pooled embryos treated with 4 mg/L BPS, repeated in triplicate. The developmental effects of BPS on sponges (*Ephydatia muelleri*) were also assessed, including morphological and RNA-seq analyses: Major findings in sponges included: decreased hatching, smaller size, delay in reaching adult stage, and abnormal morphologies observed at concentrations ranging from 4 to 16 mg/L (16 to 64 µM) BPS. Two genes, *gsto1* and *prost1.2*, were selected for qRT-PCR analysis in zebrafish based on sponge RNA-seq data (assessed in sponges treated with 4 mg/L BPS).	All outcomes assessed at 4 dpf (96 hpf). Hatching rates. Developmental morphology. Body length (head to base of tail). Heart rate (beats per 30 seconds). Circulatory score: phenotypic measurement (scale of 1-5) with 5 being normal development and 1 indicating multiple blood leaks in tissue and other extreme abnormalities. mRNA expression (qRT-PCR): glutathione-s-transferase omega 1 (*gsto1*) and prostaglandin reductase 1.2 (*prost1.2*) in 4 mg/L treatment group.	Hatching rates: Decreased in 12 mg/L group, NS decrease in all other treatment groups. Developmental morphology: Increased blood pooling in the caudal vein with increasing concentration, not quantitated. Body length: No effect. Heart rate: No effect. Circulatory score: Decreased score in 12 mg/L group. NS decrease with 4 and 8 mg/L groups. Gene expression following 4 mg/L BPS treatment: Upregulation of *gsto1* and *prost1.2,* concordant with results from sponge RNA-seq data.
Qin et al. 2023 Zebrafish (WT, AB strain), n = 50 per group, 3 replicates. Treatment: BPS (≥98% purity) in 0.002% DMSO (vehicle control); at concentration of 0 (blank control), 0, 1, or 100 µg/L from 2 hpf to 96 hpf. All assessed outcomes were compared to DMSO control.	Body length (96 hpf). Hatching rate (60, 72, and 96 hpf). Swim bladder inflation (96 hpf). Cardiac function: Sinus venosus-bulbus arteriosus (SV-BA) distance (72 hpf). Stroke volume (72 hpf). Heart rate (36, 72, and 96 hpf).	Body length: Decreased body length at1 µg/L No effect on hatching rate and swim bladder inflation. Cardiac function: SV-BA distance: Decreased distance at 1 and 100 µg/L. Stroke volume: Decreased at 100 µg/L. Heart rate:

Study Design	Outcomes assessed	Major Findings
All experimental observations occurred between 36 and 96 hpf. Gene expression analysis via RT-qPCR: 30 embryos from each treatment group at 96 hpf pooled as one sample for RNA extraction, with 4 replicates per treatment group	Thyroid hormone pathway and cardiac development gene expression using qRT-PCR: Thyroid hormone signaling-related genes: *dio2, dio3b,* and *thrb.* Thyroid hormone receptor β targets: *tfam* and *myh7.* Cardiac development-related gene: *tbx5.* Binding potential between BPS and zebrafish Thrb using homology modeling and molecular docking simulation.	Increased at 1 and 100 µg/L at 36 and 72 hpf. Increased at 100 µg/L at 96 hpf. Thyroid hormone signaling-related gene expression: No effects. Thyroid hormone receptor β targets: No effects. Cardiac development-related gene expression: No effects. Binding potential between BPS and THRβ: BPS was modeled to dock tightly in the active pockets of Thrb via three hydrogen bonds with an affinity of -2.13 kcal/mol.
Qiu et al. 2016 Zebrafish (Brass Gnrh3:EMD transgenic); identifies Gnrh3 neurons with Emerald green fluorescent protein (EMD) Treatment: BPS (purity > 98%) in 0.005% DMSO at concentrations of 0 and 100 µg/L in E3 medium from 2 hpf until 25 or 120 hpf. At 25 hpf: Effects on gonadotropin-releasing hormone 3 (Gnrh3) neuron numbers in terminal nerve (TN) and hypothalamus (HYPO). Gnrh3 neurons of forebrain populations analyzed by confocal microscopy (n=14 embryos/treatment group) Neuroendocrine-related gene expression and estrogen receptor gene expression (20 embryos per treatment group; n=6 replicates). Co-treatment (120 hours to 100 µg/L BPS only or in the presence of: ER antagonist ICI 182 780 (ICI) at 1 µM, Thyroid hormone receptor antagonist amiodarone hydrochloride (AMIO) at 1µM, or Aromatase (AROM) inhibitor fadrozole hydrochloride (FAD) at 1 µM). (50 embryos/treatment group; n = 6 replicates)	Survival rate (every 24 hrs for 120 hrs). Gnrh3 neuron numbers in the hypothalamus and terminal nerve (25 hpf). Reproductive neuroendocrine-related gene expression: 25 hpf: *era (esr1), erb (esr2b), fshb, gnrh3, kiss1, kiss1r, kiss2, kiss2r, lhb, and sv2* 120 hpf: BPS co-treatment with ICI, AMIO, or FAD: *esr1, fshb, gnrh3, kiss1, kiss1r, and lhb.*	Survival rate: No effect (data not shown). Gnrh3 neuron populations: Hypothalamus: Increased numbers of Gnrh3 neurons at 100 µg/L. Terminal nerve: No effect. Reproductive neuroendocrine-related gene expression at 25 hpf Increased expression of *kiss1, gnrh3, esr1* No effect on *esr2b, kiss1r, kiss2, kiss2r, lhb, and sv2* gene expression. 120 hpf: Co-treatment with ICI, AMIO, or FAD: BPS only: Increased *esr1, fshb, gnhr3, kiss1r, and lhb;* no effects on *kiss1*. ICI: Attenuated BPS-mediated increases in *gnrh3* and *fshb.* AMIO: Attenuated BPS-mediated increase in *kiss1r.* FAD: Attenuated BPS-mediated increases in *esr1, fshb, gnrh3, kiss1r, and lhb.*
Qiu et al. 2018 Zebrafish (WT, strain not specified), Treatment: BPS (purity > 98%) at 0, 0.1, 1, 10, 100, and 1000 µg/L in 0.005% DMSO (vehicle control) in E3 medium (also blank control) from 4 hpf to 120 hpf. Solutions were replaced every 12 hours.	Survival rate (every 24 hrs for 120 hrs). Hatching rate (at 48 and 54 hpf). Body length (120 hpf). Biochemical and molecular analyses (120 hpf): Oxidative stress indices: ROS, total antioxidant capacity (T-AOC), Cat, Sod, and lipid peroxidation (MDA) levels.	Survival rate: No effect. Hatching rates: Decreased at 1, 10, and 100 µg/L at 48 hpf and at10 and 100 µg/L at 54 hpf. Body length: Decreased at 100 and 1000 µg/L. Biochemical and molecular analyses (120 hpf):

Study Design	Outcomes assessed	Major Findings
50 to 200 embryo/larvae per treatment group; n = 4 replicates Larval homogenates at 120 hpf used for biochemical analyses (supernatant) or gene expression analysis. Co-treatment (120 hours) to 100 µg/L BPS and either 1 µM ER antagonist ICI 182 780 or 1 mM nuclear factor kappa B (NF-kB, Nfkb) antagonist pyrrolidine dithiocarbamate (PDTC) to explore potential signal transduction pathways (Esr1 and Nfkb) on immune modulation and oxidative stress during embryonic and larval development.	Nitric oxide (NO) content, total NO synthase (TNOS) activity, and inducible NO synthase (iNOS) activity and gene expression (*inos)*. Cytokine gene expression: Interleukin (*il*)*1b, il6, il10, il11a, il12a, interferon γ (ifng), tumor necrosis factor α (tnfa),* and *cc-chemokine (ccl34a.4)*. Estrogen receptor and nuclear factor-kB signaling pathway gene expression: *esr1* and nfkbgene expression. Co-treatment with ER and Nfkb antagonists. Gene expression of *ifng, il1b, il6, and tnfa*.	Oxidative stress indices: ROS, Sod: Increased at 100 and 1000 µg/L. Cat, T-AOC, MDA: Increased activity at 1000 µg/L. Total NO content, iNOS activity: Increased at 100 and 1000 µg/L. TNOS activity: Increased at 1, 100, and 1000 µg/L. *inos* expression: Increased at 10, 100, and 1000 µg/L. Cytokine gene expression: *il10, il11a*, and *cc*-chemokine Increased at 1000 µg/L. *ifng*: Increased at 10 and 1000 µg/L. *il1b* and *tnfa*: Increased at 100 and 1000 µg/L *ilb* and *il12a: Increased at* 1, 10, 100, and 1000 µg/L. *esr1* and *nfkb* gene expression: Increased at 100 and 1000 µg/L. Co-treatment with ER and Nfkb antagonists: BPS + ICI: attenuated BPS-mediated increases in *il1b, il6, and tnfa* expression. BPS + PDTC: attenuated BPS-mediated increases in *ifng, il1b, and tnfa* expression.
Qiu et al. 2020 Zebrafish (WT, AB strain). Treatment: BPS (98% purity) at 0, 0.1, 1, 10, or 100 µg/L in 0.005% DMSO (vehicle control) in E3 medium from <4 hpf-120 hpf with solutions renewed daily. 100 embryo/larvae per treatment group, n = 3 replicates Results from the transcriptomic analysis (RNA-seq) and RT-qPCR validation guided the study design.	All outcomes assessed at 120 hpf. Transcriptomic analysis. RNA-seq on larvae, Ingenuity Pathway Analysis (IPA) and qRT-PCR validation on selected differentially expressed genes (DEGs): *il21r.2, il12bb, tlr4bb, angpt2a, vipr2, nos2a, hipk2, wnt6b, slc7a11, jam2b, aqp1a.2, hnf1a,* and *csf3b.* Protein assays. iNOS or nitric oxide synthase 2 (Nos2) levels in supernatant of larval homogenates. Interleukin 12 (Il12) levels in larval homogenates. Cardiac development and function. Heart rate measured in beats per minute in 12 larvae randomly selected from each treatment group. Morphology: Heart size and form. Atrial size. Atrial to ventricle area. Neutrophil numbers.	Transcriptomic analysis: Number of DEGs compared to control. 0.1 µg/L: 594. 1 µg/L: 823. 10 µg/L: 2115. 100 µg/L: 1573. IPA predictions. Top-ranked canonical pathway at 10 and 100 µg/L: Cardiac hypertrophy signaling (enhanced). Top two upstream regulators at all BPS concentrations: Hepatocyte nuclear factor-1α (*hnf1a*) and colony-stimulating factor (*csf2*). Top predicted diseases and disorders, and toxicity at all concentrations: those related to immune diseases, inflammation, and the cardiovascular system. Highest ranked toxicity function prediction: interstitial fibrosis of heart Causal network analysis: cytokines were most relevant and significant term.

Study Design	Outcomes assessed	Major Findings
		Regulator effects: RELA, P38, MAPK, and CSF2 predicted to be induced by BPS and regulate target genes identified in the diseases, disorders, and toxicity predictions category of IPA. RT-qPCR validation. Concordance with RNA-seq results in the 13 selected DEGs. Protein assays. Nos2 activity: Increased at 10 and 100 µg/L. Il12 content: Increased at 100 µg/L. Cardiac development and function: Heart rate: Decreased (-8.9%) at 100 µg/L (figure specifies 72 hpf). Morphology: Heart size and form: No effects. Atrial size: Increased at 100 µg/L. Atrial to ventricle area: Increased (+35.1%) at 100 µg/L relative to control. Neutrophil numbers: NS increase (average +137.5% induction at 100 µg/L.
Qiu et al. 2021 Zebrafish (WT, strain not reported), (Transgenic, Gnrh3-EMD), 100 embryo/larvae per treatment group, n = 3 replicates Treatment: BPS (98% purity) at 0, 1 or 100 µg/L in 0.005% DMSO (vehicle control) in E3 medium from 2 hpf until 120 hpf for WT zebrafish, and 100 µg/L from 2 hpf to 25 hpf for transgenic Gnrh3-EMD zebrafish. A blank control was utilized with E3 medium alone. Solutions were replaced every 12 hours. At 25 hpf: Effects on Gnrh3 neuron numbers in terminal nerve (TN) and hypothalamus (HYPO) in transgenic Gnrh3-EMD zebrafish. Gnrh3 neurons of forebrain populations analyzed by confocal microscopy (n=7 embryos/treatment group). Larval homogenates at 120 hpf used for biochemical analyses (supernatant) or gene expression analysis. Co-exposure experiments with 1 µM ER antagonist ICI or 1 µM AROM inhibitor FAD in WT embryo/larvae to determine effects of signaling pathways on the expression of reproductive neuroendocrine-related genes and hormones.	Hatching rate (48 hpf). Body length (120 hpf). Movement distance within 10 min (120 hpf). Gnrh3 neuron numbers in the hypothalamus and terminal nerve (25 hpf). Hormone concentrations in supernatant of whole zebrafish homogenates (120 hpf): E2, FSH, GH and LH. Gene expression (120 hpf): Reproductive neuroendocrine-related genes (120 hpf): *kiss1, kiss2, gnrh3*, FSH beta (*fshb*), LH beta (*lhb*), atrial natriuretic peptide (*anp*), renin (*ren*), parathyroid hormone 1 (*pth1*), GH (*gh*), prolactin (*prl*). ER and CYP19-family genes: *ersr1, ersr2a, ersr2b, cyp19a1, and cyp19a2.* Co-exposure experiments.	Hatching rate: Accelerated at 100 µg/L. Body length: Decreased at 100 µg/L. Movement distance: No effect. Gnrh3 neuron populations: Hypothalamus: Increased numbers of Gnrh3 neurons at 100 µg/L. Terminal nerve: No effect. Hormone concentrations: Increased E2 in at 1 and 100 µg/L. Increased FSH at 100 µg/L. No effects: LH and GH. Gene expression: Reproductive neuroendocrine-related genes: No effect: *fshb*, *gnrh3*. Increased *prl* at 1 µg/L. Increased *kiss1, kiss2, ren, pth1,* and *gh* at 100 µg/L. Increased *lhb* and *anp* at 1 and 100 µg/L. ER and CYP19-family genes: Increased *esr1*, *esr2b, cyp19a1, and cyp19a2* at 100 µg/L. Increased esr2a at 1 and 100 µg/L. Co-exposure experiments: ICI: did not modulate the effects of BPS. FAD: significantly attenuated the BPS-mediated increase of *fshb*.

Study Design	Outcomes assessed	Major Findings
Qiu et al. 2023a Zebrafish (WT Tu strain), 400 embryo/larvae, n = 3 replicates Zebrafish transgenic lines: Tg(*cyp26a1*:eYFP) strain: to monitor expression of CYP26A1, a hydroxylase involved in retinoic acid metabolism. *thrb*$^{-/-}$ Tu strain: thyroid hormone receptor beta knockout. *cyp26a1*$^{-54D-}$ Tu strain: CYP26A1 null mutant. Treatment: BPS (≥98% purity) in 0.005% DMSO (vehicle control) at 0, 1, 10, and 100 µg/L from 2 hpf to 5 dpf. Solutions were replaced daily. Retinoids metabolism experiment in zebrafish eyes: either 0 or 100 µg/L BPS or T3 at 10 nM as a positive control from <2 hpf to 5 dpf.	Optokinetic response in WT larvae at 15 dpf: Slow phase gain = ratio of the angular velocity of zebrafish eye rotation to the grating rotation angular velocity in the slow phase. Retinoids metabolism at 5 dpf: Relative content of ocular all-*trans* retinoic acid (atRA) and its metabolites; and all-*trans* retinal (atRAL), all-*trans* retinol (atROL), and 11-cis retinal (11cRAL): atRA and metabolites (18-OH-atRA, (oxo)2-atRA, oxo-OH-atRA, 4-oxo-atRA) at 100 µg/L BPS or 10 nM T3 in WT; and without BPS treatment in *thrb*$^{-/-}$ and *cyp26a1*$^{-54D-}$ strains. atRAL, atROL, and 11cRAL at 100 µg/L BPS or 10 nM T3 in WT, *thrb*$^{-/-}$ and *cyp26a1*$^{-54D-}$ strains. Ocular *cyp26a1* mRNA expression at 5 dpf: in WT and *thrb*$^{-/-}$ zebrafish with 100 µg/L BPS or 10 nM T3, and without treatment in *thrb*$^{-/-}$ and *cyp26a1*$^{-54D-}$ zebrafish.	Optokinetic response: Decreased slow phase gain at all concentrations. Retinoids metabolism. atRA and metabolites: Decreased atRA and oxo-OH-atRA and Increased 18-OH-atRA and (oxo)2-atRA with 100 µg/L BPS in WT. atRA not detected and increased 18-OH-atRA (only metabolite peak detected) with 10 nM T3 in WT. Increased atRA and decreased (oxo)2-atRA in *thrb*$^{-/-}$ zebrafish, Increased atRA, (oxo)2-atRA, and oxo-OH-atRA in *cyp26a1*$^{-54D-}$ zebrafish. atRAL, atROL, and 11cRAL: Decreased atRAL in WT with 10 nM T3 and *thrb*$^{-/-}$ with 100 µg/L BPS. Decreased atROL in WT with 100 µg/L BPS and 10 nM T3 and in *thrb*$^{-/-}$ (NS) with 100 µg/L BPS. Decreased 11cRAL in WT with 100 µg/L BPS and 10 nM T3 and in *cyp26a1*$^{-54D-}$ (NS) with 100 µg/L BPS. Ocular *cyp26a1* expression: Increased in WT with 100 µg/L BPS or 10 nM T3. Attenuated in *thrb*$^{-/-}$ mutants with 100 µg/L BPS (NS) and 10 nM T3. Decreased in *thrb*$^{-/-}$ and *cyp26a1*$^{-54D-}$ mutants.
Qiu et al. 2023b Zebrafish (WT, Tu strain). Zebrafish (Transgenic, *sws1*; thrb), Analyses of cone cells (photoreceptor cells in the retina); *sws*: GFP labels outer segment of UV cones and *thrb*; mCherry labels red cone cells. Zebrafish (Transgenic, *huc*:GFP): Analyses on neurodevelopment. Treatment: BPS (purity ≥98%) at 0, 1, 10, or 100 µg/L in 0.005% DMSO (vehicle control). 400 embryo/larvae per treatment group, n = 3 replicates. Treatment window: WT and Transgenic, *sws1*; thrb: 2 hpf to 5 dpf. Transgenic, *Huc*:GFP: 2 hpf to 72 hpf.	Phototaxis at 5 dpf. Larvae tendency towards short- (S-), medium- (M-), and long- (L-) wave type lights measured as phototactic ratio (%). Cone cell effects at 5 dpf. Morphology. Height and width of red cone cells. Number of ribbon synapses in red cone cells. Mosaic arrays. DNA damage (comet assay): olive tail moment (OTM) values and tail DNA %. Nervous system development pertaining to light-electrical signal transduction from 24 hpf to 72 hpf. GFP intensity at 48 hpf in: Hypothalamus. Spinal nerve. Optic nerve. Development of retinal ganglion cells in retinal ganglion cell layer at 72 hpf:	Phototaxis. 1 µg/L: No effects. 10 µg/L: Decreased percentage of larvae traveling to L- and S- wave type light signals within 1 minute. 100 µg/L: Decreased percentage of larvae traveling to all light signal types. Cone cell effects. Morphology. Height: No effects. Width: Decreased at 100 µg/L. Number of ribbon synapses: Decreased at 10 and 100 µg/L. Mosaic arrays: Loose and disordered arrangement of red and UV cone cells, increased distances between red cones and between UV cones at 10 and 100 µg/L. DNA damage: Increased OTM values for both red and UV cone cells at 10 and 100 µg/L; and increased tail DNA % at 100 µg/L. Nervous system development. 48 hpf. Control and 1 µg/L: GFP signal in hypothalamus only.

Study Design	Outcomes assessed	Major Findings
	Cell length and number. Transcriptomic analysis: RNA-seq of eyes (WT) and qRT-PCR validation of 12 selected genes (*pde6a, pde6b, pde6c, guca1a, guca1b, guca1c, guca1g, opn1sw1, opn1lw1, opn1lw2, opn1mw1,* and *opn1mw2*) in the phototransduction pathway. Motor nerve neurogenesis at 84 hpf in Tg (*huc*:GFP): data provided in Supplemental Info with no reference in the main study.	10 µg/L: Signal extended from hypothalamus to spinal nerves; weak signal in optic nerve. 100 µg/L: Signal further extended from hypothalamus to spinal nerves; more intense signal in optic nerve. 72 hpf. Development of retinal ganglion cells: Extended cell length at 10 µg/L. Increased number of retinal ganglion cells at 10 and 100 µg/L. Transcriptomic analysis of eyes at 120 hpf. Number of DEGs compared to control. 1 µg/L: 2015. 10 µg/L: 5411. 100 µg/L: 7900. Select KEGG pathways enriched across all treatment groups: Apoptosis, p53 signaling, phototransduction, Wnt signaling, and MAPK signaling. Phototransduction pathway: Upregulation of key genes in phototransduction (*pde6a, guca1a, opn1lw1, opn1lw2, opn1mw1, opn1mw2* and *opn1sw1*) at 10 and 100 µg/L; and key genes in neuron axonogenesis (*her4, gap43,* and *coro1a*) and oxidative stress (*sod2, adprhl2, park7, sod1, gpx4a, gpx4b, prdx1, cyba,* and *prdx2*) at 100 µg/L. RT-qPCR validation: 8 of 12 phototransduction-associated genes assayed consistent with RNA-seq data. Precocious neurogenesis of motor nerve at 84 hpf in Transgenic, *Huc*:GFP larvae as indicated by branching development of actin-rich filopodia at all BPS concentrations.
Salahinejad et al. 2022 Zebrafish (WT, AB strain). Treatment: BPS (purity ≥ 99%) in 0.01% v/v DMSO (vehicle control) at 0, 1, 10, or 30 µg/L, with 1 µg/L E2 as positive control, for 60 days. Treated females were paired with untreated males with a configuration of 4 female fish with 4 male fish (5 replicates/treatment).	Cumulative mortality from 7 to 60 dpf. Average body length and weight, presumed at 6 months of age (see Salahinejad 2023). Behavioral tests at 6 months: Social Behavior: Shoaling/shoal cohesion and group preference. Anxiety: Novel tank test. Locomotion.	Mortality: No effect. Average body length and weight: No effects. Behavioral tests: Social behavior: Decreased interindividual distance among shoal members in 10 µg/L group. Increased number of individual excursions from shoaling group at 30 µg/L and 1 µg/L E2. Decreased novel group preference in 1 µg/L group. Anxiety: Decreased stress response as total time spent in bottom half of novel tank in 1 and 30 µg/L groups and 1 µg/L E2. Locomotion: No effect.

Study Design	Outcomes assessed	Major Findings
With E2 and 1 µg/L BPS treatments, 14/93 and 11/101 offspring, respectively were female. Therefore, only male offspring were used in this study. Egg BPS concentration: None above BPS detection limit (~0.25 µg/L) in eggs from any treatment group. 100 embryos per treatment, n = 5 replicates.	Biochemical assessments: brain arginine-vasotocin (AVT) and isotocin (IT) levels (orthologs to vasopressin and oxytocin in mammals, respectively). Gene expression in brains of male offspring (qPCR): Neuropeptide signaling system (*oxt, itr, avp, avpr1aa, avpr1ab*). Enzymatic antioxidant genes (*gpxla, cu/zn-sod [sod1], cat, mn-sod [sod2]).*	Biochemical assessments: AVT: Increased with 1 µg/L BPS treatment. IT: No effect. Gene expression: Neuropeptide signaling system: Increased *avp* in 1 and 10 µg/L groups. Decreased *avpr1aa* in 30 µg/L group compared to 1 and 10 µg/L groups. No effect on *oxt, itr,* or *avpr1ab.* Enzymatic antioxidant genes: Decreased *cat* in all treatment groups and 1 µg/L E2. Decreased *mn-sod* in 30 µg/L group. No effect on *gpxla* or *cu/zn-sod*.
Salahinejad et al. 2023 Zebrafish (WT, AB strain). Treatment: BPS (purity ≥ 99%) in 0.001% v/v DMSO (vehicle control) at concentrations 0, 1, 10, or 30 µg/L, or a positive control (E2; 1 µg/L) for 60 days, with 100% of the tank water replaced daily. Treated females paired with sexually mature unexposed males with a configuration of 4 female fish with 4 male fish (4 replicates/treatment). Authors note that ~90% of the offspring were male, therefore only the male offspring were used for assessment at 6 months following housing and maintenance in control water. Serotonin, or 5-hydroxytryptamine will be referred to as 5-HT.	Mortality: as reported in Salahinejad et al. 2022 Behavior tests: Anxiety: Light/dark box test, open field test. Boldness: Emergence from isolation chamber. Antipredator fear response: Chemical alarm cues. Effect on shoaling density (distance among shoal members) and number of excursions. Serotonergic gene expression in brains of male offspring (qPCR): 5-HT biosynthesis (*tph2*). 5-HT degradation (monoamine oxidase: *mao*). 5-HT transporters (*slc6a4a, slc6a4b*). 5-HT receptors: 5-HT1A (*htr1aa, htr1ab*), 5-HT1B (*htr1b*), 5-HT1D (*htr1d*), 5-HT2A (*htr2aa*), and 5-HT2B (*htr2b*).	Mortality: No effect; as reported in Salahinejad et al. 2022. Behavior tests: Light/dark box (anxiety): Decreased time spent in dark side of tank in 1 (NS; -9.37%), 10 (-23.67%), and 30 (-22.42%) µg/L groups, and 1 µg/L E2 (-17.31%). Increased number of entries to the light compartment in 1 (NS; +110.69%), 10 (NS; +105.97%), and 30 (+128.72%) µg/L group and 1 µg/L E2 (+111.73%). Open field test (anxiety): Increased time spent, greater track length, and increased number of visits in/to the central zone and decreased velocity within the central zone in 1(NS; +74.79%), 10 (+142.82%) and 30 (+148.61%) µg/L BPS groups and 1 µg/L E2 (+133.78%). Boldness: No effect. Antipredator fear response: Increased interindividual distance within a shoal following alarm cues in all treatment groups and 1 µg/L E2. Increased number of excursions following alarm cues in 10 and 30 µg/L groups. Serotonergic gene expression: Decreased *htr1aa*, *htr1ab*, and *mao* in 30 µg/L group and *htr1aa* and *htr1ab* (NS) with 1 µg/L E2.
Santos Musachio et al. 2023 *Drosophila melanogaster* parental flies, n = 25 females and n = 15 males per treatment group, and larvae. Treatment: BPS (purity not reported) in 0.1% DMSO (vehicle control) at 0, 0.25, 0.5, and 1 mM (equivalent to 62.57, 125.14, and 250.27 mg/L, calculated by OEHHA) administered via diet. Parental flies were treated with BPS for a seven-day breeding period, then discarded. Resulting larvae (F1 generation) were	Larval development. Reactive species (RS) and lipid peroxidation (TBARS). Antioxidant enzyme activity. Larval cell viability in larval homogenates. Mitochondrial viability (MTT assay).	Larval development. Larvae treated at 1 mM BPS had longer and thinner bodies with a melanotic mass. Decreased number of pupae formed at 0.5 (NS) and 1 mM. Decreased hatchling percentage at 0.5 and 1 mM. Reactive species and lipid peroxidation: Increased RS and MDA at 0.5 and 1 mM. Antioxidant enzyme activity: Increased Sod, and Cat at 0.5 and 1 mM,

Study Design	Outcomes assessed	Major Findings
maintained until the third instar stage of development for analysis.		Increased Cyp450 at 0.5 and 1 mM, and Increased Gst at 0.25, 0.5, and 1 mM. Cell viability: Decreased at 1 mM. Mitochondrial viability: Decreased at 1 mM.
Santos Musachio et al. 2024 Fruit flies (*Drosophila melanogaster*), n = 40 parental flies per group (15 males and 25 females). Treatment: BPS (purity not reported) in 0.001% DMSO (vehicle control) at concentration of 0, 0.25, 0.5, or 1 mM (equivalent to 62.57, 125.14, and 250.27 mg/L, calculated by OEHHA); parental flies were treated via the diet in flasks for 5 days during breeding. F1 eggs remained in their respective treatment flasks until pupal formation. 1- to 2-day old control and exposed F1 flies were evaluated.	Behavioral tests: locomotion and exploratory capacity, negative geotaxis (time to reach top of vertical tube), repetitive behaviors (grooming), aggressiveness (number of combats, or aggressive encounters, in males only), social interaction (distance between same-sex flies), learning test. Brain size (females only). Shank scaffold protein involved in synaptic development and function) levels	Locomotion: Increased number of quadrants travelled at 1mM. Negative geotaxis: Decreased climbing time at 1 mM. Repetitive behaviors: Increased number of grooming events at 0.5 (NS) and 1 mM. Aggressiveness: Increased combats at 1 mM. Social interaction: Increased distance at 0.5 and 1 mM. Learning test: Decreased percentage of learning at 1 mM. Brain size: Increased at 0.5 and 1 mM. Shank protein levels: Decreased at 0.5 and 1 mM.
Wang et al. 2019 Zebrafish (WT, Tu strain). F0: Treatment: BPS (purity ≥ 98%) in 0.002% (v/v) DMSO at 0 (blank control, dechlorinated tap water), 0 (vehicle control), 1, 10, 100 and 1000 µg/L from 2 hpf to 120 dpf. Males and females from each BPS treatment group were selected at 120 dpf to generate F1 and spawned in dechlorinated tap water. F1: 150 embryo/larvae per treatment, n = 3 replicates. 30 larvae at 5 dpf with n = 6 replicates per treatment from which n = 5 larvae selected from each treatment for yolk lipid distribution analysis.	F1: Survival rate at 24 hpf. Body length and weight at 5 dpf. Total cholesterol (TC) and LDL cholesterol content in supernatant from zebrafish homogenate (n = 6 replicates of 15 larvae per treatment) at 5 dpf. Yolk lipid content using ORO staining at 5 dpf. mRNA expression of yolk lipid metabolism-related genes in larvae at 5 dpf: *fabp2, fabp1b, fabp11a, fabp10, mtp, lpl, pparg, apobb.1, apoeb, apoa4b.1, and apoa1a.*	F1: Survival rates: Decreased at 10 and 100 µg/L. Body length: No effects. Body weight: Increased at 1, 10, and 100 µg/L. TC and LDL cholesterol levels: Decreased at 1, 10, and 100 µg/L. Yolk lipid content: Presence of residual yolk lipids in viscera or yolk area with BPS treatment. Yolk lipid metabolism genes: Increased *apoeb* in all treatment groups; increased *fabp2, fabp11a, mtp, and pparg* and decreased *lpl* at 10, 100, and 1000 µg/L; increased *fabp10* at 1 µg/L; increased *apoa1a* at 10 µg/L; and increased *fabp1b, apobb.1, and apoa1a* and decreased *fabp10* at 1000 µg/L.

Study Design	Outcomes assessed	Major Findings
Wang et al. 2020 Zebrafish embryos/larvae. WT AB strain and the transgenic line *tg* (*flk1:eGFP*) to visualize blood vessel formation. Treatment: BPS (purity ≥ 98%) in 0.002% DMSO, concentrations of 0 (blank control), 0 (solvent control), 1, 10, or 100 µg/L from 2 hpf to 24, 48, 72, 96, 120 hpf, 15 dpf and 16 dpf. Only data for treatments between 2 hpf and 120 hpf are reported here. Treatment solution renewed daily. Inhibitor treatments: SU5416, a VEGFR2 inhibitor, at 1 and 3 µM. Sample sizes. For survival and hatching rate, n = 6 tests per treatment and 100 embryos per test. For body length, n = 14 to 33. For body weight, 5 fish as a subgroup. For endogenous alkaline phosphatase activity and mRNA expression, n = 6 samples per treatment. For area of superficial ocular vessels and common cardinal vein, n = 8 embryos per treatment. For blood flow velocity, n = 12 fish per treatment. For lipid distribution from yolk, n = 25 fish.	Survival rate at 24 hpf. Hatching rate at 72 hpf. Body length and weight changes at 24, 48, 72, 96, and 120 hpf. Total angiogenesis measured by endogenous alkaline phosphatase activity at 24 and 48 hpf. mRNA expression of *flk1* and protein level of VEGFR2 at 24, 48, and 72 hpf. Blood flow velocity at 48, 72, and 96 hpf. Intersegmental vessel (ISV) formation (%) at 24 hpf. 48 hpf: Ectopic sprouting of superficial ocular vessels. Superficial ocular vessels area. Common cardinal vein area. 72 hpf: External branching of the sub-intestinal venous plexus (SIVP). Growth rate of embryonic vessels between 24 and 72 hpf. Lipid content in vessels. Co-treatment with SU5416 to evaluate the role of Vegfr2 regulation in BPS-mediated effects on sprouting. 96 hpf: Lipid transport and distribution; and yolk absorption. Lipid distribution / accumulation divided into three grades: First: small number of lipids in blood vessels Second: obvious lipids in the heart, dorsal aorta, and intersection between the dorsal aorta and ISVs. Third: large number of lipids in the ISVs, intersection between the posterior cardinal vein and ISVs, and the second-grade features. mRNA expression of lipidolysis and lipid transport genes: *acox1, p450, lpl, apoea, cd36,* and *mtp;* and endothelium-related genes: *e-sele [sele]* and *icam1.* Ratio of yolk lipid at 120 hpf.	No effects on survival or hatching rates. Body length: Decreased at 24 and 48 hpf. Increased at 120 hpf at all concentrations. Increased at 72 hpf with 1 µg/L. Body weight: Increased at 24 hpf with 10 and 100 µg/L, at 48 hpf with 10 µg/L, at 72 hpf at all concentrations, at 96 hpf with 100 µg/L, and at 120 hpf with 10 and 100 µg/L. Total angiogenesis: Increased at 24 and 48 hpf at all concentrations. mRNA expression of *flk1* and protein level of Vegfr2: Increased *flk1* at 24 and 48 hpf at 100 µg/L; and at 72 hpf at 10 and 100 µg/L. Increased Vegfr2 at 24 (100 µg/L), 48 (1 and 100 µg/L), and 72 (10 and 100 µg/L) hpf. Blood flow velocity: No effects at 48 hpf. Decreased at 72 hpf at 100 µg/L. Decreased at 96 hpf at 1 and 100 µg/L. Effects observed at different hpf: 24 hpf: Decreased % of formed intersegmental vessels at all concentrations. Increased number of ISV branches at 100 µg/L. 48 hpf: Increased superficial ocular vessel sprouting malformation rates at all concentrations. Increased common cardinal vein area at 1 and 100 µg/L. Positive correlation between area of superficial ocular vessels and common cardinal vein. 72 hpf: Increased % of larvae with ectopic sprouting at all concentrations. Increased number and length of ectopic sprouts at 100 µg/L. Increased % vessel growth at all concentrations. Co-treatment with 1 or 3 µM SU5416 inhibited BPS-stimulated increases in branch length

Study Design	Outcomes assessed	Major Findings
		96 hpf: Increased proportion of larvae with lipid accumulation in blood vessels: [Grades 1, 2, and 3] Blank control: [100%, 0%, and 0%], DMSO: [96.4%, 3.6%, and 0%], 1 µg/L: [5.6%, 13.9%, and 80.6%], 10 µg/L: [54.2%, 45.8%, and 0%], 100 µg/L: [42.3%, 46.2%, and 11.5%]. Increased larval yolk cell area and percentage of yolk lipid at all concentrations. mRNA expression: Decreased *apoea* at 1 and 100 µg/L. Decreased *cd36* and *mtp* at 100 µg/L. Increased *e-sele* and *icam1* at 100 µg/L.
Wang et al. 2023 Zebrafish (WT, AB strain), 200 fish per replicate beaker with 6 beakers for each treatment. Treatment: BPS (purity ≥ 98%) in 0.002% DMSO (vehicle control); exposure at 0, 1, 10, and 100 µg/L BPS, for multiple durations beginning at 2 hpf until 24 hpf, 48 hpf, 72 hpf, 96 hpf, 120 hpf, 40 dpf, or 90 dpf. Positive controls: endoplasmic reticulum toxicants - thapsigargin 125 µg/L and tunicamycin 250 µg/L. Behavior: 13 to 14 larvae per replicate and 6 replicates per treatment to determine the free-swimming capability under light Lipid distribution: 3 to 4 zebrafish per replicate and 6 replicates per treatment group randomly collected at 24, 48, and 120 hpf for ORO staining to measure yolk area and positive staining area in the brain; 30−40 embryos or larvae/treatment at 24, 48, and 120 hpf for Nile red staining to measure total integrated density of the yolk and brain. Gene expression analysis: 15 zebrafish per replicate and 6 replicates per treatment. Bip [hspa4]] protein levels: 12 larvae per treatment for brain Bip immunofluorescence staining. 30 larvae per replicate with 3 replicates per treatment for Bip western blot analysis. Only data for treatments between 2 hpf and 120 hpf are reported here.	Hatching rate (48 hpf). Survival rate (120 hpf). Body weight (120 hpf). Body length (120 hpf). Locomotor behavior (locomotor trajectories, total distance traveled, mean velocity, movement time, and quiescent time) under the light-to-dark transition. Lipid yolk consumption via fluorescent lipid analogue (BODIPY FL C16, palmitic acid). Lipid distribution with ORO and Nile red staining. Lipid levels: Triacylglycerol (TAG) and total cholesterol (TC). RNA-seq (48 hpf, 100 µg/L only) Gene expression analysis (48 and 120 hpf): Endoplasmic reticulum stress (*bip* and *perk*). Endoplasmic reticulum -associated degradation (*hsp70, hsp40,* and *hsp90*). Long chain fatty acid (LCFA) metabolism (*fabp7a, fabp7b, acs16,* and *hsd17b12b*). Bip protein levels.	No effects on hatching rate, survival rate, or body weight. Increased body length at all BPS concentrations. Locomotor behavior: Abnormal increased locality in inner zone and back-and-forth movements in all exposure groups. Increased total distance traveled and average speed at 1 µg/L. Decreased movement time at 100 µg/L. Lipid consumption: Increased fluorescence intensity and cross-sectional area in yolk at all exposure groups 6 hours and 24 hours following fluorescent lipid analogue injection. Lipid distribution: Yolk area: Increased in 10 and 100 µg/L groups at 24 hpf and 1 and 100 µg/L groups at 48 hpf. Yolk total integrated density: Decreased in 1 and 100 µg/L groups at 24 hpf and 100 µg/L at 120 hpf. Forebrain visualization: Decreased percentage of embryos with forebrain in all BPS groups. Larval brain lipid distribution: Decreased in all groups at 120 hpf including positive controls. Lipid levels: Larval brain lipid levels: Decreased in all BPS groups at 120 hpf including positive controls. TC: Decreased at 24 hpf and increased at 48 hpf in 1 and 100 µg/L groups. Decreased at 120 hpf in all exposure groups. TAG: Decreased at 120 hpf in 10 and 100 µg/L groups.

Study Design	Outcomes assessed	Major Findings
		LCFAs: Decreased levels in 1, 10, and 100 µg/L BPS at 48 hpf. RNA-seq: 423 DEGs: 121 upregulated and 302 downregulated. KEGG enrichment analysis: Protein processing in endoplasmic reticulum. Gene expression analysis (48 hpf): Endoplasmic reticulum stress (*bip* and *perk*): Increased *perk* in 10 and 100 µg/L groups and decreased *perk* in 1 µg/L group. Increased *bip* in all BPS groups. Endoplasmic reticulum -associated degradation (*hsp70*, *hsp40*, *hsp90*): Increased *hsp70* in all BPS groups. Increased *hsp40* in 10 and 100 µg/L groups. No effect on *hsp90*. LCFA metabolism: Increased *fabp7a* in 10 µg/L group. Increased *fabp7b* in 1, 10, and 100 µg/L groups. Decreased *acsl6* and *hsd17b12b* in 10 and 100 µg/L groups. Gene expression analysis (120 hpf): Endoplasmic reticulum stress: Increased *perk* in all BPS groups. No effect on *bip*. Endoplasmic reticulum-associated degradation: Increased *hsp70* and *hsp90* at 1 µg/L. Increased *hsp40* at 100 µg/L. LCFA metabolism: Decreased *fabp7a* in 10 and 100 µg/L groups. Decreased *acsl6* in all groups. Expression for *hsd17b12b* and *fabp7b* not reported. Bip protein levels (120 hpf): Increased in whole body homogenate at 10 µg/L and in brains at all BPS concentrations. Increased activation of endoplasmic reticulum stress pathways at 48 and 120 hpf.
Wang et al. 2024 Zebrafish (WT, AB strain) 100 fish per tank with 3 tanks for each treatment, repeated 6 times. Treatment: BPS (purity ≥ 98%) in 0.002% DMSO at concentrations of 0 (vehicle control) 1, 10, or 100 µg/L from 2 hpf to 6 dpf. Two-thirds of the treatment water was refreshed daily. Co-exposure experiments: 1 nM glucose transporter 1 (GLUT1) inhibitor BAY 876 added to exposure solution with starter diet at 5.2 dpf for all BPS	3 dpf: Apoptosis in the brain. 6 dpf: Brain Glut1 protein expression. Brain glucose uptake. Brain mitochondrial activity. Apoptosis in the brain (acridine orange staining). Thigmotaxis (or "wall-hugging")-related neurobehavior measured by percentage of time spent in the outer zone in a dark environment.	3 dpf: Increased apoptotic cells at 1 and 100 µg/L BPS. 6 dpf: No effects on brain Glut1 protein expression. Decreased brain glucose uptake at 10 and 100 µg/L BPS, and with 1 nM BAY876. Increased number of active mitochondria at 10 and 100 µg/L BPS, and with 1 nM BAY876. Apoptosis in the brain: Dose-dependent increase at 1 (NS), 10, and 100 µg/L BPS, Increased with 1 nM BAY 876 alone or co-treatment with 1 nM BAY

Study Design	Outcomes assessed	Major Findings
concentrations. 100 larvae per beaker in 4 replicate beakers for each treatment, repeated 4–5 times. Sample sizes: For brain apoptosis, n = 4–6 embryos/larvae per treatment. For brain glut1 expression, n = 6 per treatment. For brain glucose uptake, n = 10 per treatment. For brain mitochondrial activity, n = 7 per treatment. For thigmotaxis assessment, n = 17–20 per treatment. For Ca^{2+} content, n = 4 replicates per treatment with 25 larvae per replicate.	Total Ca^{2+} content.	876 and 1 µg/L BPS. No effects with co-treatment of 1 nM BAY 876 and 10 µg/L BPS. Thigmotaxis-related neurobehavior: Decreased thigmotaxis (increased activity in the inner zone) in all BPS groups and the 1 nM BAY876 group. Largest decrease in thigmotaxis with 100 µg/L BPS and BAY876 co-exposure. Addition of 16 nM FBD to 100 µg/L BPS group restored thigmotaxis. Total Ca^{2+} content: Increased at 1 and 100 µg/L.
Wei et al. 2018 Zebrafish (WT, Tu strain). Treatment: BPS (purity 99%) at 1, 10, and 100 µg/L in 0.002% (v/v) DMSO (vehicle control) from 2 hpf to 120 dpf. F0: 2 hpf to 120 dpf. Each treatment: three replicate beakers containing 150 embryos each. 12 females and 24 males selected to generate F1. F1: 500 eggs (<2 hpf) per replicate with n = 6 replicates for TH measurements. 2000 eggs cultured in the absence of BPS until 96 hpf. Sample sizes: For thyroid hormone levels, n = 6 replicates per treatment with 500 eggs per replicate. For hatching rates, n = 6 replicates per treatment with 100 embryos per replicate. For mRNA expression analysis, n = 6 replicates per treatment with 30–50 embryos or larvae per replicate. For morphology, motility, swimming speed, and lateral stripe pigmentation, n = 20 embryos/larvae per treatment. For the swirl assay, n = 4 replicates per treatment with 80 larvae per replicate. For swim bladder inflation, n = 123–358 larvae.	F1: Thyroid hormone levels (total T3 and T4) in eggs. Hatching rates at 48, 60, and 72 hpf, mRNA expression of zebrafish hatching enzyme (*zhe1*). Morphology (30 hpf embryos): Head-trunk angle. Otic vesicle length. Motility at 48 hpf. Spontaneous movement (times per min). Touch-evoked escape-response. Locomotor activity at 96 hpf. Swimming speed (cm/min). Swirl assay – swirl escape rate. mRNA expression of central nervous system (CNS)-related genes in whole larvae. 96 hpf larvae: Number and average area of lateral stripe melanocytes, mRNA expression of melanocyte morphogenesis (*crestin)* and melanin synthesis (*tyr*) genes. Swim bladder inflation, mRNA expression of genes (*sp-a [lman2], -b [psap],* and *-c [tnmd]*) encoding surfactant protein. Muscle development at 96 hpf. Trunk musculature histology. mRNA expression of myogenic-related genes.	F1: Egg TH levels: T3 increased and T4 decreased in all exposure groups. Hatching rates and related gene expression: 48 and 60 hpf: Decreased in all BPS groups. 72 hpf: Decreased at 10 and 100 µg/L. Decreased *zhe1* expression at 48 hpf in all groups. Morphology. Head-trunk angle: Decreased in all groups. Otic vesicle length: Increased in all groups. Motility. Decreased spontaneous movement and touch-evoked escape-response in all groups. Locomotor activity. Swimming speed: Decreased in all groups. Swirl-escape rate: Decreased in all groups. mRNA expression of CNS-related genes. Decreased *syn2a* at 10 and 100 µg/L. Increased *gfap* in all groups; and *gap43* & *mbp* at 100 µg/L. Lateral stripe pigmentation and related gene expression: Decreased melanocyte numbers at 10 and 100 µg/L and average stripe areas in all groups. Decreased *crestin* expression at 10 and 100 µg/L and *tyr* in all groups. Swim bladder inflation and related gene expression: Decreased percentage of fully inflated bladders and increased percentages of partially or noninflated bladders in all groups. Decreased *sp-a* at 10 and 100 µg/L; and *sp-c* in all groups.

Study Design	Outcomes assessed	Major Findings
		Muscle development. No effects on trunk musculature or mRNA expression of muscular development genes.
Wei et al. 2023 Zebrafish (WT, AB strain), n = 400 embryos/concentration, in triplicate. Treatment: BPS (purity 99%) in 0.002% (v/v) DMSO (vehicle control) at 4 and 400 nM (equivalent to 1.00 and 100.11 µg/L, calculated by OEHHA) from 2 hpf to 120 hpf. Thyroid signaling was investigated using co-exposure with 4 nM BPS and either 1 mg/L 1-850 (antagonist) or 1 nM exogenous T3 (agonist) from 2 hpf to 120 hpf.	Morphology: Body length (24 hpf). Eye length corrected for total body length (24, 48, 72, 96, and 120 hpf). Histopathology (96 and 120 hpf) and immunohistochemistry (120 hpf) of retinal tissue: ganglion cell layer (GCL), inner nuclear layer (INL), inner plexiform layer (IPL), outer nuclear layer (ONL), outer plexiform layer (OPL), retinal pigment epithelium (RPE). Visual behavior analysis (120 hpf): Phototaxis, body color adaptation (lateral stripe melanin levels), visual motor response ([VMR] movement trajectory, total distance, and speed), and distance moved per light/dark period. T4 and T3 levels (120 hpf). Activity of deiodinases (Dio2, Dio3) (120 hpf). Expression of thyroid signaling- (*thra, thrb, dio2, dio3*), thyroid hormone-mediated genes encoding the opsins- (*opn1lw1, opn1lw2, opn1sw1, opn1sw2, opn1mw1, opn1mw2, opn1mw3*), and phototransduction- (*rho, arr3a, pde6a, pde6h, grk1b*) related genes. Thrb antagonist and agonist assessments with 4 nM BPS co-treatment: VMR and gene expression (same genes as above).	Morphology: Body length: Not reported. Relative eye length: Decreased at 24 hpf in both 4 and 400 nM groups; increased at 96 hpf in 4 nM group. Retinal histopathology and immunohistochemistry: Decreased thickness of all retinal layers (GCL, INL, IPL, ONL, OPL, and RPE) at 4 and 400 nM at 120 hpf. Sparse GCL observed in 4 nM group at 120 hpf. Increased expression of Thrb protein in retinal tissues at 400 nM. Visual behavior analysis: Phototaxis: Increased proportion of time staying in half-dark circle at 400 nM. Body color adaptation: Increased lateral stripe melanin under 0-hour light stimulation at 4 nM and 6-, 9-, and 12-hour light stimulation after 4-day dark adaptation at 400 nM. VMR: Induction of hyperactivity at both 4 and 400 nM (increased movement trajectories, total 4-min moving distance, and average speed). Light/dark distance: Increased total distance during one light period at 4 nM and dark periods at 4 (one dark period) and 400 nM. Thyroid hormone levels: Decreased total T3 at 4 and 400 nM. Increased total T4 at 4 nM. Deiodinase activity: Increased Dio2 and Dio3 activity at 4 and 400 nM. mRNA expression of thyroid signaling related genes: Increased *thra, thrb*, and *dio3* and decreased *dio2* at 400 nM. mRNA expression of opsin genes: *opn1sw1*: increased at 4 nM, decreased at 400 nM. *opn1lw1, opn1lw2*, *opn1mw2*: decreased at 4 and 400 nM. *opn1mw1, opn1mw3, opn1sw2*: decreased at 400 nM. mRNA expression of phototransduction-related genes: *rho, pde6a*: decreased at 4 nM and increased at 400 nM,. *arr3a, pde6h, grk1b*: increased at 4 nM and decreased at 400 nM.

Study Design	Outcomes assessed	Major Findings
		Thrb antagonist and agonist assessments with 4 nM BPS co-treatment: VMR: T3 (agonist) co-treatment: Attenuated BPS-mediated increased moving distances in first- and third- minute light phases, second- and fourth- minute dark phases, and 4-minute light-to-dark stimulation period. 1-850 (antagonist) co-treatment: No effects. mRNA expression: T3 co-treatment: Compensated for BPS-mediated decreases in *opn1mw2* and *opn1lw1*, and attenuated BPS-mediated increases in *opn1sw1, arr3a,* and *pde6h*. 1-850 co-treatment: No effects. Compensation for BPS-mediated decreases in *opn1mw2, opn1lw1, opn1lw2,* and *pde6a*, and attenuated BPS-mediated increases in *opn1sw1* and *arr3a*.
Xiao et al. 2019 *C. elegans*, WT, N2 strain, L4-larvae. Treatment: BPS (purity ≥ 98%) in 0.1% absolute ethanol/M9 buffer (vehicle control) at concentrations of 0, 0.001, 0.01, 0.1, 1, 10 and 100 µM BPS (equivalent to 0.25, 2.50, and 25.03, 250.27 µg/L and 2.50 and 25.03 mg/L, calculated by OEHHA) for 24 hours (L4-larval stage to day 1). Reproduction assay: Exposure followed by daily transfer to a fresh plate until reproduction ceased; offspring counted at L3 stage. Lifespan assay: Exposure followed by daily transfer onto fresh plates from day 1 to day 4, with transfer every 2 days starting from day 5. Surviving *C. elegans* counted daily from first day of adulthood. Multi-generational experiment: BPS exposure for four successive generations (G1, G2, G3, G4). LC_{50} = 2.18 mM.	Acute exposure assessment: Lethality, locomotion, growth, reproduction assay, and lifespan. Antioxidant system: ROS and SOD production. Multi-generational acute exposure assessment: Locomotion behavior; growth; and reproduction.	Acute exposure assessment: Lethality: No mortality up to 0.25 mM for 24 hours. Locomotion behavior: Most negative effects at 100 µM; decreased head thrashes at ≥0.01 µM (-12-17%) and body bends (-9-20%) at all concentrations (NS at 0.001 and 0.1 µM). Growth: Body length decreased at ≥0.01 µM (-15%). Reproduction: brood size decreased at ≥0.01 µM (-35-45%).Lifespan: decreased in 0.01 (21 days), 0.1 (21 days), 1 (20 days), 10 (20 days) and 100 (18 days) µM exposures compared to controls (24 days). Antioxidant systems: ROS increased and SOD decreased at ≥ 0.01 µM Multi-generational assessments. Locomotion behavior: Head thrashes Decreased in all generations compared to control at ≥ 0.01 µM . Body bends: Decreased at 0.01 (G1-3), 0.1 (G2), 1 (G1), 10 (G1-3), and 100 (G1-2) µM . Body length: Decreased in all generations compared to control at ≥ 0.01 µM. Smaller decrements in body length at G4 compared to G1-G3 in 0.01, 10, and 100 µM groups. No change at G4 in 0.1 and 1 µM groups. Reproduction: No differences in magnitude of decreased brood size at G1 compared to G4 at 0.01, 0.1, 10, and 100 µM groups. Increased

Study Design	Outcomes assessed	Major Findings
		brood size at G4 compared to G1 in 1 µM group but brood sizes remained decreased compared to control.
Yang et al. 2018 Zebrafish (WT, AB strain) n = 50 embryos per dish, with n = 3 biological replicates per concentration. Treatment: BPS (purity not reported) in < 0.01% DMSO (vehicle control) in E3 embryo media at 0, 0.1, 1, 10, 100, or 1000 µg/L from 4 hpf to 120 hpf. Outcomes assessed at 120 hpf.	Survival rate (%). Body length (in mm). ROS and NO levels. Transcriptome analysis from RNA-seq data: DEGs with $\|\log_2$ fold-change$\|$ > 0.5 and adjusted p-value <0.05, compared to controls. Pathway enrichment analyses (using KEGG). Gene sets related to body length, ROS, and NO levels using weighted gene co-expression network analysis (WGCNA). Protein-protein interaction (PPI) network using STRING database; and identification of hub genes and their subcellular locations. Molecular docking analysis to evaluate potential interactions between hub genes and BPS.	No effects on survival rate. Decreased body length at 100 and 1000 µg/L. Increased ROS and NO levels at 100 and 1000 µg/L. Transcriptome analysis from RNA-seq data: DEGs: 1803, 3029, 3979, 3786, and 2421 DEGs at 0.1, 1, 10, 100, and 1000 µg/L BPS; 67 DEGs overlapped across all five treatment groups. Enriched pathways: 64, 17, 72, 84, and 42 KEGG pathways at 0.1, 1, 10, 100, and 1000 µg/L BPS; 15 overlapping pathways, with Metabolic pathways as the top term. WGCNA: FoxO and MAPK signaling pathways, endocytosis, and metabolic pathways significantly enriched in KEGG database; MAPK signaling and metabolic pathways present in both DEG and WGCNA analyses. PPI network and hub gene identification: six hub genes (subcellular localization); *erbb2* (transmembrane); *rrm2* and *rps27a* (cytoplasmic); *his2h3c*, *cdk1*, and *mcm5* (nuclear). Interactions between hub genes and BPS: *erbb2* predicted to interact with BPS with three hydrogen bonds.
Zhang et al. 2022 Zebrafish embryos (genetically modified (*tg*) *(flk1: eGFP), tg (cmlc2: eGFP)* and *tg (gata1a: DsRed)* or wild-type AB strain), n = 150 total embryos per concentration. Treatment: BPS (≥ 98% purity) in 0.002% DMSO (vehicle control) at 0, 1, 10 or 100 µg/L from 2 hpf to 24, 48 and 72 hpf. Embryos at 48 hpf (3 replicate samples/treatment, 30 embryos/sample) in control and 1 µg/L BPS group collected for RNA-seq analysis.	Common cardinal vein (CCV) development (24, 48 and 72 hpf). Heart function (72 hpf): Heart rate, pericardial edema rate, heart bleeding rate, heart rhythm, and blood clots. Blood flow pattern. Transcriptome analysis.	CCV development: Increased CCV growth rate from 24-48 hpf at all doses. Decreased CCV reduction ratio for lumen formation at 48 and 72 hpf at all doses. Decreased number of endothelial cells (ECs) within CCV at 10 µg/L and 100 µg/L at 24 hpf. Heart function: Increased heart rate in 10 and 100 µg/L at 72 hpf. No effect: Pericardial edema rate, heart bleeding rate, heart rhythm, and blood clots. Blood flow pattern: Increased dynamic erythrocyte fluorescence intensity in the heart and tail and number of red blood cells in the tail vein at 10 µg/L and 100 µg/L at 72 hpf. Increased static relative erythrocyte numbers in the heart in all treatment groups at 72 hpf. Transcriptome analysis: Total: 189 genes upregulated and 219 genes downregulated. CCV: EC proliferation, growth, and migration genes (*tie2*, *atf3*, *cdh5*,

Study Design	Outcomes assessed	Major Findings
		and *vegfaa*) were downregulated at 48 hpf with 1 µg/L treatment. Cardiac muscle contraction pathway: Na^{+}-K^{+} and Ca^{2+} pump genes (*cacna2sa*, *cacna2d1a*, and *cacna1sb*) were upregulated at 48 hpf with 1 µg/L treatment. Other enriched pathways: Oxidative phosphorylation pathway, carbon metabolism pathway, and endoplasmic reticulum protein processing pathway.

4.3 Mechanistic Considerations and Other Data Relevant to Developmental Toxicity

This section presents *in vivo*, *in vitro*, and epidemiologic mechanistic evidence relevant to the effects of BPS on development. This includes prenatal, embryonic, early larval, and/or parental BPS exposure in organisms, or BPS treatment of embryonic/fetal cells. Study findings are generally summarized and organized first by the type and direction of effects, followed by species (ordered from human, mouse, rat, other mammalian species, non-mammalian species), and lastly exposure period for *in vivo* studies (ordered from gestation through adulthood). When applicable, *in vivo* findings are presented first, followed by *in vitro* findings. BPS concentrations or dosages listed in the summaries are those at which effects were observed. Summary tables are included throughout this section to provide an overview of BPS effects on specific enzymes, genes, and other proteins across all studies. All effects are significant ($p \leq 0.05$) unless otherwise noted (e.g., not significant [NS]). Magnitude of effects can be found, when available, along with further study details in the respective Table for each subsection.

When discussing BPS-related effects on expression of genes and proteins, only studies reporting changes are summarized in the text of this section. More detailed information on each study's findings (i.e., increases, decreases, or no changes) on gene or protein expression is included, when available, in the summary tables under the relevant sections. In some instances, gene and protein expression findings will be provided in the text and not in a summary table (e.g., in the "Other Organelle and Sub-cellular Effects" and "Toxicogenomics" sections).

Relevant studies are summarized in this section, and tabulations of the results on whole animals are located in either Tables 4.2.1 (mammalian studies) and 4.2.2 (non-mammalian studies), or in Tables 4.3.13 (studies with mechanistic data not already included in Tables 4.2.1 and 4.2.2). Epidemiology studies with molecular data are summarized in Table 4.3.14.

4.3.1 Early Embryonic and Extraembryonic Effects

Development of the embryo and its supporting extraembryonic tissues/substances (e.g., placenta, amnion, amniotic fluid) requires tightly coordinated molecular signaling. Perturbations to these processes can have significant impacts on early developmental events such as implantation and proper establishment of the placenta and extraembryonic tissues.

The following is a list of supporting evidence for BPS-mediated effects on the early embryonic stage and extraembryonic tissues:

- Decreased blastocyst attachment rate in an *in vitro* model of human implantation, using human choriocarcinoma JEG-3 cell spheroids and human endometrial adenocarcinoma cells (Ishikawa cells), where the Ishikawa cells were exposed to 100 µM BPS for 24 hours (H Fan et al. 2021).

- Increased pluripotency markers *NANOG, OCT4, SOX2, ESG1,* and *OVOL1* in human amniotic fluid stem cells (hAFSCs) incubated with 0.1 µM BPS for 24 to 48 hours (Di Credico et al. 2023).

- Altered pluripotency markers with decreased *KLF4* and increased *OVOL1* in human fetal membrane mesenchymal stem cells (hFM-MSCs) incubated with 0.1 µM BPS for 24 to 48 hours (Di Credico et al. 2023).

- Accelerated embryo development with hatched blastocysts in bovine cumulus-oocyte complexes (COCs) used for *in vitro* fertilization (IVF) and treated with 0.05 mg/mL BPS for 24 hours (Sabry et al. 2021a).

- Decreased expression of ectodermal markers *KRT14* and *OTX2* with no effects on endodermal or mesodermal gene markers in human embryonic stem cell-derived three-dimensional embryoid bodies incubated with 100 nM BPS for 21 days (X Liang et al. 2021).

One study found no effect on embryonic development rate in bovine cumulus-oocyte complexes (Sabry et al. 2021b).

The placenta has multiple essential functions during *in utero* development, including endocrine and metabolic functions. Trophoblasts, the major placental cells, are key in establishing the uteroplacental and fetoplacental networks. Molecules such as epidermal growth factor (EGF) are important for regulating placental growth and trophoblast differentiation. Disruption of trophoblast or placental function by environmental toxicants can adversely impact embryo/fetal development and maternal health.

There is *in vivo* and *in vitro* evidence that BPS disrupts placenta/trophoblast function in mice, rats, human primary trophoblasts, and a human trophoblast cell line. The following effects were observed:

- Decreased stearic, palmitic, docosahexaenoic, octadecenoic, and hexadecenoic acids; increased dopamine-positive trophoblast giant cells and dopamine concentration; and decreased serotonin-positive trophoblast giant cells and serotonin concentration in gestational day (GD) 12.5 placentae of

pregnant C57BL/6J mice administered 200 µg/kg-day BPS for a two-week pre-mating period (Mao et al. 2020).

- Decreased DNA methylation in 6 out of 24 CpG sites in the promoter region of steroid receptor coactivator 2 (*Src2*) at 0.025 µg/kg-day, and identification of five differentially expressed genes, *LOC103689945, Fut2, Nxpe1* at both doses and *Wnt7b* and *Aabr07002659.1* at 0.025 µg/kg-day in placental tissue of GD 18 female fetuses of Wistar rats orally administered 0.025 or 4 µg/kg-day BPS from one week premating until GD 18 (Fudvoye et al. 2025).

- Decreased EGF internalization in human primary term cytotrophoblasts incubated with 1 and 10 µg/mL BPS for approximately 1 hour (Ticiani et al. 2021).

- Decreased phosphorylated EGF receptor (p-EGFR) in the human extravillous trophoblast cell line (HTR-8/SVneo) co-incubated with 1 µg/mL BPS and EGF for 15 minutes (Ticiani et al. 2022).

- Decreased EGF internalization in the HTR-8/SVneo cell line co-incubated with 1 (NS) and 10 µg/mL BPS and EGF for 5 minutes (Ticiani et al. 2022).

- Inhibited EGF-mediated proliferation at 1 µg/mL BPS for 4–6 days, cell invasion at 0.1 and 1 µg/mL BPS for 16 hours, and endovascular trophoblast differentiation at 1 µg/mL BPS for 18 hours, with decreased total network length, total segment length, mesh size, nodes, junctions, and segments in the HTR-8/SVneo cell line (Ticiani et al. 2022).

- Dose-dependently decreased EGF- EGFR binding signal in a BPS/EGFR competitive binding assay (Ticiani et al. 2021)

4.3.2 Oxidative Stress

Oxidative stress results from an imbalance of reactive oxygen species (ROS) and antioxidants. Physiological levels of ROS play an important role in embryonic and fetal development (Dennery 2007). However, excessive ROS levels and the resulting oxidative stress can result in damage to DNA, RNA, proteins, and lipids, potentially leading to a variety of downstream adverse apical effects.

There is substantial *in vivo* and *in vitro* evidence that BPS induces oxidative stress in rodent ovarian and testicular tissue; mouse embryos; zebrafish (*Danio rerio*), *Drosophila*, and *C. elegans* whole body homogenate; zebrafish eyes; a human umbilical vein endothelial cell line; and primary chicken embryonic hepatocytes. Additionally, one

epidemiologic study identified associations between prenatal BPS exposure and two markers of oxidative stress (see Table 4.3.14).

ROS production was increased by BPS in mouse ovarian tissue, mouse embryos, rat testicular tissue, zebrafish, *Drosophila*, *C. elegans*, a rat embryonic cardiac cell line, a human choriocarcinoma cell line (JEG-3), and human umbilical vein endothelial cells (HUVECs). Specifically, increased ROS production was observed in:

- Ovarian tissue of PND 4 ICR mice offspring exposed to 3.33 µg/L BPS via drinking water from GD 8.5 to PND 3, with attenuation of effect with co-treatment of BPS and the mammalian target of rapamycin (mTOR) antagonist, rapamycin (Gao et al. 2024).

- ICR mouse IVF embryos exposed to 100 µM BPS and cultured until the 2-cell (24 hours) and 4-cell (48 hours) stages, with attenuation of effect with co-treatment of BPS and superoxide dismutase (SOD) (Ning et al. 2023).

- Testes of PND 80 offspring of SD rats administered 50 µg/L BPS via drinking water from GD 1 to GD 20 (Ullah et al. 2019).

- Whole body homogenate of wildtype (WT) zebrafish exposed to 100 or 1000 µg/L BPS from 4 hpf to 120 hpf (Qiu et al. 2018).

- Whole body homogenate of WT AB strain zebrafish exposed to 100 or 1000 µg/L BPS from 4 hpf to 120 hpf (Yang et al. 2018).

- Whole body homogenate of *Drosophila* F1 third instar stage larval offspring of parental flies exposed to 0.5 or 1 mM BPS via diet for a seven-day breeding period (Santos Musachio et al. 2023).

- Whole body homogenate of *C. elegans* exposed to 0.01, 0.1, 1, 10, or 100 µM BPS from L4 larval stage to adult day 1 (Xiao et al. 2019).

- A rat embryonic cardiac cell line (H9c2) incubated with 10 and 100 µM BPS for up to 26 hours, with attenuation of effects at both concentrations with N-acetyl-L-cysteine (NAC), an oxidative stress inhibitor, and at 100 µM BPS with pyrrolidine dithiocarbamate (PDTC), an NF-κB inhibitor (Luo et al. 2023).

- JEG-3 human choriocarcinoma cells incubated for 4, 6, and 12 hours with 50 µM BPS, with attenuation of effects with NAC co-treatment (Z Li et al. 2023).

- HUVECs incubated with 10 and 100 μM BPS for up to 26 hours, with attenuation of effects at both concentrations with NAC and at 100 μM BPS with PDTC (Luo et al. 2023).

- HUVECs incubated with 300 mg/L BPS for 24 hours (Ji et al. 2022).

No effects on ROS levels were reported in:

- Two studies in WT zebrafish incubated with up to 30 mg/L BPS (Huang et al. 2023; Ji et al. 2022).

- Mouse embryonic fibroblasts incubated with up to 500 μM BPS for 24 hours (Hyun et al. 2021).

- *C. elegans* exposed to 1 mM BPS from L1 larval stage to 3-day-old adults (Hyun et al. 2021).

There was an increase in lipid peroxidation by BPS in mouse ovarian tissue, rat testicular tissue, zebrafish, *Drosophila*, and the JEG-3 choriocarcinoma cell line as detailed below:

- Ovarian tissue of PND 4 offspring of ICR mice administered 3.33 μg/L BPS via drinking water from GD 8.5 to PND 3, with attenuation of effect with co-treatment of BPS and rapamycin (Gao et al. 2024).

- Testes of PND 80 offspring of SD rats administered 50 μg/L BPS via drinking water from GD 1 to GD 20 (Ullah et al. 2019).

- Whole body homogenate of WT zebrafish exposed to 1000 μg/L BPS from 4 hpf to 120 hpf (Qiu et al. 2018).

- Whole body homogenate of *Drosophila* F1 third instar stage larval offspring of parental flies administered 0.5 or 1 mM BPS for a seven-day breeding period (Santos Musachio et al. 2023).

- JEG-3 cells incubated with 50 μM BPS for 12 hours (Z Li et al. 2023).

One epidemiologic study (see Table 4.3.14), using data from the LIFECODES cohort, reported a statistically significant association between increased urinary BPS and increased urinary 8-isoprostane (a peroxidation product of the polyunsaturated fatty acid arachidonic acid, and thus a marker of lipid peroxidation and oxidative stress) levels, both measured across four timepoints during pregnancy (Ferguson et al. 2019).

Two studies in WT zebrafish found no effects on lipid peroxidation up to 30 mg/L (Huang et al. 2023; Ji et al. 2022).

Key components of the antioxidant system were altered by BPS in mouse ovarian tissue, rat testicular tissue, zebrafish, *Drosophila*, and *C. elegans.* Effects were mixed (i.e., increased or decreased) depending on the timing and dose, likely due to a response to an acute or chronic oxidative challenge or that of an overwhelmed antioxidant system.

Decreased glutathione peroxidase (GPX) and general peroxidase levels were observed in:

- Ovarian tissue of PND 4 offspring of ICR mice administered 3.33 µg/L BPS via drinking water from GD 8.5 to PND 3, with attenuation of effect with co-treatment of BPS and rapamycin (Gao et al. 2024).
- Testes of PND 80 offspring of SD rats administered 25 or 50 µg/L BPS via drinking water from GD 1 to GD 20 (Ullah et al. 2019).
- Whole body homogenate of WT zebrafish exposed to 1 µM BPS from 0.5 hpf to 120 hpf (Huang et al. 2023).

Increased glutathione-S-transferase (Gst) activity was observed in the whole body homogenate of *Drosophila* F1 third instar stage larval offspring of parental flies administered 0.25, 0.5, or 1 mM BPS via diet for a seven-day breeding period (Santos Musachio et al. 2023).

Altered superoxide dismutase (SOD) activity:

Decreased in:

- Ovarian tissue of PND 4 offspring of ICR mice administered 3.33 µg/L BPS via drinking water from GD 8.5 to PND 3, with attenuation of effect with co-treatment of BPS and rapamycin (Gao et al. 2024).
- Testes of PND 80 offspring of SD rats administered 50 µg/L BPS via drinking water from GD 1 to GD 20 (Ullah et al. 2019).
- Whole body homogenate of WT AB strain zebrafish exposed to 3 mg/L BPS from 2 hpf to 6 dpf (Gu et al. 2019).
- Whole body homogenate of *C. elegans* exposed to 0.01, 0.1, 1, 10, or 100 µM BPS from L4 larval stage to adult day 1 (Xiao et al. 2019).

- JEG-3 cells incubated with 50 μM BPS for 4, 6 (NS), and 12 hours (Z Li et al. 2023).

Increased in:

- Whole body homogenate of WT AB strain zebrafish exposed to 0.3 mg/L BPS from 2 hpf to 6 dpf (Gu et al. 2019).
- Whole body homogenate of WT zebrafish exposed to 100 or 1000 μg/L BPS from 4 hpf to 120 hpf (Qiu et al. 2018).
- Whole body homogenate of *Drosophila* F1 third instar stage offspring of parental flies exposed to 0.5 or 1 mM BPS via diet for a seven-day breeding period (Santos Musachio et al. 2023).
- *C. elegans* exposed to 1 mM BPS from L1 larval stage to 2-day-old adults (Hyun et al. 2021).

Two studies in WT zebrafish found no effects on SOD activity up to 30 mg/L (Huang et al. 2023; Ji et al. 2022).

Altered catalase (CAT) activity:

Decreased in:

- Ovarian tissue of PND 4 offspring of ICR mice administered 3.33 μg/L BPS via drinking water from GD 8.5 to PND 3, with attenuation of effect with co-treatment of BPS and rapamycin (Gao et al. 2024).
- Testes of PND 80 offspring of SD rats administered 50 μg/L BPS via drinking water from GD 1 to GD 20 (Ullah et al. 2019).

Increased in whole body homogenate of:

- WT AB strain zebrafish exposed to 0.3 mg/L or 3 mg/L BPS from 2 hpf to 6 dpf (Gu et al. 2019).
- WT AB strain zebrafish exposed to 30 mg/L BPS from 2 hpf to 72 hpf (Ji et al. 2022).
- WT zebrafish exposed to 1000 μg/L BPS from 4 hpf to 120 hpf (Qiu et al. 2018).

- *Drosophila* F1 third instar stage larval offspring of parental flies exposed to 0.5 or 1 mM BPS via diet for a seven-day breeding period (Santos Musachio et al. 2023).

One study in WT zebrafish found no effect on Cat activity (Huang et al. 2023).

BPS altered the expression of oxidative stress-related genes in mouse ovarian and testicular tissue, mouse embryos, zebrafish whole body and eyes, and primary chicken embryonic hepatocytes (see Table 4.3.1). Specifically, gene expression was altered in:

- Ovarian tissue of PND 4 offspring of ICR mice administered 3.33 µg/L BPS via drinking water from GD 8.5 to PND 3, with attenuation of effect with co-treatment of BPS and the mTOR antagonist rapamycin (Gao et al. 2024).

- Testes of PND 60 male offspring of CD-1 mice treated with 0.5, 20, or 50 µg/kg-day BPS from GD11 until birth (Shi et al. 2018).

- ICR mouse IVF embryos exposed to 0.001, 1, or 100 µM BPS and cultured until 2-cell (24 hours) and 4-cell (48 hours) stages; co-treatment of BPS with SOD resulted in some attenuation of the effect observed with BPS alone(Ning et al. 2023).

- Whole body homogenate of 96 hpf offspring of WT AB strain zebrafish exposed to 10 µg/L BPS from 24 hpf until spawning with and without subsequent offspring BPS exposure from 24 hpf to 96 hpf (Dong et al. 2018).

- Whole body homogenate of WT zebrafish exposed to 50 µM BPS from 0.5 hpf to 120 hpf (Huang et al. 2023).

- Eyes of WT Tu strain zebrafish exposed to 100 µg/L BPS from 2 hpf to 5 dpf (Qiu et al. 2023b).

- Whole body homogenate of WT zebrafish exposed to 4 mg/L BPS from 6–10 hpf to 96 hpf (Neighmond et al. 2023).

- Whole body homogenate of male offspring of wildtype female zebrafish exposed to 1, 10, or 30 µg/L BPS for 60 days prior to mating with untreated males (Salahinejad et al. 2022).

- Primary chicken embryonic hepatocytes incubated with 300 µM BPS for 36 hours (Ma et al. 2015).

BPS altered the level of oxidative stress-related proteins (see Table 4.3.2) in the ovarian tissue of PND 4 offspring of ICR mice administered 3.33 µg/L BPS via drinking water from GD 8.5 to PND 3. These effects were attenuated with co-treatment of BPS and rapamycin (Gao et al. 2024).

BPS increased the phosphorylation of Nuclear Factor kappa B (NFKB) in rat embryonic cardiac cells (H9c2 cells) and HUVECs incubated with 100 µM BPS for up to 26 hours. Attenuation of effects were observed with co-treatment with NAC (Luo et al. 2023).

Table 4.3.1 BPS effects on oxidative stress-related gene expression.

Gene	System	Exposure Method	Treatment Conditions	Tissue	Direction	Reference
adprhl2	Zebrafish, 5 dpf	Aqueous environment	100 µg/L; 2 hpf–5 dpf	Eyes	Increased	Qiu et al. 2023b
Cat	F1 female ICR mice, PND 4	Oral (drinking water)	3.33 µg/L; GD 8.5–PND 3	Ovary	Decreased	Gao et al. 2024
Cat	F1 male CD-1 mice, PND 60	Oral (pipette)	0.5 and 20 µg/kg-day; GD 11–birth	Testes	Decreased	Shi et al. 2018
cat	F1 zebrafish, 96 hpf	Aqueous environment	10 µg/L; (F0) 24 hpf–spawning with and without (F1) 24 hpf–96 hpf exposure	Whole body	Decreased	Dong et al. 2018
cat	Zebrafish, 120 hpf	Aqueous environment	50 µM; 0.5 hpf–120 hpf	Whole body	Decreased	Huang et al. 2023
cat	F1 male zebrafish, 6 months	Aqueous environment	1, 10, and 30 µg/L; (F0 female) 60 days prior to mating	Whole body	Decreased	Salahinejad et al. 2022

Gene	System	Exposure Method	Treatment Conditions	Tissue	Direction	Reference
cu/zn-sod	F1 zebrafish, 96 hpf	Aqueous environment	10 µg/L; (F0) 24 hpf–spawning with and without (F1) 24 hpf–96 hpf exposure	Whole body	Decreased	Dong et al. 2018
cyba	Zebrafish, 5 dpf	Aqueous environment	100 µg/L; 2 hpf–5 dpf	Eyes	Increased	Qiu et al. 2023b
Glrx2	F1 female ICR mice, PND 4	Oral (drinking water)	3.33 µg/L; GD 8.5–PND 3	Ovary	Decreased	Gao et al. 2024
Gpx1	F1 female ICR mice, PND 4	Oral (drinking water)	3.33 µg/L; GD 8.5–PND 3	Ovary	Decreased	Gao et al. 2024
Gpx1	IVF ICR mouse embryos	Culture medium	100 µM; 24–48 hours	2- and 4-cell embryos	Increased	Ning et al. 2023
Gpx4	F1 male CD-1 mice	Oral (pipette)	0.5 µg/kg-day; GD 11–birth	Testes	Decreased	Shi et al. 2018
gpx4a	Zebrafish, 5 dpf	Aqueous environment	100 µg/L; 2 hpf–5 dpf	Eyes	Increased	Qiu et al. 2023b
gpx4b	Zebrafish, 5 dpf	Aqueous environment	100 µg/L; 2 hpf–5 dpf	Eyes	Increased	Qiu et al. 2023b
Gpx6	IVF ICR mouse embryos	Culture medium	100 µM; 24–48 hours	2- and 4-cell embryos	Increased	Ning et al., 2023

Gene	System	Exposure Method	Treatment Conditions	Tissue	Direction	Reference
Gst	F1 *drosophila*, third instar stage	Oral (diet)	0.25, 0.5, and 1 mM; (F0) 7 days, (F1) 0–4 days	Whole body	Decreased	Santos Musachio et al. 2023
gsto1	Zebrafish, 96 hpf	Aqueous environment	4 mg/L; 6 hpf–96 hpf	Whole body	Increased	Neighmond et al. 2023
lyz	F1 zebrafish, 96 hpf	Aqueous environment	10 µg/L; (F0) 24 hpf–spawning with and without (F1) 24 hpf–96 hpf exposure	Whole body	Increased	Dong et al. 2018
mn-sod	F1 zebrafish, 96 hpf	Aqueous environment	10 µg/L; (F0) 24 hpf–spawning with and without (F1) 24 hpf–96 hpf exposure	Whole body	Decreased	Dong et al. 2018
mn-sod	F1 male zebrafish, 6 months	Aqueous environment	30 µg/L; (F0 female) 60 days prior to mating	Whole body	Decreased	Salahinejad et al. 2022
MT4	White leghorn chicken primary embryonic hepatocytes	Culture medium	300 µM; 36 hours	Liver	Increased	Ma et al. 2015
Nd1	IVF ICR mouse embryos	Culture medium	1 and 100 µM; 24–48 hours	2- and 4-cell embryos	Decreased	Ning et al. 2023

Gene	System	Exposure Method	Treatment Conditions	Tissue	Direction	Reference
park7	Zebrafish, 5 dpf	Aqueous environment	100 µg/L; 2 hpf–5 dpf	Eyes	Increased	Qiu et al. 2023b
prdx1	Zebrafish, 5 dpf	Aqueous environment	100 µg/L; 2 hpf–5 dpf	Eyes	Increased	Qiu et al. 2023b
Prdx2	IVF ICR mouse embryos	Culture medium	0.001, 1, and 100 µM; 24–48 hours	2- and 4-cell embryos	Increased	Ning et al. 2023
prdx2	Zebrafish, 5 dpf	Aqueous environment	100 µg/L; 2 hpf–5 dpf	Eyes	Increased	Qiu et al. 2023b
prost1.2	Zebrafish, 96 hpf	Aqueous environment	4 mg/L; 6 hpf–96 hpf	Whole body	Increased	Neighmond et al. 2023
Sod1	F1 male CD-1 mice, PND 60	Oral (pipette)	20 µg/kg-day; GD 11–birth	Testes	Increased	Shi et al. 2018
Sod1	IVF ICR mouse embryos	Culture medium	100 µM; 24–48 hours	2- and 4-cell embryos	Increased	Ning et al. 2023
sod1	Zebrafish, 5 dpf	Aqueous environment	100 µg/L; 2 hpf–5 dpf	Eyes	Increased	Qiu et al. 2023b
Sod2	F1 male CD-1 mice, PND 60	Oral (pipette)	0.5, 20, 50 µg/kg-day; GD 11–birth	Testes	Decreased	Shi et al. 2018
sod2	Zebrafish, 5 dpf	Aqueous environment	100 µg/L; 2 hpf–5 dpf	Eyes	Increased	Qiu et al. 2023b

Table 4.3.2 BPS effects on oxidative stress-related protein levels.

Protein	System	Exposure Method	Treatment Conditions	Tissue	Direction	Reference
GPX1	F1 female ICR mice, PND 4	Oral (drinking water)	3.33 µg/L; GD 8.5–PND 3	Ovaries	Decreased	Gao et al. 2024
CAT	F1 female ICR mice, PND 4	Oral (drinking water)	3.33 µg/L; GD 8.5–PND 3	Ovaries	Decreased	Gao et al. 2024
SOD1	F1 female ICR mice, PND 4	Oral (drinking water)	3.33 µg/L; GD 8.5–PND 3	Ovaries	Decreased	Gao et al. 2024

4.3.3 Genetic Damage

Environmental toxicants can cause genetic damage during development either directly or through processes such as oxidative stress. DNA repair mechanisms in the embryo are particularly important during early development as rapidly dividing cells are transitioning from relying on mRNA transcripts from the maternal genome to transcripts from the embryo's own (zygotic) genome. DNA repair is especially important in stabilizing and controlling the integrity of embryonic chromatin. Disruption to DNA repair mechanisms can increase the chance of adverse *de novo* mutations and downstream apoptosis from unrepaired DNA damage (Ménézo et al. 2010).

One epidemiologic study (see Table 4.3.14), using data from the LIFECODES cohort, reported a marginally significant association between urinary BPS levels and urinary 8-hydroxydeoxyguanosine (8-OHdG), a biomarker of oxidative damage to DNA, both measured across four timepoints during pregnancy (Ferguson et al. 2019).

One study in *C. elegans* observed decreased expression of DNA damage response- and checkpoint activation-related genes in *C. elegans* exposed to 500 µM BPS from larval stage 1 to 24 hours post-larval stage 4 (Chen et al. 2016).

4.3.4 Epigenetic Alterations

Epigenetics refers to the regulation of gene expression through heritable and stable modifications that do not involve changes to the DNA sequence. Epigenetic processes, including DNA/RNA methylation, post-translational histone modification, chromatin packaging, and regulation of gene expression by non-coding RNAs (e.g., microRNAs), affect the activity and availability of DNA for expression (Arzuaga et al. 2019; Donkin and Barrès 2018). Epigenetic processes play an essential role in every stage of development, including in cellular differentiation and organogenesis, among others. For example, DNA methylation and demethylation is critical during germ cell development and early embryogenesis (Gopinathan and Diekwisch 2022).

There is evidence that BPS induces epigenetic alterations, including DNA and histone methylation and changes in the expression of genes and protein levels involved in epigenetic processes, in mice and zebrafish, human fetal membrane mesenchymal stromal cells, and human amniotic fluid stem cells. Additionally, one epidemiologic study evaluated the association between urinary BPS during gestation and the placental DNA methylation of 99 cytosine-guanine dinucleotide (CpG) sites present across four reproduction-related genes.

BPS induced alterations in DNA methylation, histone methylation, or DNA methyltransferase localization in the gonadal tissue of mice and zebrafish. Specifically, the following effects were observed:

- Aberrant localization of the methylation protein DMNT3B in the testes of F3 PND 6 male descendants of F0 CD-1 mice administered 0.5 or 50 µg/kg-day BPS via oral pipetting from GD 7 until birth (Shi et al. 2019b).
- Altered histone methylation levels in the oocytes of 5-week-old offspring of ICR mice orally administered 2 or 10 µg/kg-day BPS from GD 12.5 to GD 15.5 (MY Zhang et al. 2020).
- Increased DNA methylation in the testes of untreated 120 dpf F1 offspring of WT AB strain F0 zebrafish exposed to 100 µg/L BPS from 3 hpf to 120 dpf (Hao et al. 2022).
- Increased DNA methylation in the ovaries of untreated 120 dpf WT AB strain F2 descendants of F0 zebrafish exposed to 1 µg/L BPS from 3 hpf to 120 dpf (Hao et al. 2022).

One epidemiologic study (see Table 4.3.14) evaluated data from the Shanghai-Minhang Birth Cohort Study and reported no statistically significant associations between urinary BPS during pregnancy and placental CpG methylation in 99 CpG sites from four reproduction-related genes: *FGF13*, *PCDH8, RBMXL2*, and *SPACA1* (J Chen et al. 2024).

BPS altered the expression of several genes involved in DNA and histone methylation and demethylation and other epigenetic processes in mouse testicular tissue, zebrafish gonadal tissue and whole body, human fetal membrane mesenchymal stromal cells, and human amniotic fluid stem cells (see Table 4.3.3). Specifically, gene expression was altered in the:

- Testes of F3 PND 6 descendants of F0 CD-1 mice administered 50 µg/kg-day BPS via oral pipetting from GD 7 until birth (Shi et al. 2019b).
- Testes of F1 PND 60 offspring of CD-1 mice administered 0.5, 20, or 50 µg/kg-day BPS via oral pipetting from GD 11 until birth (Shi et al. 2018).
- Whole body homogenate of WT AB strain zebrafish embryos exposed to 27 µM BPS from 1 hpf to 24 hpf, with no effects at 96 hpf (Blanc et al. 2019).

- Testes and ovaries in unexposed 120 dpf F1 and F2 zebrafish following F0 exposure of 1 or 100 µg/L BPS from 3 hpf to 120 dpf (Hao et al. 2022).

- Whole body homogenate of WT AB strain zebrafish exposed to 0.01, 0.03, 0.1, 0.3, or 1 µM BPS from 4 hpf to 120 hpf (Gyimah et al. 2021a).

- Human fetal membrane-mesenchymal stromal cells (hFM-MSCs) incubated with 0.1 µM BPS for 24 to 48 hours (Di Credico et al. 2023).

- Human amniotic fluid stem cells (hAFSCs) incubated with 0.1 µM BPS for 24 to 48 hours (Di Credico et al. 2023).

BPS altered the protein levels involved in histone methylation in mouse ovarian tissue (see Table 4.3.4). Specifically, the following effects were observed:

- Decreased H3K4me3 and increased H3K9me3, both markers of histone methylation, in the ovaries of PND 21 offspring of ICR mice orally administered 2 or 10 µg/kg-day BPS from GD 12.5 to GD 15.5 (MY Zhang et al. 2020).

BPS altered gene expression, protein levels and post-translational modification of factors involved in sperm development and maturation, including:

- Decreased AKT and pAKT protein levels, a marker of impaired sperm motility via reduced PI3K-AKT mediated energy activation, in adult male offspring of Wistar rats administered 0.4 or 4 µg/kg BPS from GD 4 to GD 21 (Molangiri et al. 2022).

- Decreased *Tex101* and *Spo11* mRNA expression was also observed at 0.4 µg/kg-day in the testis of adult male offspring (Molangiri et al. 2022).

- Increased TEX11 protein expression at 0.4 and 4.0 µg/kg-day in the testis of adult male offspring (Molangiri et al. 2022)

Table 4.3.3 BPS effects on expression of genes involved in epigenetic processes.

Gene	System	Exposure Method	Treatment Conditions	Tissue	Direction	Reference
Dnmt1	F1 male CD-1 mice, PND 60	Oral (pipette)	20 µg/kg-day; GD 11–birth	Testes	Increased	Shi et al. 2018
dmnt1	Zebrafish, 72 hpf	Aqueous environment	0.1 µM; 4 hpf–72 hpf	Whole body	Increased	Gyimah et al. 2021a
dnmt1	Zebrafish, 48 hpf	Aqueous environment	0.03, 0.3, and 1 µM; 4 hpf–48 hpf	Whole body	Decreased	Gyimah et al. 2021a
dnmt1	Zebrafish, 96 hpf	Aqueous environment	0.01, 0.03, 0.1, 0.3, and 1 µM; 4 hpf–96 hpf	Whole body	Decreased	Gyimah et al. 2021a
dnmt1	Zebrafish, 120 hpf	Aqueous environment	0.03, 0.1, 0.3, and 1 µM; 4 hpf–120 hpf	Whole body	Increased	Gyimah et al. 2021a
dnmt1	F1 Zebrafish; 120 dpf	Aqueous environment	1 and 100 µg/L; (F0) 3 hpf–120 dpf	Testes	Decreased	Hao et al. 2022
dnmt1	F2 Zebrafish; 120 dpf	Aqueous environment	1 µg/L; (F0) 3 hpf–120 dpf	Ovaries	Decreased	Hao et al. 2022
DNMT1	Human stem cells	Culture medium	0.1 µM; 24–48 hours	Amniotic fluid	Increased	Di Credico et al. 2023
DNMT3A	Human mesenchymal stem cells	Culture medium	0.1 µM; 24–48 hours	Fetal membrane	Increased	Di Credico et al. 2023
DNMT3A	Human stem cells	Culture medium	0.1 µM; 24–48 hours	Amniotic fluid	Decreased	Di Credico et al. 2023

Gene	System	Exposure Method	Treatment Conditions	Tissue	Direction	Reference
dnmt3, dnmt3bb.2	Zebrafish, 48 hpf	Aqueous environment	1 µM; 4 hpf–48 hpf	Whole body	Decreased	Gyimah et al. 2021a
dnmt3, dnmt3bb.2	Zebrafish, 96 hpf	Aqueous environment	0.01, 0.03, 0.1, 0.3, 1 µM; 4 hpf–96	Whole body	Decreased	Gyimah et al. 2021a
dnmt3, dnmt3bb.2	Zebrafish, 120 hpf	Aqueous environment	0.01, 0.3, and 1 µM; 4 hpf–120 hpf	Whole body	Increased	Gyimah et al. 2021a
dnmt3, dnmt3bb.2	F1 Zebrafish; 120 dpf	Aqueous environment	1 and 100 µg/L; (F0) 3 hpf–120 dpf	Ovaries	Increased	Hao et al. 2022
dnmt3, dnmt3bb.2	F1 Zebrafish; 120 dpf	Aqueous environment	1 and 100 µg/L; (F0) 3 hpf–120 dpf	Testes	Decreased	Hao et al. 2022
dnmt3, dnmt3bb.2	F2 Zebrafish; 120 dpf	Aqueous environment	100 µg/L; (F0) 3 hpf–120 dpf	Testes	Decreased	Hao et al. 2022
Dnmt3b	F1 male CD-1 mice, PND 60	Oral (pipette)	50 µg/kg-day; GD 11–birth	Testes	Increased	Shi et al. 2018
Dnmt3l	F3 male CD-1 mice, PND 3	Oral (pipette)	50 µg/kg-day; GD 7–birth	Testes	Increased	Shi et al. 2019b
dnmt4, dnmt3bb.1	Zebrafish, 120 hpf	Aqueous environment	0.01, 0.03, 0.1, 0.3, and 1 µM; 4 hpf–120 hpf	Whole body	Increased	Gyimah et al. 2021a
dnmt4, dnmt3bb.1	F1 Zebrafish; 120 dpf	Aqueous environment	1 and 100 µg/L; (F0) 3 hpf–120 dpf	Testes and ovaries	Decreased	Hao et al. 2022
dnmt4, dnmt3bb.1	F2 Zebrafish; 120 dpf	Aqueous environment	1 and 100 µg/L; (F0) 3 hpf–120 dpf	Testes	Decreased	Hao et al. 2022

Gene	System	Exposure Method	Treatment Conditions	Tissue	Direction	Reference
dnmt5, dnmt3bb.3	Zebrafish, 24 hpf	Aqueous environment	0.01, 0.03, 0.1, 0.3, and 1 µM; 4 hpf–24 hpf	Whole body	Decreased	Gyimah et al. 2021a
dnmt5, dnmt3bb.3	Zebrafish, 48 hpf	Aqueous environment	0.01 and 0.1 µM; 4 hpf–48 hpf	Whole body	Increased	Gyimah et al. 2021a
dnmt5, dnmt3bb.3	Zebrafish, 96 hpf	Aqueous environment	0.01 and 0.03 µM; 4 hpf–96 hpf	Whole body	Decreased	Gyimah et al. 2021a
dnmt5, dnmt3bb.3	Zebrafish, 120 hpf	Aqueous environment	0.01, 0.03, 0.1, 0.3, and 1 µM; 4 hpf–120 hpf	Whole body	Increased	Gyimah et al. 2021a
dnmt5, dnmt3bb.3	F1 Zebrafish; 120 dpf	Aqueous environment	100 µg/L; (F0) 3 hpf–120 dpf	Ovaries	Decreased	Hao et al. 2022
dnmt5, dnmt3bb.3	F1 and F2 Zebrafish; 120 dpf	Aqueous environment	1 and 100 µg/L; (F0) 3 hpf–120 dpf	Testes	Decreased	Hao et al. 2022
dnmt6, dnmt3ab	Zebrafish, 72 hpf	Aqueous environment	1 µM; 4 hpf–72 hpf	Whole body	Increased	Gyimah et al. 2021a
dnmt6, dnmt3ab	Zebrafish, 96 hpf	Aqueous environment	0.01, 0.03, and 1 µM; 4 hpf–96 hpf	Whole body	Decreased	Gyimah et al. 2021a
dnmt6, dnmt3ab	Zebrafish, 120 hpf	Aqueous environment	0.01, 0.03, 0.1, 0.3, and 1 µM; 4 hpf–120 hpf	Whole body	Increased	Gyimah et al. 2021a
dnmt6, dnmt3ab	F1 Zebrafish; 120 dpf	Aqueous environment	1 µg/L; (F0) 3 hpf–120 dpf	Ovaries	Decreased	Hao et al. 2022
dnmt6, dnmt3ab	F1 Zebrafish; 120 dpf	Aqueous environment	100 µg/L; (F0) 3 hpf–120 dpf	Testes	Decreased	Hao et al. 2022

Gene	System	Exposure Method	Treatment Conditions	Tissue	Direction	Reference
dnmt6, dnmt3ab	F2 Zebrafish; 120 dpf	Aqueous environment	1 and 100 µg/L; (F0) 3 hpf–120 dpf	Testes and ovaries	Decreased	Hao et al. 2022
dnmt7, dnmt3ba	Zebrafish, 48 hpf	Aqueous environment	0.01, 0.03, and 0.3 µM; 4 hpf–48 hpf	Whole body	Decreased	Gyimah et al. 2021a
dnmt7, dnmt3ba	Zebrafish, 96 hpf and 120 hpf	Aqueous environment	0.01, 0.03, 0.1, 0.3, and 1 µM; 4 hpf–96 hpf and 120 hpf	Whole body	Decreased	Gyimah et al. 2021a
dnmt7, dnmt3ba	F1 Zebrafish; 120 dpf	Aqueous environment	1 µg/L; (F0) 3 hpf–120 dpf	Ovaries	Decreased	Hao et al. 2022
dnmt7, dnmt3ba	F1 Zebrafish, 120 dpf	Aqueous environment	1 and 100 µg/L; (F0) 3 hpf–120 dpf	Testes	Decreased	Hao et al. 2022
dnmt7, dnmt3ba	F2 Zebrafish, 120 dpf	Aqueous environment	100 µg/L; (F0) 3 hpf–120 dpf	Testes and ovaries	Decreased	Hao et al. 2022
dnmt8, dnmt3aa	Zebrafish, 48 hpf	Aqueous environment	0.1, 0.3, and 1 µM; 4 hpf–48 hpf	Whole body	Increased	Gyimah et al. 2021a
dnmt8, dnmt3aa	Zebrafish, 120 hpf	Aqueous environment	0.01, 0.03, 0.1, 0.3, and 1 µM; 4 hpf–120 hpf	Whole body	Increased	Gyimah et al. 2021a
dnmt8, dnmt3aa	F1 Zebrafish; 120 dpf	Aqueous environment	100 µg/L; (F0) 3 hpf–120 dpf	Ovaries	Increased	Hao et al. 2022
dnmt8, dnmt3aa	F1 Zebrafish, 120 dpf	Aqueous environment	1 and 100 µg/L; (F0) 3 hpf–120 dpf	Testes	Decreased	Hao et al. 2022
dnmt8, dnmt3aa	F2 Zebrafish, 120 dpf	Aqueous environment	100 µg/L; (F0) 3 hpf–120 dpf	Ovaries	Increased	Hao et al. 2022

Gene	System	Exposure Method	Treatment Conditions	Tissue	Direction	Reference
dnmt8, dnmt3aa	F2 Zebrafish, 120 dpf	Aqueous environment	100 µg/L; (F0) 3 hpf–120 dpf	Testes	Decreased	Hao et al. 2022
dnmt8, dnmt3aa	F2 Zebrafish, 120 dpf	Aqueous environment	1 µg/L; (F0) 3 hpf–120 dpf	Testes	Increased	Hao et al. 2022
Dot1l	F1 male CD-1 mice, PND 60	Oral (pipette)	20 and 50 µg/kg-day; GD 11–birth	Testes	Increased	Shi et al. 2018
Kmt2e	F1 male CD-1 mice, PND 60	Oral (pipette)	0.5, 20, and 50 µg/kg-day; GD 11–birth	Testes	Decreased	Shi et al. 2018
Setd1a	F1 male CD-1 mice, PND 60	Oral (pipette)	0.5 µg/kg-day; GD 11–birth	Testes	Decreased	Shi et al. 2018
Setd1b	F1 male CD-1 mice, PND 60	Oral (pipette)	0.5, 20, and 50 µg/kg-day; GD 11–birth	Testes	Decreased	Shi et al. 2018
Suz12	F1 male CD-1 mice, PND 60	Oral (pipette)	0.5, 20, and 50 µg/kg-day; GD 11–birth	Testes	Decreased	Shi et al. 2018
TET1	Human mesenchymal stem cells	Culture medium	0.1 µM; 24–48 hours	Fetal membrane	Decreased	Di Credico et al. 2023
TET1	Human stem cells	Culture medium	0.1 µM; 24–48 hours	Amniotic fluid	Increased	Di Credico et al. 2023
tet1	F1 Zebrafish; 120 dpf;	Aqueous environment	1 and 100 µg/L; (F0) 3 hpf–120 dpf	Testes and ovaries	Increased	Hao et al. 2022

Gene	System	Exposure Method	Treatment Conditions	Tissue	Direction	Reference
tet1	F2 Zebrafish; 120 dpf;	Aqueous environment	100 µg/L; (F0) 3 hpf–120 dpf	Ovaries	Increased	Hao et al. 2022
TET3	Human mesenchymal stem cells	Culture medium	0.1 µM; 24–48 hours	Fetal membrane	Increased	Di Credico et al. 2023
TET3	Human stem cells	Culture medium	0.1 µM; 24–48 hours	Amniotic fluid	Increased	Di Credico et al. 2023
tet3	F1 Zebrafish; 120 dpf	Aqueous environment	1 and 100 µg/L; (F0) 3 hpf–120 dpf	Ovaries	Increased	Hao et al. 2022
tet3	F1 Zebrafish; 120 dpf	Aqueous environment	100 µg/L; (F0) 3 hpf–120 dpf	Testes	Increased	Hao et al. 2022
tet3	F2 Zebrafish; 120 dpf	Aqueous environment	1 µg/L; (F0) 3 hpf–120 dpf	Testes	Decreased	Hao et al. 2022

Table 4.3.4 BPS effects on levels of proteins involved in epigenetic processes.

Protein	System	Exposure Method	Treatment Conditions	Tissue	Direction	Reference
H3K4me3	F1 female ICR mice, PND 21	Oral (unspecified)	2 and 10 µg/kg-day; GD 12.5–GD 15.5	Ovaries	Decreased	MY Zhang et al. 2020
H3K9me3	F1 female ICR mice, PND 21	Oral (unspecified)	2 and 10 µg/kg-day; GD 12.5–GD 15.5	Ovaries	Increased	MY Zhang et al. 2020

4.3.5 Cell Proliferation, Apoptosis, and Autophagy

Development involves multiple spatiotemporal processes that rely on tightly regulated cell proliferation, apoptosis, and autophagy that if disrupted, can lead to detrimental effects on the developing organism.

BPS altered cell proliferation in the following experimental *in vitro* models: human embryonic cerebral organoids, human fetal membrane-mesenchymal stromal cells, and human amniotic fluid stromal cells. Specifically, the following effects were observed:

- Decreased cell proliferation with no effect on apoptosis in human embryonic H9 stem cell-derived cerebral organoids treated with 10 or 100 nM BPS from culture days 20–34 (Abdulla et al. 2024).

- Smaller organoids with decreased thickness of ventricular/subventricular zones in a human embryonic H9 stem cell-derived cerebral organoid treated with 10 or 100 nM BPS from culture days 20–34 (Abdulla et al. 2024).

- Increased cell proliferation in hFM-MSCs and hAFSCs incubated with 0.1 µM BPS for 12, 24, 36, and/or 48 hours (Di Credico et al. 2023).

BPS induced apoptosis in mouse ovarian and testicular tissue, zebrafish whole body and brain, bovine COCs, a rat embryonic cardiac cell line, HUVECs, and a human placenta-on-a-chip model. Specifically, the following effects were observed:

- Increased apoptosis, as indicated by an increased number of TUNEL-positive cells, with chromatin aggregation and oocyte vacuolization in ovarian tissue of PND 4 offspring of ICR mice administered 3.33 µg/L BPS via drinking water from GD 8.5 to PND 3. These effects were attenuated with co-treatment of BPS and rapamycin (Gao et al. 2024).

- Increased proportion of TUNEL-positive tubules and increased number of TUNEL-positive cells per tubule in the testes of PND 12 offspring of CD-1 mice administered 0.5, 20, or 50 µg/kg-day BPS via oral pipetting from GD 11 until birth (Shi et al. 2018).

- Increased apoptosis in the brain and the whole body of WT AB strain zebrafish exposed to 0.3 or 3 mg/L BPS from 2 hpf to 6 dpf, with highest levels in the brain (Gu et al. 2019).

- Dose-dependently increased apoptosis in the brain of 6 dpf WT AB strain zebrafish exposed to 1 (NS), 10, or 100 µg/L BPS from 2 hpf to 6 dpf (Wang et al. 2024).

- Increased DNA fragmentation, a marker of apoptosis, in 2 to 4 cell, 8 to 16 cell, and blastocyst stage embryos derived from bovine COCs treated with 0.05 mg/mL BPS for 24 hours and used for IVF (Saleh et al. 2021).

- Increased numbers of apoptotic cells in H9c2 cells and HUVECs incubated with 100 µM BPS for 26 hours. Attenuation of effects was observed with NAC, PDTC, and NAC + PDTC co-treatments (Luo et al. 2023).

- Increased percentage of late apoptotic cells and necrotic cells in syncytiotrophoblast-like cells (STBs), decreased percentage of late apoptotic cells in cytotrophoblasts (CTBs) and HUVECs, and decreased percentage of necrotic cells in CTBs in a placenta-on-a-chip model exposed to 150 ng/mL BPS for 72 hours (Vidal et al. 2024).

Two studies found no effect on apoptosis markers in mice and mouse embryos (Ning et al. 2023; Shi et al. 2018).

BPS altered autophagy in ovarian tissue of offspring of exposed mice. Impaired autophagy with fewer autophagosomes in the cytoplasm of oocytes and somatic cells was observed in the ovarian tissue of PND 4 offspring of ICR mice administered 3.33 µg/L BPS via drinking water from GD 8.5 to PND 3. These effects were attenuated with co-treatment of BPS and rapamycin (Gao et al. 2024).

BPS altered expression of cell proliferation-, apoptosis-, and/or autophagy-related genes in mouse gonadal tissue, human-derived stem cells, and embryonic chicken hepatocytes (Table 4.3.5).

Altered cell proliferation-related gene expression was observed in:

- Ovaries of GD 15.5 female offspring of ICR mice orally administered 2 or 10 µg/kg-day BPS from GD 12.5 to GD 15.5 (MY Zhang et al. 2020).

- hFM-MSCs and hAFSCs incubated with 0.1 µM BPS for 24, 36, and 48 hours (Di Credico et al. 2023).

Altered apoptosis-related gene expression was observed in:

- Ovarian tissue of PND 4 female offspring of ICR mice administered 3.33 µg/L BPS via drinking water from GD 8.5 to PND 3. These effects were attenuated with co-treatment of BPS and rapamycin (Gao et al. 2024).

- Testes of PND 60 offspring of CD-1 mice administered 0.5, 20, or 50 µg/kg-day BPS via drinking water from GD 11 until birth (Shi et al. 2018).

- Primary embryonic chicken hepatocytes incubated with 300 μM BPS for 36 hours (Ma et al. 2015).

Altered autophagy-related gene expression was observed in the ovarian tissue of PND 4 female offspring of ICR mice administered 3.33 μg/L BPS via drinking water from GD 8.5 to PND 3 and were attenuated with co-treatment of BPS and rapamycin (Gao et al. 2024).

BPS altered levels of cell proliferation-, apoptosis- and/or autophagy-related proteins in mouse ovarian tissue, rat adipose tissue, rat embryonic cardiac cells, and HUVECs (see Table 4.3.6). Specifically, the following effects were observed:

- Altered levels of a cell proliferation-related protein in the ovaries of GD 15.5 female offspring of ICR mice orally administered 2 or 10 μg/kg-day BPS from GD 12.5 to GD 15.5 (MY Zhang et al. 2020).

Altered levels of apoptosis-related proteins in:

- Ovarian tissue of PND 4 offspring of mice administered 3.33 μg/L BPS via drinking water from GD 8.5 to PND 3. These effects were attenuated with co-treatment of BPS and rapamycin (Gao et al. 2024).

- Adipose tissue of PND 90 male offspring of Wistar rats administered 0.4 or 4 μg/L BPS via oral gavage from GD 4 to GD 21 (Molangiri et al. 2023).

- H9c2 cells and HUVECs incubated with 100 μM for up to 26 hours, with attenuation of effects with NAC, PDTC, and NAC + PDTC co-treatments (Luo et al. 2023).

Altered levels of autophagy-related proteins in:

- Ovarian tissue of PND 4 offspring of mice administered 3.33 μg/L BPS via drinking water from GD 8.5 to PND 3. These effects were attenuated with co-treatment of BPS and rapamycin (Gao et al. 2024).

Table 4.3.5 BPS effects on expression of cell proliferation-, apoptosis-, and autophagy-related genes.

Gene	System	Exposure Method	Treatment Conditions	Tissue	Direction	Reference
Cell Proliferation						
KI67	Human mesenchymal stem cells	Culture medium	0.1 µM; 24–48 hours	Fetal membrane	Increased	Di Credico et al. 2023
KI67	Human stem cells	Culture medium	0.1 µM; 24–48 hours	Amniotic fluid	Increased	Di Credico et al. 2023
Stra8	F1 female ICR mice, GD 15.5	Oral (unspecified)	2 and 10 µg/kg-day; GD 12.5–GD 15.5	Ovaries	Increased	MY Zhang et al. 2020
Apoptosis						
Bad	F1 male CD-1 mice, PND 60	Oral (pipette)	0.5, 20, and 50 µg/kg-day; GD 11–birth	Testes	Decreased	Shi et al. 2018
Bax	F1 female ICR mice, PND 4	Oral (drinking water)	3.33 µg/L; GD 8.5–PND 3	Ovary	Increased	Gao et al. 2024
Bax	F1 male CD-1 mice, PND 60	Oral (pipette)	0.5, 20, and 50 µg/kg-day; GD 11–birth	Testes	Decreased	Shi et al. 2018
Bcl2	F1 female ICR mice, PND 4	Oral (drinking water)	3.33 µg/L; GD 8.5–PND 3	Ovary	Decreased	Gao et al. 2024
Casp3	F1 ICR female mice, PND 4	Oral (drinking water)	3.33 µg/L; GD 8.5–PND 3	Ovary	Increased	Gao et al. 2024

Gene	System	Exposure Method	Treatment Conditions	Tissue	Direction	Reference
Casp9	F1 ICR female mice, PND 4	Oral (drinking water)	3.33 µg/L; GD 8.5–PND 3	Ovary	Increased	Gao et al. 2024
Cycs	F1 male CD-1 mice, PND 60	Oral (pipette)	0.5 µg/kg-day; GD 11–birth	Testes	Increased	Shi et al. 2018
LOC100859733	White leghorn chicken primary hepatocytes	Culture medium	300 µM; 36 hours	Liver	Increased	Ma et al. 2015
Autophagy						
Becn2	F1 ICR female mice, PND 4	Oral (drinking water)	3.33 µg/L; GD 8.5–PND 3	Ovary	Decreased	Gao et al. 2024
Lc3b/Lc3a	F1 ICR female mice, PND 4	Oral (drinking water)	3.33 µg/L; GD 8.5–PND 3	Ovary	Decreased	Gao et al. 2024

Table 4.3.6 BPS effects on levels of cell proliferation-, apoptosis-, and cell autophagy-related proteins.

Protein	System	Exposure Method	Treatment Conditions	Tissue	Direction	Reference
Cell proliferation						
STRA8	F1 female ICR mice, GD 15.5	Oral (unspecified)	2 and 10 µg/kg-day; GD 12.5–GD 15.5	Ovaries	Increased	MY Zhang et al. 2020
Apoptosis						
BAX	F1 female ICR mice, PND 4	Oral (drinking water)	3.33 µg/L; GD 8.5–PND 3	Ovary	Increased	Gao et al. 2024
BAX	Rat embryonic cardiac cells	Culture medium	100 µM; 26 hours	Heart	Increased	Luo et al. 2023
BAX	HUVECs	Culture medium	100 µM; 26 hours	Umbilical vein endothelium	Increased	Luo et al. 2023
BCL2	F1 female ICR mice, PND 4	Oral (drinking water)	3.33 µg/L; GD 8.5–PND 3	Ovary	Decreased	Gao et al. 2024
BCL2	Rat embryonic cardiac cells	Culture medium	100 µM; 26 hours	Heart	Decreased	Luo et al. 2023
BCL2	HUVECs	Culture medium	100 µM; 26 hours	Umbilical vein endothelium	Decreased	Luo et al. 2023
CASP3	F1 male Wistar rats, PND 90	Oral (gavage)	0.4 and 4 µg/kg; GD 4–GD 21	Adipose tissue	Increased	Molangiri et al. 2023

Protein	System	Exposure Method	Treatment Conditions	Tissue	Direction	Reference
CASP3	Rat embryonic cardiac cells	Culture medium	100 µM; 26 hours	Heart	Increased	Luo et al. 2023
CASP3	HUVECs	Culture medium	100 µM; 26 hours	Umbilical vein endothelium	Increased	Luo et al. 2023
CHOP	F1 male Wistar rats, PND 90	Oral (gavage)	0.4 and 4 µg/kg; GD 4–GD 21	Adipose tissue	Increased	Molangiri et al. 2023
Cl-/Pro-Cas-3	F1 female ICR mice, PND 4	Oral (drinking water)	3.33 µg/L; GD 8.5–PND 3	Ovary	Increased	Gao et al. 2024
Cl-/Pro-Cas-9	F1 female ICR mice, PND 4	Oral (drinking water)	3.33 µg/L; GD 8.5–PND 3	Ovary	Increased	Gao et al. 2024
Autophagy						
BECN1	F1 female ICR mice, PND 4	Oral (drinking water)	3.33 µg/L; GD 8.5–PND 3	Ovary	Decreased	Gao et al. 2024
LC3B/LC3A	F1 female ICR mice, PND 4	Oral (drinking water)	3.33 µg/L; GD 8.5–PND 3	Ovary	Decreased	Gao et al. 2024
P62	F1 female ICR mice, PND 4	Oral (drinking water)	3.33 µg/L; GD 8.5–PND 3	Ovary	Increased	Gao et al. 2024
p-mTOR/mTOR	F1 female ICR mice, PND 4	Oral (drinking water)	3.33 µg/L; GD 8.5–PND 3	Ovary	Increased	Gao et al. 2024
pULK1/ULK1	F1 female ICR mice, PND 4	Oral (drinking water)	3.33 µg/L; GD 8.5–PND 3	Ovary	Decreased	Gao et al. 2024

4.3.6 Effects on the Endocrine System

The endocrine system is critical in supporting and regulating development from conception and beyond. During gestation, one major route of communication between the maternal organs and tissues, placenta, and the embryo/fetus is via endocrine signaling. Processes including implantation, maternal vessel remodeling, placental development and function, and embryo/fetal development depend on hormones including gonadotropins, sex hormones, and thyroid hormones to function properly.

There is substantial *in vivo* and *in vitro* evidence that BPS induces endocrine changes in mice, rats, zebrafish, *Drosophila*, chicken embryos, bovine blastocysts, primary fetal ovine adipocytes, primary chicken embryonic hepatocytes, a human endometrial cell line, and a human *in vitro* placenta model.

Gonadotropins and other related hormones

Luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin, and human chorionic gonadotropin (hCG) levels were altered by BPS in rat plasma, whole body zebrafish, and a human *in vitro* placenta model. Specifically, the following effects were observed:

- Decreased plasma LH and FSH levels in PND 80 male offspring of SD rats administered 50 µg/L BPS via drinking water from GD 1 to GD 20 (Ullah et al. 2019).

- Increased FSH levels in whole body homogenate WT zebrafish exposed to 100 µg/L BPS from 1 hpf to 120 hpf (Qiu et al. 2021).

- In a human multi-culture placenta-on-a-chip exposed to 150 ng/mL BPS for 72 hours, there was decreased prolactin in STBs; increased prolactin in CTBs, maternal decidual cells, and fetal stromal cells; decreased β-hCG subunit in placental vascular endothelial cells (PVECs), and increased β-hCG subunit in STBs, decidual cells, CTBs, and HUVECs (Vidal et al. 2024).

- Increased anti-Müllerian hormone (AMH) glycoprotein levels in blastocysts of *in vitro* fertilized bovine COCs treated with 0.05 mg/mL BPS for 24 hours (Saleh et al. 2021).

One study found no effect on LH or growth hormone levels in the whole body homogenate of WT zebrafish treated with 1 or 100 µg/L BPS from 2 to 120 hpf (Qiu et al. 2021).

Testosterone

Testosterone levels were altered by BPS in mouse serum, rat plasma, and zebrafish plasma. Testosterone levels were decreased in male offspring with mixed directionality in female offspring.

Decreased testosterone levels were observed in:

- Serum of untreated F3 PND 60 male descendants of CD-1 mice administered 50 µg/kg-day BPS from GD 7 until birth (Shi et al. 2019b).
- Serum of PND 35 and 8-month old female offspring of CD-1 mice administered 0.5 or 5 mg/kg-dose and 0.5 mg/kg-dose BPS, respectively, via twice daily oral gavage from GD 10.5 to GD 17.5, with no effects at PND 56 or 14 months of age (Tucker et al. 2018).
- Plasma of PND 80 male offspring of SD rats administered 50 µg/L BPS via drinking water from GD 1 to GD 20 (Ullah et al. 2019).
- Plasma of unexposed male F1 offspring of F0 WT AB strain zebrafish exposed to 100 µg/L BPS from 3 hpf to 120 hpf, with NS decrease in unexposed F2 males (Hao et al. 2022).

Increased testosterone levels were observed in:

- Serum of 9-month-old female offspring of CD-1 mice administered 50 µg/kg-day BPS from GD 11 until birth (Shi et al. 2019a).
- Serum of PND 28 female offspring of CD-1 mice administered 0.05 mg/kg-dose BPS via twice daily oral gavage from GD 10.5 to GD 17.5, with no effects at PND 56 or 14 months of age (Tucker et al. 2018).

One study found no effect on testosterone levels in male offspring of CD-1 mice treated with 0.5, 20, or 50 µg/kg-day from GD 11 until birth (Shi et al. 2018).

One study found no effect on testosterone plasma levels of unexposed F2 female offspring of WT AB strain F0 zebrafish exposed to 1 or 100 µg/L BPS from 3 hpf to 120 hpf (Hao et al. 2022).

Dehydroepiandrosterone

One study found decreased dehydroepiandrosterone (DHEA) in the offspring of CD-1 mice administered 0.5 mg/kg-dose BPS via twice daily oral gavage from GD 10.5 to GD 17.5, at 8- and 3-months of age respectively, with no effect at PND 56 or 14-months-old (Tucker et al. 2018).

Estradiol

Estradiol (E2) levels were increased by BPS in mouse and rat serum and whole body zebrafish, specifically in:

- Serum of male offspring of CD-1 mice administered 50 µg/kg-day BPS via oral pipetting from GD 11 until birth (Shi et al. 2018).
- Serum of PND 80 male offspring of SD rats administered 50 µg/L BPS via drinking water from GD 1 to GD 20 (Ullah et al. 2019).
- Whole body homogenate of WT zebrafish exposed to 1 or 100 µg/L BPS from 1 hpf to 120 hpf (Qiu et al. 2021).
- The plasma of unexposed F1 and F2 male offspring of WT AB strain F0 zebrafish exposed to 100 µg/L BPS from 3 hpf to 120 hpf (Hao et al. 2022).

One study evaluating the female offspring of CD-1 mice administered BPS via gavage from GD 10.5 to GD 17.5 found time-dependent effects on serum E2 levels (Tucker et al. 2018).

- Increased in PND 20 female offspring at 0.5 or 5 mg/kg-day.
- Decreased in 8-month-old female offspring at 0.05 mg/kg-day.
- No effects at PND 56 or 14-months-old.

One study reported decreased estradiol levels in JEG-3 human choriocarcinoma cells incubated with 50 µM BPS for 2, 4, 6, and 12 hours. Attenuation of effects were observed with NAC and glycogen synthase kinase (GSK) co-treatments (Z Li et al. 2023).

One study found no effect on E2 levels in female offspring of CD-1 mice treated with 0.5, 20, or 50 µg/kg-day from GD 11 until birth (Shi et al. 2019a).

One study found no effect on E2 levels in untreated F3 PND 60 male descendants of CD-1 mice administered 0.5 or 50 µg/kg-day BPS from GD 7 until birth (Shi et al. 2019b).

One study found no effect on plasma E2 levels of unexposed F2 female offspring of WT AB strain F0 zebrafish exposed to 1 or 100 µg/L BPS from 3 hpf to 120 hpf (Hao et al. 2022).

Estrogen receptor activity and signaling pathway activation were increased by BPS in zebrafish liver and tail somites, and human endometrial cells. Specifically, the following effects were observed:

- Increased ER activity and signaling pathway activation as detected via GFP induction in the heart at 20 and 50 mg/L BPS and liver and tail somites at 50 mg/L BPS in transgenic Tg(ERE:Gal4ff)(UAS:GFP) zebrafish exposed from 1 hpf to 96 hpf. Complete attenuation of effect with co-exposure of BPS and ER antagonist ICI 182,780 (ICI) was observed in the heart and tail, suggesting dependence on classic ER signaling (Moreman et al. 2017).

BPS was predicted to bind to zebrafish estrogen receptor (ER) in docking models. Receptor binding assays or modeling can provide insights into a chemical's endocrine-disrupting potential:

- BPS had greater binding affinity to Esr2b than Esr1 or Esr2a in docking models, with no effect of BPS on ER proteins or gene expression in zebrafish treated with 0.5, 5, or 25 mg/L BPS from 1.5 hpf to 4 dpf (Mu et al. 2018).

- BPS had greater binding affinity to Esr2b and Esr1 than Esr2a in docking models (Kubota et al. 2023).

- BPS had weak binding affinity for zebrafish estrogen receptors zfERα, zfERβ1, and zfERβ2 as determined using a competitive binding assay. These receptors were incubated with 1 nM [^{3}H]-E2 with or without 0.01, 0.1, 1, 10, or 100 nM radio-inert E2 or 0.1, 1, 10, 100, 1000, and 10,000 nM BPS (Cano-Nicolau et al. 2016).

Aromatase

- Increased (NS) aromatase B (AroB)-positive cells in the caudal hypothalamus in WT AB strain zebrafish exposed to 0.1 or 1 µM BPS from 2 to 144 hpf (Coumailleau et al. 2020).

- Increased brain aromatase activity as detected via GFP induction in transgenic Tg(*cyp19a1b*:GFP) zebrafish exposed to 30 or 60 µM BPS from 0 hpf to 4 dpf. Co-treatment with ER antagonist ICI or anti-androgenic drug flutamide had no effect on BPS-mediated GFP-induction, indicating a differential estrogenic response (Le Fol et al. 2017).

Estradiol/ testosterone ratio

The E2/testosterone ratio was increased in the plasma of unexposed F1 male and female offspring and in F2 male offspring of WT AB strain F0 zebrafish exposed to 100 µg/L BPS from 3 hpf to 120 hpf. There was no effect in F2 females (Hao et al. 2022).

Corticosterone

- Increased plasma corticosterone levels in PND 90 male offspring of Wistar rats administered 0.4 µg/kg-day BPS via oral gavage from GD 4 to GD 21 was observed (Molangiri et al. 2023).

Progesterone

Progesterone levels were altered in mouse serum and a human placenta-on-a-chip model. Specifically, the following effects were observed:

- Decreased serum progesterone in the offspring of CD-1 mice administered 5 mg/kg-dose BPS via twice daily oral gavage from GD 10.5 to GD 17.5, at 3-months of age, with no effect at PND 20, PND 28, PND 35, PND 56, 8-months-old, or 14-months-old (Tucker et al. 2018).

- Decreased progesterone in PVECs, STBs, CTBs, maternal decidual, and fetal stromal cells, and slightly increased in HUVECs in a multi-culture placenta model exposed to 150 ng/mL BPS for 72 hours (Vidal et al. 2024).

Thyroid hormones

Thyroid hormones are essential for development, and in particular, neurodevelopment. BPS altered the levels of triiodothyronine (T3) and thyroxine (T4) levels in whole body zebrafish and zebrafish eggs. Specifically, the following effects were observed:

Decreased:

- T4 in the fertilized whole eggs (<2 hpf) of parental WT Tu strain zebrafish exposed to 1, 10, or 100 µg/L BPS from 2 hpf to 120 dpf (Wei et al. 2018).
- Total T3 in WT AB strain zebrafish whole body homogenate exposed to 4 or 400 nM BPS from 2 hpf to 120 hpf (Wei et al. 2023).

Increased:

- T3 and T4 in a concentration-dependent manner in whole body homogenate of WT zebrafish exposed to 2 (NS), 10 (NS), or 50 (NS for T4) mg/L BPS from 4 hpf to 120 hpf (Lee et al. 2019).
- T3 in the fertilized whole eggs (<2 hpf) of parental WT AB strain zebrafish exposed to 1, 10, or 100 µg/L BPS from 2 hpf to 120 dpf (Wei et al. 2018).
- Total T4 in whole body homogenate of AB zebrafish exposed to 4 nM BPS from 2 hpf to 120 hpf (Wei et al. 2023).

Thyroid hormone receptors

Based on the following observations, BPS likely binds to thyroid hormone receptors (THR) and decreases the binding of endogenous thyroid hormones in non-cellular models. Altered binding or interaction of thyroid hormones with THR may result in dysregulation of thyroid hormone signaling, which is key for many developmental processes:

- Decreased association constant between T3 and thyroid hormone receptor β (THRB) with 1.5 µM BPS treatment in a competitive binding assay, indicating competitive antagonism (Lu et al. 2018).
- Decreased interaction between T3 and THRB with co-treatment of 5 or 50 µM BPS and T3 for 2.5 hours co-treatment as visualized with β-galactosidase activity in a recombinant yeast two-hybrid assay, indicating BPS antagonism of THRB (Lu et al. 2018).

- Potential BPS binding with THRB as demonstrated with docking simulation data using homology modeling (Qin et al. 2023).

- BPS was predicted to alter the conformation of the THRB ligand binding domain in a molecular dynamic simulation, potentially altering its binding affinity for thyroid hormones (Lu et al. 2018).

The activities of iodothyronine deiodinases 2 (DIO2; thyroid hormone-activating) and 3 (DIO3; thyroid hormone-inactivating), enzymes involved in thyroid hormone metabolism, were increased in the retinal tissue of WT AB strain zebrafish larva exposed to 4 and 400 nM BPS from 2 hpf to 120 hpf (Wei et al. 2023). DIO2 and DIO3 are integral in regulating thyroid hormone signaling in the photoreceptors, the light-sensing cells of the retina, and imbalanced expression may affect retinal development.

Endocrine-related gene expression

BPS altered the expression of the following endocrine-related genes in mouse gonadal and mammary gland tissue; rat testicular and brain tissue; zebrafish whole body, gonadal, brain, and liver tissue; chicken embryo liver tissue; primary chicken embryonic hepatocytes; a human choriocarcinoma cell line; and a human endometrial cell line (Table 4.3.7):

Steroid hormone receptor genes

- Increased ER gene expression in:

    - Mammary glands of female offspring of mice administered 200 µg/kg-day BPS from GD 8 to PND 2 (Kolla and Vandenberg 2019).

    - Whole body homogenate of Brass GnRH3-EMD transgenic zebrafish exposed to 100 µg/L BPS from 2 hpf to 120 hpf. This effect was attenuated with co-treatment of BPS and fadrozole hydrochloride, an aromatase inhibitor (Qiu et al. 2016).

    - Whole body homogenate of WT zebrafish exposed to 100 or 1000 µg/L BPS from 4 hpf to 120 hpf (Qiu et al. 2018).

    - Whole body homogenate of WT AB strain zebrafish exposed to 1 or 100 µg/L BPS from 1 hpf to 120 hpf (Qiu et al. 2021).

    - Primary undifferentiated preadipocytes derived from the fetal perirenal adipose tissue of male Polypay Dorset crossbred sheep incubated with 0.5 mg/kg BPS from GD 30 to GD 100 (Pu et al. 2017).

- Decreased androgen receptor gene expression in the testes of PND 90 male offspring of Wistar rats administered 0.4 or 4 µg/kg-day BPS from GD 4 to GD 21 (Molangiri et al. 2022).

- Decreased progesterone receptor gene expression in mammary gland tissue in 8-month-old female offspring of CD-1 mice administered 5 mg/kg-dose BPS via twice daily oral gavage from GD 10.5 to GD 17.5 (Tucker et al. 2018).

- Decreased blastocyst attachment rate in an *in vitro* model of human implantation, using human choriocarcinoma JEG-3 cell spheroids and human endometrial adenocarcinoma cells (Ishikawa cells), where the Ishikawa cells were exposed to 100 µM BPS for 24 hours, was attenuated with progesterone receptor (PGR) knockdown via siRNA treatment (H Fan et al. 2021).

One study reported no effects of BPS on the gene expression of *Esr1, Ar,* or G protein-coupled estrogen receptor 1 (*Gper1)* in the mammary gland tissue of female offspring of CD-1 mice treated twice daily with 0.05 to 5 mg/kg-dose (0.1 to 10 mg/kg-day) BPS from GD 10.5 to 17.5 (Tucker et al. 2018).

Altered expression of steroidogenesis-related genes was observed in:

- Testes of PND 60 male offspring of CD-1 mice administered 0.5, 20, or 50 µg/kg-day BPS from GD 11 until birth (Shi et al. 2018).

- Ovaries of 3-month-old female offspring of CD-1 mice administered 0.5 µg/kg-day BPS from GD 11 until birth (Shi et al. 2019a).

- Testes of untreated F3 PND 60 male descendants of CD-1 mice administered 0.5 or 50 µg/kg-day BPS from GD 7 until birth (Shi et al. 2019b).

- Brains of PND 21 female offspring of Wistar rats administered subcutaneous BPS at 10 µg/kg-day from GD 12 until birth (Castro et al. 2015).

- Whole body homogenate of WT AB strain zebrafish exposed to 30 µM BPS from 72 to 96 hpf (Kubota et al. 2023).

- Whole body homogenate of WT zebrafish exposed to 1 or 100 µg/L BPS from 1 hpf to 120 hpf (Qiu et al. 2021).

- Whole brain and caudal hypothalamus of WT zebrafish exposed to 1 µM BPS from 0 -1 dpf to 7 dpf (Cano-Nicolau et al. 2016).

- Ovaries and testes of unexposed 120 dpf F1 and F2 female and male offspring of WT AB strain zebrafish exposed to 1 or 100 µg/L BPS from 3 hpf to 120 dpf (Hao et al. 2022).

- JEG-3 human choriocarcinoma cells incubated with 25 and 100 µM BPS for 12 hours, and 50 µM BPS for 2, 4, 6, 12, and 24 hours. Co-treatments with NAC or GSK were administered at 50 µM BPS at the 12 hour timepoint, and attenuation of effect was observed with both co-treatments (Z Li et al. 2023).

- Primary chicken embryonic hepatocytes incubated with 300 µM BPS for 36 hours (Ma et al. 2015).

Altered expression of thyroid-related genes, was observed in:

- Whole body homogenate of WT zebrafish exposed to 2, 10, or 50 mg/L BPS from 4 hpf to 120 hpf (Lee et al. 2019).

- Whole body homogenate of WT AB strain zebrafish exposed to 400 nM BPS from 2 hpf to 120 hpf (Wei et al. 2023).

- Whole body homogenate of zebrafish exposed to 1 µM BPS from 0 to 72 hpf (Lu et al. 2018).

- Livers of chicken embryos exposed *in ovo* to 52.8 µg/g egg BPS on day 0 and assessed on day 22 (Crump et al. 2016).

- Primary chicken embryonic hepatocytes incubated with 300 µM BPS for 36 hours (Ma et al. 2015).

Other endocrine-related genes:

- Increased expression of glucocorticoid receptor (*NR3C1*) in primary undifferentiated preadipocytes derived from the fetal perirenal adipose tissue of male Polypay Dorset crossbred sheep incubated with 0.5 mg/kg BPS from GD 30 to GD 100 (Pu et al. 2017).

- Decreased expression of vitellogenin (*vtg*), an estrogen-responsive gene, in whole body homogenate of WT AB strain zebrafish exposed to 30 µM BPS from 72 to 96 hpf (Kubota et al. 2023).

- Increased estrogen-sensitive mRNA expression of *APOB* and *VTG* in primary white leghorn chicken embryonic hepatocytes incubated with 300 µM BPS for 36 hours (Ma et al. 2015).

Endocrine-related protein levels

BPS altered levels of endocrine-related proteins in zebrafish retinal tissue, human choriocarcinoma cells, and bovine blastocysts (Table 4.3.8):

- Increased anti-Müllerian hormone (AMH) glycoprotein levels in blastocysts of *in vitro* fertilized bovine COCs treated with 0.05 mg/mL BPS for 24 hours (Saleh et al. 2021).
- Increased AMH receptor 2 (AMHR2) in blastocysts of bovine *in vitro* fertilized oocytes from COCs treated with 0.05 mg/mL BPS for 24 hours (Saleh et al. 2021).
- Decreased CYP19A1 levels in JEG-3 human choriocarcinoma cells incubated with 50 μM BPS for 12 hours; attenuation of effect observed with NAC or GSK co-treatments (Z Li et al. 2023).

Table 4.3.7 BPS effects on endocrine-related gene expression.

Gene	System	Exposure Method	Treatment Conditions	Tissue	Direction	Reference
Steroid hormone receptor genes						
Ar	F1 male Wistar rats, PND 90	Oral (gavage)	0.4 and 4 µg/kg-day; GD 4–GD 21	Testes	Decreased	Molangiri et al. 2022
ESR1	Male Polypay Dorset sheep	Subcutaneous injection	0.5 mg/kg-day; GD 30–GD 100	Cultured primary undifferentiated preadipocytes	Increased	Pu et al. 2017
Esr1	F1 female mice, PND 31	Oral (pipette)	200 µg/kg-day; GD 8–PND 2	Mammary gland	Increased	Kolla and Vandenberg 2019
esr1	Zebrafish; 120 hpf	Aqueous environment	100 µg/L; 2 hpf–120 hpf	Whole body	Increased	Qiu et al. 2016
esr1	Zebrafish; 120 hpf	Aqueous environment	100 and 1000 µg/L; 4 hpf–120 hpf	Whole body	Increased	Qiu et al. 2018
esr1	Zebrafish; 120 hpf	Aqueous environment	100 µg/L; 1 hpf–120 hpf	Whole body	Increased	Qiu et al. 2021
ESR2	Male Polypay Dorset sheep	Subcutaneous injection	0.5 mg/kg-day; GD 30–GD 100	Cultured primary undifferentiated preadipocytes	Increased	Pu et al. 2017
esr2a	Zebrafish; 120 hpf	Aqueous environment	1 and 100 µg/L; 1 hpf–120 hpf	Whole body	Increased	Qiu et al. 2021
esr2b	Zebrafish; 120 hpf	Aqueous environment	100 µg/L; 1 hpf–120 hpf	Whole body	Increased	Qiu et al. 2021

Gene	System	Exposure Method	Treatment Conditions	Tissue	Direction	Reference
Pgr	F1 female CD-1 mice, 8 months	Oral (gavage)	5 mg/kg-day; GD 10.5–GD 17.5	Mammary gland	Decreased	Tucker et al. 2018
Steroidogenesis-related genes						
cyp11a, cyp11a1.1	F1 female zebrafish, 120 dpf	Aqueous environment	100 µg/L; (F0) 3 hpf–120 dpf	Ovaries	Decreased	Hao et al. 2022
cyp11a, cyp11a1.1	F1 male zebrafish, 120 dpf	Aqueous environment	1 and 100 µg/L; (F0) 3 hpf–120 dpf	Testes	Decreased	Hao et al. 2022
cyp11a, cyp11a1.1	F2 female zebrafish, 120 dpf	Aqueous environment	1 µg/L; (F0) 3 hpf–120 dpf	Ovaries	Increased	Hao et al. 2022
cyp11a, cyp11a1.1	F1 male zebrafish, 120 dpf	Aqueous environment	1 and 100 µg/L; (F0) 3 hpf–120 dpf	Testes	Decreased	Hao et al. 2022
Cyp11a1	F1 male CD-1 mice, PND 60	Oral (pipette)	0.5 and 20 µg/kg-day; GD 11–birth	Testes	Increased	Shi et al. 2018
Cyp11a1	F1 female CD-1 mice; 3 months	Oral (pipette)	0.5 µg/kg-day; GD 11–birth	Ovaries	Increased	Shi et al. 2019a
cyp17, cyp17a1	F1 and F2 zebrafish, 120 dpf	Aqueous environment	1 and 100 µg/L; (F0) 3 hpf–120 dpf	Testes and ovaries	Decreased	Hao et al. 2022
cyp19a, cyp19a1a	F1 female zebrafish, 120 dpf	Aqueous environment	1 µg/L; (F0) 3 hpf–120 dpf	Ovaries	Decreased	Hao et al. 2022
cyp19a, cyp19a1a	F2 female zebrafish, 120 dpf	Aqueous environment	100 µg/L; (F0) 3 hpf–120 dpf	Ovaries	Increased	Hao et al. 2022

Gene	System	Exposure Method	Treatment Conditions	Tissue	Direction	Reference
cyp19a, cyp19a1a	F2 male zebrafish, 120 dpf	Aqueous environment	100 µg/L; (F0) 3 hpf–120 dpf	Testes	Decreased	Hao et al. 2022
cyp19a, cyp19a1a	Zebrafish; 120 hpf	Aqueous environment	100 µg/L; 1 hpf–120 hpf	Brain	Increased	Qiu et al. 2021
Cyp19a1	F1 male CD-1 mice, PND 60	Oral (pipette)	50 µg/kg-day; GD 11–birth	Testes	Increased	Shi et al. 2018
Cyp19a1	F3 male CD-1 mice, PND 60	Oral (pipette)	0.5 and 50 µg/kg-day; GD 7–birth	Testes	Increased	Shi et al. 2019b
cyp19a1b	Zebrafish; 96 hpf	Aqueous environment	30 µM; 72 hpf–96 hpf	Whole body	Increased (NS)	Kubota et al. 2023
cyp19a1b	Zebrafish; 7 dpf	Aqueous environment	1 µM; 0 -1 dpf–7 dpf	Whole brain, caudal hypothalamus	Increased	Cano-Nicolau et al. 2016
cyp19a2, cyp19a1b	Zebrafish; 120 hpf	Aqueous environment	100 µg/L; 1 hpf–120 hpf	Whole body	Increased	Qiu et al. 2021
CYP19A1	JEG-3; human choriocarcinoma cell line	Culture medium	25 µM; 12 hours 50 µM; 4, 6, and 12 hours	Placenta	Decreased	Li et al. 2023
CYP19A1	JEG-3; human choriocarcinoma cell line	Culture medium	50 µM; 24 hours	Placenta	Increased	Li et al. 2023

Gene	System	Exposure Method	Treatment Conditions	Tissue	Direction	Reference
CYP19A1	JEG-3; human choriocarcinoma cell line	Culture medium	100 µM; 12 hours	Placenta	Increased	Li et al. 2023
hsd17b, hsd17b3	F1 female zebrafish, 120 dpf	Aqueous environment	100 µg/L; (F0) 3 hpf–120 dpf	Ovaries	Increased	Hao et al. 2022
hsd17b, hsd17b3	F1 male zebrafish, 120 dpf	Aqueous environment	1 and 100 µg/L; (F0) 3 hpf–120 dpf	Testes	Increased	Hao et al. 2022
hsd17b, hsd17b3	F2 female zebrafish, 120 dpf	Aqueous environment	100 µg/L; (F0) 3 hpf–120 dpf	Ovaries	Decreased	Hao et al. 2022
hsd17b, hsd17b3	F2 male zebrafish, 120 dpf	Aqueous environment	1 µg/L; (F0) 3 hpf–120 dpf	Testes	Increased	Hao et al. 2022
hsd3b, hsd3b2	F1 female zebrafish, 120 dpf	Aqueous environment	1 µg/L; (F0) 3 hpf–120 dpf	Ovaries	Decreased	Hao et al. 2022
hsd3b, hsd3b2	F1 and F2 male zebrafish, 120 dpf	Aqueous environment	1 and 100 µg/L; (F0) 3 hpf–120 dpf	Testes	Decreased	Hao et al. 2022
hsd3b, hsd3b2	F2 female zebrafish, 120 dpf	Aqueous environment	1 and 100 µg/L; (F0) 3 hpf–120 dpf	Ovaries	Decreased	Hao et al. 2022
HSD3B1	White longhorn chicken primary embryonic hepatocytes	Culture medium	300 µM; 36 hours	Liver	Decreased	Ma et al. 2015
Srd5a3, 5α-R3	F1 female Wistar rats; PND 21	Subcutaneous injection	10 µg/kg-day; GD 12–birth	Brain	Decreased	Castro et al. 2015

Gene	System	Exposure Method	Treatment Conditions	Tissue	Direction	Reference
Star	F1 male CD-1 mice, PND 60	Oral (pipette)	0.5 and 20 µg/kg-day; GD 11–birth	Testes	Increased	Shi et al. 2018
Star	F3 male CD-1 mice, PND 60	Oral (pipette)	0.5 and 50 µg/kg-day; GD 7–birth	Testes	Increased	Shi et al. 2019b
star	F1 female zebrafish, 120 dpf	Aqueous environment	1 µg/L; (F0) 3 hpf–120 dpf	Ovaries	Decreased	Hao et al. 2022
star	F1 male zebrafish, 120 dpf	Aqueous environment	1 and 100 µg/L; (F0) 3 hpf–120 dpf	Testes	Increased	Hao et al. 2022
star	F2 male and female zebrafish, 120 dpf	Aqueous environment	100 µg/L; (F0) 3 hpf–120 dpf	Testes and ovaries	Decreased	Hao et al. 2022
Thyroid-related genes						
crh, crhb	Zebrafish; 120 hpf	Aqueous environment	2 mg/L; 4 hpf–120 hpf	Whole body	Increased	Lee et al. 2019
DIO1	Chicken embryos; day 22	Air cell injection	52.8 µg/g egg; injected Day 0	Liver	Increased	Crump et al. 2016
dio2	Zebrafish; 120 hpf	Aqueous environment	400 nM; 2 hpf–120 hpf	Whole body	Decreased	Wei et al. 2023
dio3, dio3b	Zebrafish; 120 hpf	Aqueous environment	400 nM; 2 hpf–120 hpf	Whole body	Increased	Wei et al. 2023
hhex	Zebrafish; 120 hpf	Aqueous environment	2, 10, and 50 mg/L; 4 hpf–120 hpf	Whole body	Increased	Lee et al. 2019

Gene	System	Exposure Method	Treatment Conditions	Tissue	Direction	Reference
IGF1	White leghorn chicken primary embryonic hepatocytes	Culture medium	300 µM; 36 hours	Liver	Decreased	Ma et al. 2015
thra, thraa	Zebrafish; 120 hpf	Aqueous environment	400 nM; 2 hpf–120 hpf	Whole body	Increased	Wei et al. 2023
thrb	Zebrafish; 72 hpf	Aqueous environment	1 µM; 0 hpf–72 hpf	Whole body	Increased	Lu et al. 2018
thrb	Zebrafish; 120 hpf	Aqueous environment	400 nM; 2 hpf–120 hpf	Whole body	Increased	Wei et al. 2023
THRSP	White leghorn chicken primary embryonic hepatocytes	Culture medium	300 µM; 36 hours	Liver	Decreased	Ma et al. 2015
tpo	Zebrafish; 120 hpf	Aqueous environment	2, 10, and 50 mg/L; 4 hpf–120 hpf	Whole body	Increased	Lee et al. 2019
tshb, tshba	Zebrafish; 120 hpf	Aqueous environment	2 mg/L; 4 hpf–120 hpf	Whole body	Increased	Lee et al. 2019
tshr	Zebrafish; 120 hpf	Aqueous environment	2 mg/L; 4 hpf–120 hpf	Whole body	Increased	Lee et al. 2019
ttr	Zebrafish; 120 hpf	Aqueous environment	2 and 10 mg/L; 4 hpf–120 hpf	Whole body	Increased	Lee et al. 2019

Gene	System	Exposure Method	Treatment Conditions	Tissue	Direction	Reference
ugt1ab	Zebrafish; 120 hpf	Aqueous environment	2, 10, and 50 mg/L; 4 hpf–120 hpf	Whole body	Increased	Lee et al. 2019
Other						
APOB	White longhorn chicken primary embryonic hepatocytes	Culture medium	300 µM; 36 hours	Liver	Increased	Ma et al. 2015
GR, NR3C1	Male Polypay Dorset sheep	Subcutaneous injection	0.5 mg/kg-day; GD 30–GD 100	Cultured primary undifferentiated preadipocytes	Increased	Pu et al. 2017
vtg	Zebrafish; 96 hpf	Aqueous environment	30 µM; 72 hpf–92 hpf	Whole body	Decreased	Kubota et al. 2023
VTG	White longhorn chicken primary embryonic hepatocytes	Culture medium	300 µM; 36 hours	Liver	Increased	Ma et al. 2015

Table 4.3.8 BPS effects on endocrine-related protein levels.

Protein	System	Exposure Method	Treatment Conditions	Tissue	Direction	Reference
AMH	Bovine blastocysts	Culture medium	0.05 mg/mL; 24 hours	Whole blastocyst	Increased	Saleh et al. 2021
AMHRII, AMHR2	Bovine blastocysts	Culture medium	0.05 mg/mL; 24 hours	Whole blastocyst	Increased	Saleh et al. 2021
CYP19A1	JEG-3; human choriocarcinoma cell line	Culture medium	50 µM; 12 hours	Placenta	Decreased	Li et al. 2023

4.3.7 Target Organ Systems

There is mechanistic and supportive evidence that BPS toxicity targets the development of specific organ systems, including the central nervous, visual, and immune systems.

Central nervous system effects

BPS was reported to alter the *in vitro* proliferation and differentiation of hippocampal neural stem cells and neurons. Primary hippocampal neural stem cells and neurons from GD 14 Wistar rat embryos were cultured with up to 150 µM BPS for up to 72 hours (Tiwari et al. 2024):

- Decreased number and size of primary neurospheres treated with 150 µM BPS for 24 hours.
- Decreased proliferation of primary neural stem cells treated with 0.001 to 100 µM BPS for 48 hours.
- Inhibition of neuronal differentiation and induction of glial differentiation of primary neural stem cells treated with 150 µM BPS for 48 hours.
- Decreased dendritic length of primary hippocampal neurons treated with 0.001 to 100 µM BPS for 72 hours.

There is evidence that BPS altered expression of genes involved in neurodevelopment in rat and zebrafish brain tissue, whole body zebrafish, and H9 stem cell derived-cerebral organoids (see Table 4.3.9).

Altered gene expression of central nervous system neurotransmitters in:

- Prefrontal cortex of female offspring of Wistar rats administered 10 µg/kg-day BPS subcutaneously from GD 12 until birth (Castro et al. 2015).

- Brains of 6-month-old adult male offspring of female WT AB strain zebrafish exposed to 30 µg/L BPS for 60 days prior to mating with untreated males (Salahinejad et al. 2023).

- Whole body homogenate of WT AB strain zebrafish exposed to 3 mg/L BPS from 2 hpf to 6 dpf (Gu et al. 2019).

- WT Tu strain zebrafish whole larvae exposed to 1, 10, or 100 µg/L BPS from 2 hpf to 120 hpf (Wei et al. 2018).

- Whole body homogenate of WT AB strain zebrafish exposed to 1 µM BPS from 8 hpf to 120 hpf (Bai et al. 2023).

Altered expression of neuroendocrine-related genes in:

- Whole body homogenate of Brass GnRH3-EMD transgenic zebrafish exposed to 100 µg/L BPS from 2 hpf to 25 hpf (Qiu et al. 2016).
    - Co-exposure with ICI, an ER antagonist, attenuated the increased expression of *grnh3* and *fshb*.
    - Co-exposure with AMIO, a THR antagonist, attenuated the increased expression of *kiss1r*.
    - Co-exposure with fadrozole hydrochloride, an aromatase inhibitor, attenuated the increased expression of *kiss1r, gnrh3, ihb,* and *fshb*.
- Hypothalamus of WT zebrafish exposed to 1 or 100 µg/L BPS from 1 hpf to 120 hpf (Qiu et al. 2021).
    - Co-exposure with ICI did not modulate the effects of BPS.
    - Co-exposure with fadrozole hydrochloride, attenuated the increased expression of *fshb*.

Altered expression of other genes involved in neurodevelopment in:

- Whole body homogenate of WT AB strain zebrafish exposed to 3 mg/L BPS from 2 hpf to 6 dpf (Gu et al. 2019).
- Whole body homogenate of WT AB strain zebrafish exposed up to 1 µM from 4 hpf to 120 hpf (Gyimah et al. 2021b).
- Whole body homogenate of WT Tu strain zebrafish exposed to 1, 10, or 100 µg/L BPS from 2 hpf to 120 hpf (Wei et al. 2018).

There is evidence that BPS altered the expression of neural differentiation-related genes and proteins in human embryonic H9 stem cell-derived cerebral organoids incubated with 100 nM on culture days 20–34 (see Table 4.3.9 and 4.3.10) (Abdulla et al. 2024).

Visual system effects

BPS altered the expression of genes related to ocular development in zebrafish eyes (see Table 4.3.9).

In retinal tissue of WT AB zebrafish exposed to 4 or 400 nM BPS from 2 hpf to 120 hpf (Wei et al. 2023), there was:

- Decreased expression of opsin-related genes *opn1mw2* and *opn1lw1* at 400 nM and phototransduction-related genes *arr3a* and *pde6hv* at 4 and 400 nM. Co-exposure with T3 or 1-850, a Thrb antagonist, ameliorated this effect.
- Decreased expression of opsin-related gene *opn1lw2* at 400 nM. Co-exposure with I-850, but not T3, ameliorated this effect.
- Decreased expression of phototransduction-related gene *pde6a* at 4 and 400 nM. Co-exposure with T3, but not 1-850, ameliorated this effect.
- Increased expression of opsin-related gene *opn1sw1* at 400 nM. Co-exposure with T3 or 1-850 attenuated this effect.

In WT Tu strain zebrafish exposed to 100 µg/L BPS from 2 hpf to 120 hpf, ocular *cyp26a1* gene expression was increased (Qiu et al. 2023a).

BPS altered Gap43 expression in the retina of WT AB strain zebrafish exposed to 0.3 or 3 mg/L BPS from 2 hpf to 6 dpf (Gu et al. 2019).

Ocular retinoids metabolism, i.e., the relative contents of ocular all-*trans* retinoic acid (atRA) and its metabolites (18-OH-atRA, (oxo)2-atRA, oxo-OH-atRA, and 4-oxo-atRA) and all-*trans* retinal, all-*trans* retinol, and 11-cis retinal, was altered with BPS exposure in WT, thyroid hormone receptor beta knockout (*thrb*$^{-/-}$), and CYP26A1 null mutant (*cyp26a1*$^{-54D-}$) Tu strain zebrafish exposed to 100 µg/L BPS from 2 hpf to 120 hpf (Qiu et al. 2023a).

Immune system and inflammation effects

One epidemiologic study (see Table 4.3.14), using data from the Michigan Mother and Infant Pairs pregnancy cohort, reported that urinary BPS levels measured at delivery were positively associated with maternal plasma levels of vascular endothelial growth factor (VEGF), an inflammatory biomarker, in an unadjusted model (Kelley et al. 2019).

BPS induced immunotoxic effects in a human placenta-on-a-chip model incubated with 150 ng/mL BPS for 72 hours (see Table 4.3.10) (Vidal et al. 2024). Specifically, there was:

- A diminished anti-inflammatory state, with decreased levels of granulocyte macrophage colony-stimulating factor (GMCSF) in STBs and HUVECs
- Increased GMCSF in decidual cells
- Decreased interleukin (IL)1B and IL6 in STBs, and increased IL6 in CTBs and decidual cells
- Decreased tumor necrosis factor alpha (TNFA) in stromal cells.

BPS altered the expression of immune-related genes in whole body zebrafish (see Table 4.3.9).

In whole body homogenate of WT Tu strain zebrafish exposed to 1000 µg/L BPS from 4 hpf to 120 hpf. Co-exposure with ER and nuclear factor kappa B (NFKB) antagonists attenuated the effects, suggesting these pathways mediate BPS immunotoxic effects (Qiu et al. 2018).

In whole body homogenate of offspring of WT AB strain zebrafish exposed to 10 µg/L BPS from 24 hpf until spawning, with and without subsequent offspring BPS exposure from 24 hpf to 96 hpf (Dong et al. 2018).

BPS altered immune-related proteins in rat liver tissue and whole body zebrafish (see Table 4.3.10). Specifically, the following effects were observed:

- Increased pro-inflammatory cytokines in the livers of male offspring of Wistar rats administered 0.4 or 4 µg/kg-day BPS from GD 4 to GD 21 (Molangiri et al. 2023).
- Increased Il-12 content in whole body homogenate of WT AB strain zebrafish exposed to 100 µg/L from 4 hpf to 120 hpf. BPS induced cardiotoxicity that may have been mediated by immune dysregulation (Qiu et al. 2020).

Table 4.3.9 BPS effects on organ system-related gene expression.

Gene	System	Exposure Method	Treatment Conditions	Tissue	Direction	Reference
Central nervous system						
Neurotransmitter-related genes						
chrna1	Zebrafish; 120 hpf	Aqueous environment	1 µM; 8 hpf–120 hpf	Whole body	Decreased	Bai et al. 2023
Cyp2d4	F1 female Wistar rats, PND 21	Subcutaneous injection	10 µg/kg-day; (F0) GD 12–birth, (F1) PND 1–PND 21	Prefrontal cortex	Increased	Castro et al. 2015
Drd1 (NS)	F1 female Wistar rats, PND 21	Subcutaneous injection	10 µg/kg-day; (F0) GD 12–birth, (F1) PND 1–PND 21	Prefrontal cortex	Decreased	Castro et al. 2015
Drd3 (NS)	F1 female Wistar rats, PND 21	Subcutaneous injection	10 µg/kg-day; (F0) GD 12–birth, (F1) PND 1–PND 21	Prefrontal cortex	Decreased	Castro et al. 2015
htr1aa	F1 male zebrafish, 6 months	Aqueous environment	30 µg/L; (F0 females) 60 days premating	Brain	Decreased	Salahinejad et al. 2023
htr1ab	F1 male zebrafish, 6 months	Aqueous environment	30 µg/L; (F0 females) 60 days premating	Brain	Decreased	Salahinejad et al. 2023
mao	F1 male zebrafish, 6 months	Aqueous environment	30 µg/L; (F0 females) 60 days premating	Brain	Decreased	Salahinejad et al. 2023
syn2a	Zebrafish, 6 dpf	Aqueous environment	3 mg/L; 2 hpf–6 dpf	Whole body	Decreased	Gu et al. 2019
syn2a	Zebrafish, 120 hpf	Aqueous environment	10 and 100 µg/L; 2 hpf–120 hpf	Whole body	Decreased	Wei et al. 2018

Gene	System	Exposure Method	Treatment Conditions	Tissue	Direction	Reference
Neuroendocrine-related genes						
anp, nppa	Zebrafish; 120 hpf	Aqueous environment	1 and 100 µg/L; 1 hpf–120 hpf	Whole body	Increased	Qiu et al. 2021
fshb	Zebrafish; 25 hpf	Aqueous environment	100 µg/L; 2 hpf–25 hpf	Whole body	Increased	Qiu et al. 2016
gh, gh1	Zebrafish; 120 hpf	Aqueous environment	100 µg/L; 1 hpf–120 hpf	Whole body	Increased	Qiu et al. 2021
gnrh3	Zebrafish; 25 hpf	Aqueous environment	100 µg/L; 2 hpf–25 hpf	Whole body	Increased	Qiu et al. 2016
lhb	Zebrafish; 25 hpf	Aqueous environment	100 µg/L; 2 hpf–25 hpf	Whole body	Increased	Qiu et al. 2016
lhb	Zebrafish; 120 hpf	Aqueous environment	1 and 100 µg/L; 1 hpf–120 hpf	Whole body	Increased	Qiu et al. 2021
kiss1	Zebrafish; 120 hpf	Aqueous environment	100 µg/L; 1 hpf–120 hpf	Whole body	Increased	Qiu et al. 2021
kiss1r, kiss1ra	Zebrafish; 25 hpf	Aqueous environment	100 µg/L; 2 hpf–25 hpf	Whole body	Increased	Qiu et al. 2016
kiss2	Zebrafish; 120 hpf	Aqueous environment	100 µg/L; 1 hpf–120 hpf	Whole body	Increased	Qiu et al. 2021
prl	Zebrafish; 120 hpf	Aqueous environment	1 µg/L; 1 hpf–120 hpf	Whole body	Increased	Qiu et al. 2021

Gene	System	Exposure Method	Treatment Conditions	Tissue	Direction	Reference
pth1, pth1a	Zebrafish; 120 hpf	Aqueous environment	100 µg/L; 1 hpf–120 hpf	Whole body	Increased	Qiu et al. 2021
ren	Zebrafish; 120 hpf	Aqueous environment	100 µg/L; 1 hpf–120 hpf	Whole body	Increased	Qiu et al. 2021
Neurodevelopmental-related genes						
a1-tubulin	Zebrafish, 6 dpf	Aqueous environment	0.3 and 3 mg/L; 2 hpf–6 dpf	Whole body	Decreased	Gu et al. 2019
a-tubulin	Zebrafish, 120 hpf	Aqueous environment	0.03, 0.1, 0.3, and 1 µM; 4 hpf–120 hpf	Whole body	Increased	Gyimah et al. 2021b
elavl3	Zebrafish, 6 dpf	Aqueous environment	3 mg/L; 2 hpf–6 dpf	Whole body	Decreased	Gu et al. 2019
elavl3	Zebrafish, 120 hpf	Aqueous environment	0.03 and 1 µM; 4 hpf–120 hpf	Whole body	Increased	Gyimah et al. 2021b
gap43	Zebrafish, 6 dpf	Aqueous environment	0.3 and 3 mg/L; 2 hpf–6 dpf	Whole body	Decreased	Gu et al. 2019
gap43	Zebrafish, 24hpf	Aqueous environment	0.03 µM; 4 hpf–24 hpf	Whole body	Increased	Gyimah et al. 2021b
gap43	Zebrafish, 120 hpf	Aqueous environment	0.01, 0.03, 0.1, 0.3, and 1 µM; 4 hpf–120 hpf	Whole body	Increased	Gyimah et al. 2021b
gap43	Zebrafish, 120 hpf	Aqueous environment	100 µg/L; 2 hpf–120 hpf	Whole body	Increased	Wei et al. 2018

Gene	System	Exposure Method	Treatment Conditions	Tissue	Direction	Reference
gfap	Zebrafish, 6 dpf	Aqueous environment	3 mg/L; 2 hpf–6 dpf	Whole body	Decreased	Gu et al. 2019
gfap	Zebrafish, 72 hpf	Aqueous environment	1 µM; 4 hpf–72 hpf	Whole body	Increased	Gyimah et al. 2021b
gfap	Zebrafish, 96 hpf	Aqueous environment	0.1 and 0.3 µM; 4 hpf–96 hpf	Whole body	Increased	Gyimah et al. 2021b
gfap	Zebrafish, 120 hpf	Aqueous environment	0.03, 0.1, 0.3 and 1 µM; 4 hpf–120 hpf	Whole body	Increased	Gyimah et al. 2021b
gfap	Zebrafish, 120 hpf	Aqueous environment -	1, 10, and 100 µg/L; 2 hpf–120 hpf	Whole body	Increased	Wei et al. 2018
MAP2	Human embryonic stem cell-derived cerebral organoid	Aqueous environment	100 nM; Culture days 20–34	Derived from H9 cell line	Decreased	Abdulla et al. 2024
mbp	Zebrafish, 6 dpf	Aqueous environment	3 mg/L; 2 hpf–6 dpf	Whole body	Decreased	Gu et al. 2019
mbp	Zebrafish, 48 hpf	Aqueous environment	0.03 and 0.1 µM; 4 hpf–48 hpf	Whole body	Increased	Gyimah et al. 2021b
mbp	Zebrafish, 120 hpf	Aqueous environment	0.1 µM; 4 hpf–120 hpf	Whole body	Increased	Gyimah et al. 2021b
mbp	Zebrafish, 120 hpf	Aqueous environment	100 µg/L; 2 hpf–120 hpf	Whole body	Increased	Wei et al. 2018

Gene	System	Exposure Method	Treatment Conditions	Tissue	Direction	Reference
mstn1	Zebrafish, 24 hpf	Aqueous environment	0.3 and 1 µM; 4 hpf–24 hpf	Whole body	Increased	Gyimah et al. 2021b
mstn1	Zebrafish, 120 hpf	Aqueous environment	0.01, 0.03, 0.1, 0.3, and 1 µM; 4 hpf–120 hpf	Whole body	Increased	Gyimah et al. 2021b
mstn1	Zebrafish, 96 hpf	Aqueous environment	0.3 and 1 µM; 4 hpf–96 hpf	Whole body	Decreased	Gyimah et al. 2021b
mstn1	Zebrafish, 72 hpf	Aqueous environment	0.01, 0.03, 0.1, 0.3, and 1 µM; 4 hpf–72 hpf	Whole body	Decreased	Gyimah et al. 2021b
ngn1, neurog1	Zebrafish, 120 hpf	Aqueous environment	0.01, 0.03, 0.1, 0.3, and 1 µM; 4 hpf–120 hpf	Whole body	Increased	Gyimah et al. 2021b
TUJ1	Human embryonic stem cell-derived cerebral organoid	Culture medium	100 nM; Culture days 20–34	Derived from H9 cell line	Decreased	Abdulla et al. 2024
vegfa, vegfaa	Zebrafish, 120 hpf	Aqueous environment	0.01, 0.03, 0.1, 0.3, and 1 µM; 4 hpf–120 hpf	Whole body	Increased	Gyimah et al. 2021b
vegfa, vegfaa	Zebrafish, 96 hpf	Aqueous environment	0.01, 0.03, 0.3, and 1 µM; 4 hpf–96 hpf	Whole body	Decreased	Gyimah et al. 2021b
vegfa, vegfaa	Zebrafish, 72 hpf	Aqueous environment	1 µM; 4 hpf–72 hpf	Whole body	Increased	Gyimah et al. 2021b
wnt8a	Zebrafish, 48 hpf	Aqueous environment	0.01, 0.03, and 0.1 µM; 4 hpf–48 hpf	Whole body	Increased	Gyimah et al. 2021b

Gene	System	Exposure Method	Treatment Conditions	Tissue	Direction	Reference
wnt8a	Zebrafish, 120 hpf	Aqueous environment	0.3 and 1 µM; 4 hpf–120 hpf	Whole body	Increased	Gyimah et al. 2021b
wnt8a	Zebrafish, 48 hpf	Aqueous environment	0.3 and 1 µM; 4 hpf–48 hpf	Whole body	Decreased	Gyimah et al. 2021b
wnt8a	Zebrafish, 96 hpf	Aqueous environment	0.01, 0.03, 0.1, 0.3, and 1 µM; 4 hpf–96 hpf	Whole body	Decreased	Gyimah et al. 2021b
Visual System						
arr3a	Zebrafish, 120 hpf	Aqueous environment	400 nM; 2 hpf–120 hpf	Eye	Decreased	Wei et al. 2023
arr3a	Zebrafish, 120 hpf	Aqueous environment	4 nM; 2 hpf–120 hpf	Eye	Increased	Wei et al. 2023
cyp26a1	Zebrafish, 120 hpf	Aqueous environment	100 µg/L; 2 hpf–120 hpf	Eye	Increased	Qiu et al. 2023a
grk1b	Zebrafish, 120 hpf	Aqueous environment	400 nM; 2 hpf–120 hpf	Eye	Decreased	Wei et al. 2023
grk1b	Zebrafish, 120 hpf	Aqueous environment	4 nM; 2 hpf–120 hpf	Eye	Increased	Wei et al. 2023
opn1lw1	Zebrafish, 120 hpf	Aqueous environment	4 and 400 nM; 2 hpf–120 hpf	Eye	Decreased	Wei et al. 2023
opn1lw2	Zebrafish, 120 hpf	Aqueous environment	4 and 400 nM; 2 hpf–120 hpf	Eye	Decreased	Wei et al. 2023

Gene	System	Exposure Method	Treatment Conditions	Tissue	Direction	Reference
opn1mw1	Zebrafish, 120 hpf	Aqueous environment	400 nM; 2 hpf–120 hpf	Eye	Decreased	Wei et al. 2023
opn1mw2	Zebrafish, 120 hpf	Aqueous environment	4 and 400 nM; 2 hpf–120 hpf	Eye	Decreased	Wei et al. 2023
opn1mw3	Zebrafish, 120 hpf	Aqueous environment	400 nM; 2 hpf–120 hpf	Eye	Decreased	Wei et al. 2023
opn1sw1	Zebrafish, 120 hpf	Aqueous environment	4 nM; 2 hpf–120 hpf	Eye	Increased	Wei et al. 2023
opn1sw1	Zebrafish, 120 hpf	Aqueous environment	400 nM; 2 hpf–120 hpf	Eye	Decreased	Wei et al. 2023
opn1sw2	Zebrafish, 120 hpf	Aqueous environment	400 nM; 2 hpf–120 hpf	Eye	Decreased	Wei et al. 2023
pde6a	Zebrafish, 120 hpf	Aqueous environment	4 nM; 2 hpf–120 hpf	Eye	Increased	Wei et al. 2023
pde6h	Zebrafish, 120 hpf	Aqueous environment	400 nM; 2 hpf–120 hpf	Eye	Decreased	Wei et al. 2023
pde6h	Zebrafish, 120 hpf	Aqueous environment	4 nM; 2 hpf–120 hpf	Eye	Increased	Wei et al. 2023
rho	Zebrafish, 120 hpf	Aqueous environment	4 nM; 2 hpf–120 hpf	Eye	Increased	Wei et al. 2023

Gene	System	Exposure Method	Treatment Conditions	Tissue	Direction	Reference
Immune System						
cc-chemokine	Zebrafish, 120 hpf	Aqueous environment	1000 µg/L; 4 hpf–120 hpf	Whole body	Increased	Qiu et al. 2018
il10	Zebrafish, 120 hpf	Aqueous environment	1000 µg/L; 4 hpf–120 hpf	Whole body	Increased	Qiu et al. 2018
il11a	Zebrafish, 120 hpf	Aqueous environment	1000 µg/L; 4 hpf–120 hpf	Whole body	Increased	Qiu et al. 2018
il12a	Zebrafish, 120 hpf	Aqueous environment	1, 10, 100, and 1000 µg/L; 4 hpf–120 hpf	Whole body	Increased	Qiu et al. 2018
il1b	Zebrafish, 120 hpf	Aqueous environment	100 and 1000 µg/L; 4 hpf–120 hpf	Whole body	Increased	Qiu et al. 2018
il6	Zebrafish, 120 hpf	Aqueous environment	1, 10, 100, and 1000 µg/L; 4 hpf–120 hpf	Whole body	Increased	Qiu et al. 2018
ifng	Zebrafish, 120 hpf	Aqueous environment	10 and 1000 µg/L; 4 hpf–120 hpf	Whole body	Increased	Qiu et al. 2018
ifn, ifnphi1	F1 zebrafish, 96 hpf	Aqueous environment	10 µg/L; (F0) 24 hpf–spawning with (F1) 24 hpf-96 hpf	Whole body	Decreased	Dong et al. 2018
mmp13	F1 zebrafish, 96 hpf	Aqueous environment	10 µg/L; (F0) 24 hpf–spawning with (F1) 24 hpf–96 hpf	Whole body	Increased	Dong et al. 2018
mx	F1 zebrafish, 96 hpf	Aqueous environment	10 µg/L; (F0) 24 hpf–spawning alone and with (F1) 24 hpf–96 hpf	Whole body	Decreased	Dong et al. 2018

Gene	System	Exposure Method	Treatment Conditions	Tissue	Direction	Reference
nfkb	Zebrafish, 120 hpf	Aqueous environment	100 and 1000 µg/L; 4 hpf–120 hpf	Whole body	Increased	Qiu et al. 2018
rag1	F1 zebrafish, 96 hpf	Aqueous environment	10 µg/L; (F0) 24 hpf–spawning alone and with (F1) 24 hpf–96 hpf	Whole body	Decreased	Dong et al. 2018
rag2	F1 zebrafish, 96 hpf	Aqueous environment	10 µg/L; (F0) 24 hpf–spawning alone and with (F1) 24 hpf–96 hpf	Whole body	Decreased	Dong et al. 2018
tlr2	F1 zebrafish, 96 hpf	Aqueous environment	10 µg/L; (F0) 24 hpf–spawning alone and with (F1) 24 hpf–96 hpf	Whole body	Decreased	Dong et al. 2018
tlr3	F1 zebrafish, 96 hpf	Aqueous environment	10 µg/L; (F0) 24 hpf–spawning alone and with (F1) 24 hpf–96 hpf	Whole body	Decreased	Dong et al. 2018
tnfa	Zebrafish, 120 hpf	Aqueous environment	100 and 1000 µg/L; 4 hpf–120 hpf	Whole body	Increased	Qiu et al. 2018
tnfa	F1 zebrafish, 96 hpf	Aqueous environment	10 µg/L; (F0) 24 hpf–spawning alone and with (F1) 24 hpf–96 hpf	Whole body	Decreased	Dong et al. 2018
trif	F1 zebrafish, 96 hpf	Aqueous environment	10 µg/L; (F0) 24 hpf–spawning alone and with (F1) 24 hpf–96 hpf	Whole body	Decreased	Dong et al. 2018

Table 4.3.10 BPS effects on organ system-related protein levels.

Protein	System	Exposure Method	Treatment Conditions	Tissue	Direction	Reference
Central nervous system						
MAP2	Human embryonic stem cell-derived cerebral organoid	Culture medium	100 nM; Culture days 20–34	Derived from H9 cell line	Decreased	Abdulla et al. 2024
PAX6	Human embryonic stem cell-derived cerebral organoid	Culture medium	100 nM; Culture days 20–34	Derived from H9 cell line	Decreased	Abdulla et al. 2024
TUJ1	Human embryonic stem cell-derived cerebral organoid	Culture medium	100 nM; Culture days 20–34	Derived from H9 cell line	Decreased	Abdulla et al. 2024
Visual system						
Gap43	Zebrafish, 6 dpf	Aqueous environment	0.3 and 3 mg/L; 2 hpf–6 dpf	Retina	Decreased	Gu et al. 2019
Immune system						
COX2	F1 male Wistar rats, PND 90	Oral (gavage)	0.4, and 4 µg/kg-day; GD 4–GD 21	Liver	Increased	Molangiri et al. 2023
COX2	F1 male Wistar rats, PND 90	Oral (gavage)	0.4, and 4 µg/kg-day; GD 4–GD 21	Adipose tissue	Increased	Molangiri et al. 2023
CRP	F1 male Wistar rats, PND 90	Oral (gavage)	0.4, and 4 µg/kg-day; GD 4–GD 21	Liver	Increased	Molangiri et al. 2023

Protein	System	Exposure Method	Treatment Conditions	Tissue	Direction	Reference
CRP	F1 male Wistar rats, PND 90	Oral (gavage)	0.4 µg/kg-day; GD 4–GD 21	Adipose tissue	Increased	Molangiri et al. 2023
CSF2, GMCSF	Multi-culture placenta on a chip	Culture medium	150 ng/mL; 72 hours	STBs	Decreased	Vidal et al. 2024
CSF2, GMCSF	Multi-culture placenta on a chip	Culture medium	150 ng/mL; 72 hours	HUVECs	Decreased	Vidal et al. 2024
CSF2, GMCSF	Multi-culture placenta on a chip	Culture medium	150 ng/mL; 72 hours	Decidual cells	Increased	Vidal et al. 2024
Il12	Zebrafish, 120 hpf	Aqueous environment	100 µg/L; 4 hpf–120 hpf	Whole body	Increased	Qiu et al. 2020
IL1B	Multi-culture placenta on a chip	Culture medium	150 ng/mL; 72 hours	STBs	Decreased	Vidal et al. 2024
IL1B	F1 male Wistar rats, PND 90	Oral (gavage)	0.4, and 4 µg/kg-day; GD 4–GD 21	Liver	Increased	Molangiri et al. 2023
IL1B	F1 male Wistar rats, PND 90	Oral (gavage)	0.4, and 4 µg/kg-day; GD 4–GD 21	Adipose tissue	Increased	Molangiri et al. 2023
IL6	Multi-culture placenta on a chip	Culture medium	150 ng/mL; 72 hours	STBs	Decreased	Vidal et al. 2024
IL6	Multi-culture placenta on a chip	Culture medium	150 ng/mL; 72 hours	CTBs	Increased	Vidal et al. 2024
IL6	Multi-culture placenta on a chip	Culture medium	150 ng/mL; 72 hours	Decidual cells	Increased	Vidal et al. 2024

Protein	System	Exposure Method	Treatment Conditions	Tissue	Direction	Reference
IL6	F1 male Wistar rats, PND 90	Oral (gavage)	0.4, and 4 µg/kg-day; GD 4–GD 21	Liver	Increased	Molangiri et al. 2023
Nos2	Zebrafish, 120 hpf	Aqueous environment	10 and 100 µg/L; 4 hpf–120 hpf	Whole body	Increased	Qiu et al. 2020
TNFA	Multi-culture placenta on a chip	Culture medium	150 ng/mL; 72 hours	Stromal cells	Decreased	Vidal et al. 2024
TNFA	F1 male Wistar rats, PND 90	Oral (gavage)	0.4, and 4 µg/kg-day; GD 4–GD 21	Liver	Increased	Molangiri et al. 2023

Metabolic Effects

The following studies provide metabolism-related effects that are supportive of BPS-induced apical effects outlined in sections 4.2.2 and 4.2.3. Metabolism-related effects were found in mice, rats, zebrafish, and mouse embryonic fibroblasts.

- Decreased non-fasted blood glucose levels in PND 21- and 12-week-old male offspring of Non-Obese Diabetic Excluded Flora (NODEF) mice administered 3 µg/kg-day BPS from breeding day 1 to birth (McDonough et al. 2021b).

- Increased serum non-esterified fatty acids and triglyceride levels with no effect on total cholesterol in 12-week old male offspring of ICR mice administered 50 µg/kg-day BPS via gavage from GD 0.5 to GD 18.5 (Zhang et al. 2023).

- Increased plasma docosahexaenoic acid (DHA) in PND 90 male and female offspring of Wistar rats administered 0.4 µg/kg-day BPS via gavage from GD 4 to GD 21(Varma et al. 2023).

- Increased glucose levels in whole body homogenate of WT AB strain zebrafish exposed to 0.3 and 1 µM BPS from 4 hpf to 120 hpf (Gyimah et al. 2021a).

- Decreased brain glucose uptake without changes in brain glucose transporter 1 (glut1) protein expression in WT AB strain zebrafish exposed to 10 or 100 µg/L BPS from 2 hpf to 6 dpf. Decreased brain glucose uptake was also achieved with BAY 876, a glucose transporter 1 inhibitor (Wang et al. 2024).

- Decreased total cholesterol and LDL cholesterol in male zebrafish offspring of WT Tu strain zebrafish exposed to 1, 10, or 100 µg/L BPS from 2 hpf to 120 dpf (Wang et al. 2019).

- Decreased brain lipid levels and decreased total cholesterol in WT AB strain zebrafish exposed to 1, 10, or 100 µg/L BPS, decreased triacylglycerol with 10 and 100 µg/L BPS from 2 hpf to 120 hpf, and decreased long chain fatty acids with 1, 10, or 100 µg/L BPS from 2 hpf to 48 hpf (Wang et al. 2023).

- Increased lipid accumulation in the 3T3-L1 pre-adipocyte mouse embryonic fibroblast cell line incubated with 200 nM BPS for 10 days (Kulsange et al. 2024).

BPS altered expression of metabolism-related genes in mouse adipose tissue, rat liver tissue, sheep adipose tissue, whole body zebrafish, chicken embryonic livers, primary sheep adipocytes, primary chicken embryonic hepatocytes, human three-dimensional

embryoid bodies, and hepatocyte-like cells derived from embryonic stem cells (see Table 4.3.11).

Altered expression of adipose-related genes in:

- Epidydimal adipose tissue of male offspring of C57BL/6N mice fed a high fat diet and administered 5 or 50 mg/kg-day BPS from GD 9 to GD 18 (Ahn et al. 2020).
- Adipose tissue of male fetuses of Polypay Dorset crossbred sheep administered 0.5 mg/kg BPS from GD 30 to GD 100 (Pu et al. 2017).
- Primary differentiated fetal adipocytes from GD 120 male fetuses of Polypay Dorset crossbred sheep administered 0.5 mg/kg BPS from GD 30 to GD 100 (Pu et al. 2017).

Altered expression of hepatic and lipid metabolism-related genes in:

- Livers of male offspring of Wistar rats administered 0.4 or 4 µg/kg-day BPS from GD 4 to GD 21 (Molangiri et al. 2023).
- Whole body homogenate of untreated F1 offspring of WT Tu strain F0 zebrafish exposed to 1, 10, 100, or 1000 µg/L BPS from 2 hpf to 120 dpf (Wang et al. 2019).
- Whole body homogenate of WT AB strain zebrafish exposed to 1, 10 or 100 µg/L BPS from 2 hpf to 120 hpf (Wang et al. 2023).
- Livers of chicken embryos exposed *in ovo* to 52.8 µg BPS/g egg (Crump et al. 2016).
- Primary white leghorn chicken embryonic hepatocytes incubated with 300 µM BPS for 36 hours (Ma et al. 2015).
- Human embryoid bodies (lipid metabolism-related genes) and hepatocyte-like cells (hepatic marker, *HNF4A*), both derived from human embryonic stem cells and incubated with 100 nM BPS for 21 and 18 days, respectively (X Liang et al. 2021).

Altered expression of pancreas- and insulin-related metabolic genes in:

- Whole body homogenate of WT AB strain zebrafish exposed to 0.01, 0.03, 0.1, 0.3, or 1 μM BPS from 4 hpf to 120 hpf (Gyimah et al. 2021a).

BPS altered the level of metabolic proteins in rats and *Drosophila* (Table 4.3.12):

- Altered adipose and hepatic protein expression, including increased adipose differentiation-related protein (ADRP), PPARA, and FGF21 hepatokine, and decreased PPARG in male offspring of Wistar rats administered 0.4 or 4 μg/kg-day BPS from GD 4 to GD 21 (Molangiri et al. 2023).

- Increased total Cyp450 activity in the whole body homogenate of *Drosophila* F1 third instar stage larvae of parental flies administered 0.5 or 1 mM BPS via diet for a seven-day breeding period (Santos Musachio et al. 2023).

Table 4.3.11 BPS effects on metabolism-related gene expression.

Gene	System	Exposure Method	Treatment Conditions	Tissue	Direction	Reference
Adipose-related						
Adipoq	F1 male C57BL/6N mice, 10 weeks	Oral (drinking water)	5 and 50 mg/kg; GD 9–GD 18	Epididymal fat pad	Increased	Ahn et al. 2020
ADIPOQ	Male Polypay Dorset sheep	Subcutaneous injection	0.5 mg/kg; GD 30–GD 100	Adipose tissue	Decreased	Pu et al. 2017
ADIPOQ	Male Polypay Dorset sheep	Subcutaneous injection	0.5 mg/kg; GD 30–GD 100	Cultured primary differentiated adipocytes	Increased	Pu et al. 2017
Cebpa	F1 male C57BL/6N mice, 10 weeks	Oral (drinking water)	50 mg/kg; GD 9–GD 18	Epididymal fat pad	Increased	Ahn et al. 2020
Fabp4	F1 male C57BL/6N mice, 10 weeks	Oral (drinking water)	50 mg/kg; GD 9–GD 18	Epididymal fat pad	Increased	Ahn et al. 2020
FABP4	Male Polypay Dorset sheep	Subcutaneous injection	0.5 mg/kg; GD 30–GD 100	Cultured primary differentiated adipocytes	Increased	Pu et al. 2017
Lpl	F1 male C57BL/6N mice, 10 weeks	Oral (drinking water)	5 and 50 mg/kg; GD 9–GD 18	Epididymal fat pad	Increased	Ahn et al. 2020
Pparg	F1 male C57BL/6N mice, 10 weeks	Oral (drinking water)	5 and 50 mg/kg; GD 9–GD 18	Epididymal fat pad	Increased	Ahn et al. 2020

Gene	System	Exposure Method	Treatment Conditions	Tissue	Direction	Reference
Hepatic- and lipid metabolism-related						
Acaca	F1 male Wistar rats, PND 90	Oral (gavage)	4 µg/kg-day; GD 4–GD 21	Liver	Increased	Molangiri et al. 2023
acsl6	Zebrafish; 48 hpf	Aqueous environment	10 and 100 µg/L; 2 hpf–120 hpf	Whole body	Decreased	Wang et al. 2023
acsl6	Zebrafish; 120 hpf	Aqueous environment	1, 10 and 100 µg/L; 2 hpf–120 hpf	Whole body	Decreased	Wang et al. 2023
ACSL5	Chicken embryos, Day 22	Air cell injection	52.8 µg/g egg; Day 0	Liver	Increased	Crump et al. 2016
ACSL5	White leghorn chicken hepatocytes	Culture medium	300 µM BPS; 36 hours	Liver	Increased	Ma et al. 2015
ALAS1	White leghorn chicken hepatocytes	Culture medium	300 µM BPS; 36 hours	Liver	Increased	Ma et al. 2015
apoa1a	F1 zebrafish; 120 hpf	Aqueous environment	10 and 1000 µg/L; (F0) 2 hpf–120 dpf	Whole body	Increased	Wang et al. 2019
APOA4	Embryoid bodies	Culture medium	100 nM BPS; 21 days	Human embryonic stem cells	Increased	X Liang et al. 2021
apobb.1	F1 zebrafish; 120 hpf	Aqueous environment	1000 µg/L; (F0) 2 hpf–120 dpf	Whole body	Increased	Wang et al. 2019

Gene	System	Exposure Method	Treatment Conditions	Tissue	Direction	Reference
apoeb	F1 zebrafish; 120 hpf	Aqueous environment	1, 10, 100, and 1000 µg/L; (F0) 2 hpf–120 dpf	Whole body	Increased	Wang et al. 2019
CYP1A4	White leghorn chicken hepatocytes	Culture medium	300 µM BPS; 36 hours	Liver	Increased	Ma et al. 2015
CYP3A37	White leghorn chicken hepatocytes	Culture medium	300 µM BPS; 36 hours	Liver	Increased	Ma et al. 2015
CYP7B1	Chicken embryos, Day 22	Air cell injection	52.8 µg/g egg; Day 0	Liver	Increased	Crump et al. 2016
fabp10	F1 zebrafish; 120 hpf	Aqueous environment	1 µg/L; (F0) 2 hpf–120 dpf	Whole body	Increased	Wang et al. 2019
fabp10	F1 zebrafish; 120 hpf	Aqueous environment	1000 µg/L; (F0) 2 hpf–120 dpf	Whole body	Decreased	Wang et al. 2019
fabp1b	F1 zebrafish; 120 hpf	Aqueous environment	1000 µg/L; (F0) 2 hpf–120 dpf	Whole body	Increased	Wang et al. 2019
fabp2	F1 zebrafish; 120 hpf	Aqueous environment	10, 100, and 1000 µg/L; (F0) 2 hpf–120 dpf	Whole body	Increased	Wang et al. 2019
fabp7a	Zebrafish; 48 hpf	Aqueous environment	10 µg/L; 2 hpf–120 hpf	Whole body	Increased	Wang et al. 2023
fabp7a	Zebrafish; 120 hpf	Aqueous environment	10 and 100 µg/L; 2 hpf–120 hpf	Whole body	Decreased	Wang et al. 2023

Gene	System	Exposure Method	Treatment Conditions	Tissue	Direction	Reference
fabp7b	Zebrafish; 48 hpf	Aqueous environment	1, 10, and 100 µg/L; 2 hpf–120 hpf	Whole body	Increased	Wang et al. 2023
fabp11a	F1 zebrafish; 120 hpf	Aqueous environment	10, 100, and 1000 µg/L; (F0) 2 hpf–120 dpf	Whole body	Increased	Wang et al. 2019
Fads2	F1 male Wistar rats, PND 90	Oral (gavage)	4 µg/kg-day; GD 4–GD 21	Liver	Increased	Molangiri et al. 2023
Fasn	F1 male Wistar rats, PND 90	Oral (gavage)	4 µg/kg-day; GD 4–GD 21	Liver	Increased	Molangiri et al. 2023
FGB	Embryoid bodies	Culture medium	100 nM BPS; 21 days	Human embryonic stem cells	Increased	X Liang et al. 2021
HNF4A	Hepatocyte-like cells	Culture medium	100 nM BPS; 18 days	Human embryonic stem cells	Increased	X Liang et al. 2021
Hsd11b1	F1 male Wistar rats, PND 90	Oral (gavage)	0.4 µg/kg-day; GD 4–GD 21	Adipose tissue	Increased	Molangiri et al. 2023
Hsd11b1	F1 male Wistar rats, PND 90	Oral (gavage)	0.4 and 4 µg/kg-day; GD 4–GD 21	Liver	Increased	Molangiri et al. 2023
Hsd11b2	F1 male Wistar rats, PND 90	Oral (gavage)	4 µg/kg-day; GD 4–GD 21	Liver	Increased	Molangiri et al. 2023
hsd17b12b	Zebrafish; 48 hpf	Aqueous environment	10 and 100 µg/L; 2 hpf–120 hpf	Whole body	Decreased	Wang et al. 2023

Gene	System	Exposure Method	Treatment Conditions	Tissue	Direction	Reference
LBFABP	White leghorn chicken hepatocytes	Culture medium	300 µM BPS; 36 hours	Liver	Increased	Ma et al. 2015
lpl	F1 zebrafish; 120 hpf	Aqueous environment -	10, 100, and 1000 µg/L; (F0) 2 hpf–120 dpf	Whole body	Decreased	Wang et al. 2019
mtp	F1 zebrafish; 120 hpf	Aqueous environment	10, 100, and 1000 µg/L; (F0) 2 hpf–120 dpf	Whole body	Increased	Wang et al. 2019
Nampt	F1 male Wistar rats, PND 90	Oral (gavage)	4 µg/kg-day; GD 4–GD 21	Liver	Increased	Molangiri et al. 2023
Ppara	F1 male Wistar rats, PND 90	Oral (gavage)	4 µg/kg-day; GD 4–GD 21	Liver	Increased	Molangiri et al. 2023
pparg	F1 zebrafish; 120 hpf	Aqueous environment	10, 100, and 1000 µg/L; (F0) 2 hpf–120 dpf	Whole body	Increased	Wang et al. 2019
Prkaa2	F1 male Wistar rats, PND 90	Oral (gavage)	4 µg/kg-day; GD 4–GD 21	Liver	Increased	Molangiri et al. 2023
SLCO1A2	White leghorn chicken hepatocytes	Culture medium	300 µM BPS; 36 hours	Liver	Increased	Ma et al. 2015
Srebf1	F1 male Wistar rats, PND 90	Oral (gavage)	4 µg/kg-day; GD 4–GD 21	Liver	Increased	Molangiri et al. 2023
SULT1B1	Chicken embryos, Day 22	Air cell injection	52.8 µg/g egg; Day 0	Liver	Increased	Crump et al. 2016

Gene	System	Exposure Method	Treatment Conditions	Tissue	Direction	Reference
UGT1A9	Chicken embryos, Day 22	Air cell injection	52.8 µg/g egg; Day 0	Liver	Increased	Crump et al. 2016
Pancreas- and insulin-related						
foxa2	Zebrafish, 48 hpf	Aqueous environment	0.3 and 1 µM; 4 hpf– 48 hpf	Whole body	Increased	Gyimah et al. 2021a
foxa2	Zebrafish, 120 hpf	Aqueous environment	0.01, 0.03, 0.1, 0.3, and 1 µM; 4 hpf–120 hpf	Whole body	Increased	Gyimah et al. 2021a
foxa2	Zebrafish, 72 hpf	Aqueous environment	0.01, 0.03, 0.1, 0.3, and 1 µM; 4 hpf–72 hpf	Whole body	Decreased	Gyimah et al. 2021a
foxa2	Zebrafish, 96 hpf	Aqueous environment	1 µM; 4 hpf–96 hpf	Whole body	Decreased	Gyimah et al. 2021a
ins	Zebrafish, 48 hpf	Aqueous environment	1 µM; 4 hpf– 48 hpf	Whole body	Increased	Gyimah et al. 2021a
ins	Zebrafish, 96 hpf	Aqueous environment	0.01, 0.1, 0.3, and 1 µM; 4 hpf–96 hpf	Whole body	Increased	Gyimah et al. 2021a
ins	Zebrafish, 120 hpf	Aqueous environment	0.01, 0.1, 0.3, and 1 µM; 4 hpf–120 hpf	Whole body	Increased	Gyimah et al. 2021a
ins	Zebrafish, 72 hpf	Aqueous environment	0.3 and 1 µM; 4 hpf–72 hpf	Whole body	Decreased	Gyimah et al. 2021a
isl1	Zebrafish, 96 hpf	Aqueous environment	0.01 and 0.03 µM; 4 hpf–96 hpf	Whole body	Decreased	Gyimah et al. 2021a

Gene	System	Exposure Method	Treatment Conditions	Tissue	Direction	Reference
isl1	Zebrafish, 120 hpf	Aqueous environment	0.01, 0.1, 0.3, and 1 µM; 4 hpf–120 hpf	Whole body	Increased	Gyimah et al. 2021a
pdx1	Zebrafish, 48 hpf	Aqueous environment	0.01, 0.03, and 1.0 µM; 4 hpf–48 hpf	Whole body	Increased	Gyimah et al. 2021a
pdx1	Zebrafish, 96 hpf	Aqueous environment	0.03, 0.1, 0.3, and 1 µM; 4 hpf–96 hpf	Whole body	Increased	Gyimah et al. 2021a
pdx1	Zebrafish, 120 hpf	Aqueous environment	0.01, 0.03, 0.1, 0.3, and 1 µM; 4 hpf–120 hpf	Whole body	Increased	Gyimah et al. 2021a
ptfla1	Zebrafish, 24 hpf	Aqueous environment	0.1 µM; 4 hpf– 24 hpf	Whole body	Increased	Gyimah et al. 2021a
ptfla1	Zebrafish, 48 hpf	Aqueous environment	0.01 µM; 4 hpf– 48 hpf	Whole body	Increased	Gyimah et al. 2021a
ptfla1	Zebrafish, 120 hpf	Aqueous environment	0.01, 0.03, 0.1, 0.3, and 1 µM; 4 hpf–120 hpf	Whole body	Increased	Gyimah et al. 2021a

Table 4.3.12 BPS effects on metabolism-related protein levels.

Protein	System	Exposure Method	Treatment Conditions	Tissue	Direction	Reference
ADRP	F1 male Wistar rats, PND 90	Oral (gavage)	0.4 and 4 µg/kg-day; GD 4–GD 21	Liver	Increased	Molangiri et al. 2023
FABP4	F1 male Wistar rats, PND 90	Oral (gavage)	0.4 and 4 µg/kg-day; GD 4–GD 21	Adipose tissue	Increased	Molangiri et al. 2023
FGF21	F1 male Wistar rats, PND 90	Oral (gavage)	0.4 and 4 µg/kg-day; GD 4–GD 21	Liver	Increased	Molangiri et al. 2023
HSD11B1	F1 male Wistar rats, PND 90	Oral (gavage)	4 µg/kg-day; GD 4–GD 21	Adipose tissue	Increased	Molangiri et al. 2023
PPARA	F1 male Wistar rats, PND 90	Oral (gavage)	0.4 and 4 µg/kg-day; GD 4–GD 21	Liver	Increased	Molangiri et al. 2023
PPARG	F1 male Wistar rats, PND 90	Oral (gavage)	0.4 and 4 µg/kg-day; GD 4–GD 21	Adipose tissue	Decreased	Molangiri et al. 2023

Nitric Oxide

Nitric oxide (NO) plays a key regulatory role in implantation, placentation, embryo development, and vascular function (Gouge et al. 1998; Krause et al. 2011), and on immune response and inflammation (Bogdan 2001). Perturbations to NO levels and expression of associated genes and protein levels (e.g., nitric oxide synthase [NOS]) can have both tissue-specific and system-level effects. While NO is essential for embryonic development, an absence or excess of NO has been associated with teratogenic effects (Alexander et al. 2007).

BPS increased NOS activity and/or NO levels in whole body zebrafish and human umbilical vein endothelial cells:

- Increased inducible NOS (iNOS) or NOS2 activity in whole body homogenate of zebrafish exposed to 10 and 100 µg/L from 4 hpf to 120 hpf. BPS induced cardiotoxicity that may have been mediated by immune dysregulation (Qiu et al. 2020).

- Increased iNOS and total NOS activity in whole body homogenate of wildtype zebrafish exposed to 1, 100, or 1000 µg/L for total NOS, and 100 and 1000 µg/L for iNOS from 4 hpf to 120 hpf (Qiu et al. 2018).

- Increased phosphorylated endothelial NOS (eNOS) and eNOS activity without a change to total eNOS protein level in HUVECs incubated with 0.1 and 1 µM (eNOS activity) and 1 µM (phosphorylated eNOS) BPS for 6 hours (Hu et al. 2024).

- Increased NO levels in whole body homogenate of wildtype zebrafish exposed to 100 or 1000 µg/L BPS from 4 hpf to 120 hpf (Qiu et al. 2018; Yang et al. 2018).

- Increased NO levels in HUVECs incubated with 1 µM BPS for 24 hours (Hu et al. 2024).

Gene expression

- Upregulated iNOS (*nos2a*) gene expression in whole body homogenate of WT zebrafish exposed to 10, 100, or 1000 µg/L BPS from 4 hpf to 120 hpf (Qiu et al. 2018).

- Upregulated eNOS (*NOS3*) gene expression in HUVECs incubated with 0.01, 0.1, and 1 (NS) µM BPS (Hu et al. 2024).

Other Organelle and Sub-cellular Effects

- One epidemiologic study (see Table 4.3.14), using data from a birth cohort in Wuhan, China, reported an inverse association between first trimester urinary BPS and lower umbilical cord blood mitochondrial DNA copy number levels in male offspring. No statistically significant associations were reported for female offspring or in unstratified analyses (L Wang et al. 2021).

- Increased number of active/functional mitochondria in the brains of WT AB strain zebrafish exposed to 10 or 100 µg/L BPS from 2 hpf to 6 dpf. Increased number of active brain mitochondria was also observed with exposure to BAY 876, a glut1 inhibitor (Wang et al. 2024).

- Altered endoplasmic reticulum stress-related marker expression in whole body homogenates of WT AB strain zebrafish exposed to 1, 10, or 100 µg/L BPS from 2 hpf up to 120 hpf (Wang et al. 2023). Specifically:

    - At 48 hpf, there was increased expression of endoplasmic reticulum stress response genes *bip* at all concentrations and *perk* at 10 and 100 µg/L, and decreased *perk* at 1 µg/L BPS.

    - At 48 hpf, there was increased expression of endoplasmic reticulum degradation genes *hsp70* at all concentrations, *hsp40* at 10 and 100 µg/L, and no effects on *hsp90*.

    - At 120 hpf, there was increased gene expression of *perk* at all concentrations and no effects on *bip*, and increased *hsp70* and *hsp90* at 1 µg/L and *hsp40* at 100 µg/L BPS.

    - At 120 hpf, protein levels of the endoplasmic reticulum chaperone protein, Bip were increased at 10 µg/L in whole body homogenates and all concentrations in the brain.

- Increased adenosine triphosphate (ATP) levels and decreased mitochondrial membrane potential in *C. elegans* exposed to 1 mM BPS from F1 larval stage to 2-day- and 3-day-old adult stage, respectively (Hyun et al. 2021).

- No effects on mitochondrial permeability transition pore opening or ATP levels in mouse embryonic fibroblasts incubated with up to 500 µM BPS for 24 hours (Hyun et al. 2021).

- Increased protein levels of ATF4, p-eIF2α/eIF2α, and p-PERK/PERK, involved in endoplasmic reticulum stress-associated eIF2α/ATF4 signaling pathway in JEG-3

human choriocarcinoma cells incubated with 50 μM BPS for 12 hours. Attenuation of effects with NAC or GSK co-treatments (Z Li et al. 2023).

Toxicogenomics

Toxicogenomics measures toxicant-mediated molecular changes using tools including transcriptomics, proteomics, metabolomics, and epigenomics. These data can help elucidate mechanisms of toxicity and are increasingly being used in toxicology research and risk assessment (Meier et al. 2025). In this document, 19 studies (three mammalian, nine non-mammalian, five *in vitro,* and two molecular epidemiology studies) used toxicogenomic methods to characterize BPS-mediated molecular effects. High-level study summaries are provided below.

Transcriptomics

The most widely assessed parameter, transcriptome-wide analysis via RNA-sequencing (RNA-seq) provides quantitative information on the mRNA expression of tens of thousands of genes. Genes with significant differences in expression levels between, for example, treatment and control groups are defined as differentially expressed genes (DEGs). These DEGs can be input into bioinformatic tools such as the Kyoto Encyclopedia of Genes and Genomes (KEGG) for insights into potential biological/molecular pathways and processes that are enriched or overlap with identified DEGs.

Two studies in mice, one study in rats, six studies in zebrafish, one study each in Chinese medaka, *C. elegans*, and sponges, and three *in vitro* studies utilized RNA-seq. One of the mouse studies (Zhang et al. 2023) utilized miRNA-sequencing to assess BPS-induced transcriptomic signatures. Overall, RT-qPCR validation of specific or target genes was consistent with RNA-seq results. Biological pathways and gene ontology terms that were consistently identified across studies included MAPK signaling and/or cellular, glucose or lipid metabolism (Huang et al. 2023; B Li et al. 2024; Qiu et al. 2023b; Yang et al. 2018; Zhang et al. 2022) and cardiac/cardiovascular-related terms including contractility, hypertrophy, and endothelial cell-related processes (Mao et al. 2020; Peshdary et al. 2021; Qiu et al. 2020; Zhang et al. 2022). Study-specific transcriptomic analysis summaries are listed below:

RNA-sequencing:

- Eleven DEGs were reported with one upregulated gene *Actn2* and ten downregulated genes in the placental tissue obtained on GD12.5 in C57BL/6J mice treated with 200 µg/day BPS (Mao et al. 2020).

- Five DEGs were reported in the placental tissue obtained on GD 18 in Wistar rats treated with 0.025 µg/kg-day from one week premating until GD 18. Three DEGs, *Loc103689945, Fut2,* and *Nxpe1* were reported with 4 µg/kg-day BPS, and overlapped with the DEGS identified with 0.025 µg/kg-day (Fudvoye et al. 2025).

- Transcriptomics analysis identified enriched pathways related to cellular energy metabolism, including fatty acid, amino acid, and glucose metabolism pathways in WT zebrafish exposed to 50 µM BPS from 0.5 hpf to 120 hpf (Huang et al. 2023).

- Transcriptomics analysis identified 594, 823, 2115 and 1573 DEGs in WT AB strain zebrafish treated with 0.1, 1, 10, and 100 µg/L BPS, respectively, from ~4 hpf to 120 hpf. The top-ranked canonical pathway was cardiac hypertrophy signaling at 10 and 100 µg/L BPS, with top predicted diseases and disorders related to immune diseases, inflammation, and the cardiovascular system at all concentrations (Qiu et al. 2020).

- Transcriptomics analysis indicated effects of BPS on metabolic and MAPK signaling pathways. There were 1803, 3029, 3979, 3786, and 2421 DEGs and 64, 17, 72, 84, and 42 enriched KEGG pathways identified in WT AB strain zebrafish exposed to 0.1, 1, 10, 100, or 1000 µg/L BPS, respectively, from 4 hpf to 120 hpf. Across all five treatment groups, there was an overlap of 67 DEGs and 15 KEGG pathways (Yang et al. 2018).

- Transcriptomics analysis of WT AB strain zebrafish embryos exposed to 1 µg/L BPS from 2 hpf to 48 hpf indicated changes in common cardinal vein-related genes and the cardiac muscle contraction pathway (Zhang et al. 2022). Specifically:

    - Na^+-K^+ and Ca^{2+} pump genes *cacna2sa, cacna2d1a,* and *cacna1sb* were upregulated at 48 hpf with 1 µg/L BPS treatment.

    - Endothelial cell proliferation, growth, and migration genes *tie2, atf3, cdh5,* and *vegfaa* were downregulated at 48 hpf with 1 µg/L BPS treatment.

    - Other enriched or overrepresented KEGG pathways included the oxidative phosphorylation, carbon metabolism, and protein processing in the endoplasmic reticulum pathways (Zhang et al. 2022).

- Transcriptomics analysis identified 423 DEGs with 121 upregulated and 302 downregulated genes in WT AB strain zebrafish exposed to 100 µg/L BPS from 2 hpf to 48 hpf. Protein processing in the endoplasmic reticulum was identified as an enriched KEGG pathway (Wang et al. 2023).

- Transcriptomics analysis of the eyes of 120 hpf WT Tu strain zebrafish treated with 1, 10, or 100 µg/L BPS identified 2015, 5411, and 7900 DEGs, respectively. At all concentrations, enriched KEGG pathways including Apoptosis, p53 signaling, Wnt signaling, MAPK signaling, and phototransduction (Qiu et al. 2023b).

- Altered gene expression in metabolism and immune- or disease-related genes via transcriptomic analysis in Chinese medaka fish exposed to 20, 200, or 2000 ng/L BPS from the blastula stage (~6.5 to 10 hpf) to 15 dpf (B Li et al. 2024).

- Top gene ontology terms included embryonic development and reproduction, and 878 differentially expressed genes were identified in *C. elegans* exposed to 500 µM BPS from L1 to 24 hours post-L4 (Chen et al. 2016).

- Based on RNA-seq data in sponge (*Ephydatia muelleri*) gemmules treated with 4 mg/L BPS, two upregulated genes, glutathione-s-transferase omega (*gsto1*) and prostaglandin synthase 1 (*prost1.2*) were assessed for gene expression in WT zebrafish treated with 4 mg/L from 6-10 hpf to 96 hpf. Increased expression of both *gsto1* and *prost1.2* was observed (Neighmond et al. 2023).

- Transcriptomics analysis identified 0, 1, 3420, and 5004 DEGs in H9 human embryonic stem cells treated with 1, 10, 300, and 400 µM BPS, respectively, for three days. Pathway and benchmark concentration analyses were run at 300 µM BPS. The Ingenuity Pathway Analysis tool identified 99 pathways and 658 upstream regulators significantly affected. Top canonical pathways included Superpathway of Cholesterol Biosynthesis and Role of NFAT in Cardiac Hypertrophy and microRNAs were the top upstream regulators affected (Peshdary et al. 2021).

- In Lehle et al. (2024), induced pluripotent stem cells (iPSCs) reprogrammed from mouse embryonic fibroblasts from an embryonic day 13.5 male were incubated

with 1, 50, or 100 µM BPS for 24 hours. Transcriptomic and epigenomic analyses were conducted.

  - Transcriptomics analysis identified a concentration-dependent increase in the number of DEGs. There were 1332, 4065, and 5078 DEGs with 1, 50, and 100 µM BPS, respectively. There were 1211 DEGs that overlapped across the three concentrations.

  - In another experiment, mouse iPSCs and primordial germ cell-like cells (PGCLCs) differentiated from epiblast-like cells derived from mouse iPSCs were incubated with 1 µM BPS for 24 hours. Both transcriptomic and epigenomic analyses were conducted. Transcriptomics analysis identified more DEGs in PGCLCs (1890 DEGs) than iPSCs (1037 DEGs). Immunocytochemical analysis to detect hormone and other nuclear receptors (ESR1, ESR2, AR, PPARG, and RXRA) in iPSCs and PGCLCs detected ESR2 in BPS-treated iPSCs with no detection of the other receptors. In PGCLCs, none of the assessed receptors were detected.

  - To examine the effects of BPS treatment on pluripotent to germline transition, iPSCs were incubated with 1 µM BPS, and then differentiated into epiblast-like cells and then into PGCLCs. Transcriptomic and epigenomic analyses were conducted. In total, there were 1637 DEGs in directly exposed iPSCs and 1437 DEGs in subsequently derived PGCLCs. There were 138 overlapping DEGs (8.4%) between these two cell-types. KEGG pathway analysis of these 138 DEGs identified enrichment of cell cycle and apoptosis pathways (Lehle et al. 2024).

- Metabolism-associated KEGG pathways including cholesterol metabolism, complement and coagulation cascades, fat digestion and absorption, and the PPAR signaling and Hedgehog signaling pathways were enriched in human embryonic stem cell-derived three-dimensional embryoid bodies incubated with 100 nM BPS for 21 days (X Liang et al. 2021).

  - Lipid metabolism-related genes were upregulated including genes encoding several apolipoproteins (*APOA4, APOC3, APOA2, APOB,* and *APOA1*), a fetoprotein produced in the developing liver (*AFP*), and proteins involved in erythropoiesis and coagulation (*FGG* and *FGA*).

  - Overall, there were 185 DEGs with 159 upregulated and 26 downregulated DEGs.

Micro-RNA (miRNA) sequencing

- Differentially expressed miRNAs were identified in serum exosomes and the white adipose tissue of 12-week-old male offspring of ICR mice treated with 50 µg/kg-day BPS via oral gavage from GD 0.5 to GD 18.5. Expression of miR-29a-3p was decreased in both exosomes and white adipose tissue (Zhang et al. 2023).

Proteomics

Two *in vitro* studies assessed and characterized BPS-mediated proteomic signatures.

- Proteomics analysis identified 489 and 803 differentially expressed proteins in human embryonic stem cell-derived cerebral organoids treated with 10 and 100 nM BPS, respectively, for 14 days. There were 204 shared differentially expressed proteins that included proteins involved in neuronal differentiation and nervous system development, Wnt signaling, cell fate commitment, and forebrain regionalization. At both concentrations, decreased size and proliferation of cerebral organoids was observed. At 100 nM BPS, there was decreased thicknesses of ventricular and subventricular zones within neural rosettes. (Abdulla et al. 2024).

- Proteomics analysis reported 69 upregulated proteins and 248 downregulated proteins in 3T3-L1 pre-adipocytes treated with 200 nM BPS for up to 10 days. Pathway analysis identified enrichment of Propanoate metabolism, Biosynthesis of unsaturated fatty acids, Fatty acid metabolism, and PPAR signaling pathways. (Kulsange et al. 2024).

Metabolomics

One epidemiologic study (see Table 4.3.14) estimated the associations between prenatal urinary BPS, measured once each during the first, second, and third trimesters, and neonatal metabolite profiles using data from the Generation R Study in The Netherlands (Blaauwendraad et al. 2021):

- Average BPS levels across pregnancy were associated with lower umbilical cord blood concentrations of overall alkyl-lysophosphatidylcholines and saturated alkyl-lysophosphatidylcholines. Lysophosphatidylcholine may play a role in delivering long chain polyunsaturated fatty acids to support fetal development.

- First trimester BPS levels were associated with higher umbilical cord blood concentrations of overall acyl-carnitines, and as subcategories, small-, medium-, and large-chain acyl-carnitines.

- Third-trimester BPS levels were associated with lower umbilical cord blood concentrations of overall acyl-carnitines, and as subcategories, small- and large-chain acyl-carnitines; and overall and saturated non-esterified fatty acids and mono-unsaturated acyl-lysophosphatidyl-cholines (Blaauwendraad et al. 2021).

Metabolomics analysis identified effects on fatty acids in the placental tissue obtained on GD12.5 in C57BL/6J mice treated with 200 µg/day BPS. Stearic acid, hexadecanoic (palmitic) acid, docosahexaenoic acid, and octadecenoic acid were decreased (Mao et al. 2020).

Epigenomics

One epidemiologic study (see Table 4.3.14) estimated the associations between prenatal urinary BPS exposure measured at 8 to 14 weeks gestation and epigenome-wide DNA methylation in umbilical cord blood. This study analyzed data from the Michigan Mother-Infant Pairs pregnancy cohort and reported an association between urinary BPS during gestation and one differentially methylated CpG site, cg06871344 in *VPS53* which encodes vacuolar protein sorting-associated protein 53 (McCabe et al. 2020).

In Lehle et al. (2024), induced pluripotent stem cells (iPSCs) reprogrammed from mouse embryonic fibroblasts from an embryonic day 13.5 male were incubated with 1, 50, or 100 µM BPS for 24 hours, there were 12,173, 30,841, and 25,560 combined hypo- and hyper-methylated differentially methylated cytosines at 1, 50, and 100 µM, respectively.

In another experiment, mouse iPSCs and primordial germ cell-like cells (PGCLCs) differentiated from epiblast-like cells derived from mouse iPSCs were incubated with 1 µM BPS for 24 hours. There were 13,959 and 7100 differentially methylated CpG sites for iPSCs and PGCLCs, respectively.

To examine the effects of BPS treatment on pluripotent to germline transition, iPSCs were incubated with 1 µM BPS, and then differentiated into epiblast-like cells and then into PGCLCs. There were lower numbers of BPS-associated differentially methylated CpG sites in PGCLCs (28,169) compared to directly exposed iPSCs (38,105), with 3.7% overlap (Lehle et al. 2024).

Table 4.3.13 Developmental toxicity: studies with mechanistic data not already included in Tables 4.2.1 and 4.2.2

Study Design	Outcomes assessed	Major Findings
Abdulla et al. 2024 *In vitro*: H9 cell line (human embryonic stem cell-derived cerebral organoid) on a multi-channel microfluidic chip; 16 organoids per chip (4 chambers); n=4-12 organoids (sample size varied by assay). Treatment: BPS (purity not reported) in culture media (specific vehicle not reported) at concentrations of 0, 10, and 100 nM (equivalent to 2.50 and 25.03 µg/L, calculated by OEHHA) from Culture Days 20-34. Organoids were collected on Day 34 for analyses.	Bright field microscopic imaging. Cell proliferation (immunostaining for Ki67). Apoptosis (TUNEL assay). Neural differentiation (immunostaining and reverse transcription quantitative polymerase chain reaction [RT-qPCR] for PAX6 [forebrain marker], MAP2, SOX2 [stem cell marker], and TUJ1 [neuronal marker] mRNA and protein). Proteomic analysis (8334 proteins from each organoid; included analysis of neuronal differentiation markers [PAX6 and TUJ1], stem cell markers [SOX2 and NES], neuronal marker [DCX], and cell proliferation [MKI67]). RT-qPCR of relevant genes identified by proteomic analysis (*KI67, TUJ1, SOX2, CDON, ID1, LHX1, WNT2B, WNT7B, WNT8B, FZD2, NTRK2*, and *BCAT1*).	Cellular morphology: Decreased size of organoids at 10 and 100 nM. Cell proliferation: Decreased Ki67 positive (+) cells at 10 and 100 nM. Apoptosis: No effect. Neural differentiation: Decreased expression of MAP2 and TUJ1 protein and mRNA, and PAX6 protein at 100 nM. Decreased thickness of ventricular zone/subventricular zone within neural rosettes at 100 nM. Proteomics: 489 differentially expressed proteins (DEPs) at 10 nM (281 upregulated and 208 downregulated), 803 DEPs at 100 nM (376 upregulated and 427 downregulated), with 204 shared DEPs (110 upregulated and 91 downregulated). Shared DEPs at 10 and 100 nM included: proteins involved in neuron differentiation (10 upregulated, 7 downregulated), nervous system development (5 upregulated, 8 downregulated), Wnt signaling pathway (6 upregulated, 7 downregulated), cell fate commitment (4 upregulated, 2 downregulated), and forebrain regionalization (1 upregulated, 2 downregulated). RT-qPCR of lipid metabolism, neuron differentiation, and forebrain regionalization genes: Lipid metabolism: Decreased expression of *BCAT1* at 100nM. Neuron differentiation: Decreased expression of *NTRK2* at 100 nM. Forebrain regionalization: Decreased expression of *WNT7B*, *WNT8B*, *FZD2*, and *LHX1* at 100 nM.
Blanc et al. 2019 *In vivo:* Zebrafish, wildtype AB strain, n = 20 embryos per experiment repeated 1-2 times.	Zebrafish embryo/larvae: Gene expression analysis (qPCR): DNA methyltransferases (*dnmt1, dnmt3aa, dnmt3ab,* and *dnmt3ba*), histone deacetylases (*hdac1* and *hdac3*), and histone demethylase (*kdm5ba*).	Zebrafish embryo/larvae: Gene expression analysis: Decreased *hdac3* at 24 hpf No effects at 96 hpf.

Study Design	Outcomes assessed	Major Findings
Treatment: BPS (purity > 98%) at 27 µM (equivalent to 6.76 mg/L, calculated by OEHHA) in 0.1% v/v DMSO (vehicle control) from 1 hpf to 24 hpf or 96 hpf. The study authors intended to use the LC_{10}, extrapolated from concentration-response curve analyses based on results from a simplified semi-static Fish Embryo Acute Toxicity test following 96 hours exposure. However, as BPS was not acutely toxic to embryo/larvae, a concentration of 27 µM BPS was selected based on acute toxicity results of its analogue, BPA.		
Di Credico et al. 2023 *In vitro*: Human fetal membrane mesenchymal stromal cells (hFM-MSCs) and human amniotic fluid stem cells (hAFSCs). Treatment: BPS (purity not reported) at 0 or 0.1 µM (equivalent to 25.03 µg/L, calculated by OEHHA) for 24 to 48 hours.	Cell proliferation (up to 48 hours). Ki67 (G2-M phase/cell proliferation marker). Pluripotency gene markers (24 hours): *NANOG, OCT4, SOX2, KLF4, ESG1, and OVOL1.* Epigenetic regulator genes (24 hours): *DNMT1, DNMT3A, TET1, TET2,* and *TET3.* Mitochondrial membrane potential (24 hours).	Cell proliferation: Increased at 12, 24, 36, and 48 hours in hFM-MSCs Increased at 24, 36, and 48 hours in hAFSCs. G2-M phase/cell proliferation marker: Increased Ki67 in hFM-MSCs and hAFSCs. Pluripotency gene markers in hFM-MSCs: Decreased *KLF4*, Increased *OVOL1*, and No effect on *NANOG*, *OCT4*, *SOX2*, or *ESG1*. Epigenetic regulator genes in hFM-MSCs: Increased *DNMT3A* and *TET3*, Decreased *TET1*, and No effect on *DNMT1* or *TET2*. Pluripotency gene markers in hAFSCs: Increased *NANOG, OCT4, SOX2, ESG1,* and *OVOL1*. No effect on *KLF4*. Epigenetic regulator genes in hAFSCs: Increased *DNMT1, TET1*, and *TET3*, Decreased *DNMT3A*, and No effect on *TET2*. Mitochondrial membrane potential: No effect.

Study Design	Outcomes assessed	Major Findings
H Fan et al. 2021 *In vitro*: Ishikawa (human endometrial adenocarcinoma) and JEG-3 (human choriocarcinoma) cell lines. Treatment: BPS (98% purity) in 0.1% DMSO (vehicle control) at 0, 0.001, 0.01, 0.1, 1, 10, or 100 µM (equivalent to 0.25, 2.50, 25.03, and 250.27 µg/L and 2.50 and 25.03 mg/L, calculated by OEHHA) from 24 to 72 hours with and without 1 µM estrogen receptor antagonists ICI 182,780 (ICI), MPP dihydrochloride, PHTPP, or G15.	The following assays were conducted in Ishikawa cells: Cell proliferation (24, 48, and 72 hours). Cell viability (24 hours). Hormone receptor protein levels (24 hours): estrogen receptors (ESR1, ESR2, and GPR30) and progesterone receptor (PGR; isoforms A and B). Estrogen responsive element reporter assay with and without estrogen receptor antagonists: ICI, MPP dihydrochloride [ESR1 antagonist], PHTPP [ESR2 antagonist], or G15 [GPR30 antagonist]. Transcriptome analysis with qPCR validation (10 µM BPS; 24 hours): Total number of genes above 1.5-fold change. Gene expression with and without ICI or G15 (10 µM BPS; 24 hours). JEG-3 spheroid attachment rate (24 hours).	Cell proliferation: Decreased proliferation rate at 100 µM at 24, 48, and 72 hours. Cell viability: Decreased cell viability at 100 µM at 24 hours. Estrogen receptor protein levels: Decreased ESR1 and ESR2 at 10 and 100 µM, and Decreased GPR30 at 1, 10, and 100 µM. Progesterone receptor protein level: Increased PGR isoforms A and B at 1, 10, and 100 µM. Estrogen responsive element reporter assay: Luciferase signal increase with BPS alone at 10 µM, Attenuated signal with ICI and MPP at 10 µM, and No effect with PHTTP or G15 at 10 µM. Transcriptome analysis: 26 upregulated genes and 5 downregulated genes. Gene expression with and without ICI and G15. Top 3: *THBS1* (+3.84-fold), *PGR* (+3.74-fold), *NPPC* (+2.78-fold). Endometrial receptivity-related: *ANO1* (+2.69-fold), *TGFA* (+2.21-fold), and *OLFM1* (+1.77-fold). Attenuated with ICI, but not G15, in THBS1 and PGR and Attenuated in with ICI and partial attenuation with G15 in NPPC, ANO1, TGFA, and OLFM1. JEG-3 spheroid attachment rate: Decreased attachment rate at 100 µM, and Attenuated attachment rate at 100 µM with PGR siRNA.
Hu et al. 2024 *In vitro*: Primary human umbilical vein endothelial cells (HUVECs), n=4 biological replicates. Treatment: BPS (≥97% purity) in 0.1% DMSO at concentrations 0, 10^{-8}, 10^{-7}, 10^{-6}, or 10^{-5} M (0, 0.01, 0.1, 1, or 10 µM; equivalent to 2.50, 25.03, and 250.27 µg/L and 2.50 mg/L, calculated by OEHHA) for 6 or 24 hours; cells were co-treated with 10^{-7} M triiodothyronine [T3] for one assay.	NO level with and without T3 co-treatment. Endothelial NO synthase (eNOS) mRNA expression (24 hours) with BPS treatment only. eNOS protein and phosphorylation levels (6 hours), with and without T3 co-treatment. eNOS activity (6 hours).	NO level: Increased at 1 µM (+68%) BPS; at 0.01 (+39%), 0.1 (+52%), and 1 (+37%) µM with BPS + T3 co-treatment; and with T3 alone (+53%). eNOS mRNA expression: Increased at 0.01, 0.1, and 1 (NS) µM BPS. eNOS protein and phosphorylation levels: Increased phosphorylated eNOS at Ser1177 at 1 µM BPS; no effects with BPS + T3 co-treatment or T3 alone. No effect on total eNOS protein levels.

Study Design	Outcomes assessed	Major Findings
Most assays were performed with doses up to 1 µM; Nitric oxide (NO) level assay only used cells treated at 10 µM No effect of BPS treatment on cell viability up to 10 µM.		eNOS activity: Increased at 0.1 (+43%) and 1 (+28%) µM with BPS; and at 0.01 (+64%), 0.1 (54%), and 1 (+108%) µM with BPS + T3 co-treatment. Note – effect with BPS + T3 at high dose appeared significant, though not reported as such in figure.
Ji et al. 2022 *In vitro*: Primary HUVECs; biological replicates not reported. Treatment: BPS (98% purity) at 0, 20*, 50, 100, 200, 300, 400, 500 or 1000 mg/L for 24 h. *Concentration only reported in ROS assay, but not in the study methods. Cell culture medium was renewed daily. Cell viability: Decreased with 400, 500, and 1000 mg/L BPS treatments.	Endothelial cell tube formation assay: total branching points, length of the master segment, and length of the branch at 300 mg/L (the highest non-cytotoxic concentration). ROS generation at 20 mg/L and 300 mg/L.	Endothelial cell tube formation assay: No effects on number of branch points, length of master segments, or length of the branch on endothelial tube formation. ROS generation: No effect at 20 mg/L. Increased at 300 mg/L (+100%).
Kubota et al. 2023 *In vivo*: Zebrafish larvae, wildtype AB strain. Treatment: BPS (98% purity) in 0.1% DMSO (v/v) at 0, 0.3, 1, 3, 10, and 30 µM (equivalent to 75.08, 250.27, 750.83, 2502.75, and 7508.25 µg/L, calculated by OEHHA) from 72 to 96 hpf. *In silico*: Zebrafish Esr1, Esr2a, and Esr2b were modeled based on human ESR1 and ESR2 X-ray crystal structures using Molecular Operating Environment Program software.	Gene expression (*cyp19a1b* and *vtg1*). Docking simulation binding scores (kcal/mol): E2 or BPS for Esr1, Esr2a, and Esr2b.	Gene expression: NS induction of *cyp19a1b* (<2-fold) at 30 µM, and Decreased *vtg1* at 30 µM. Docking simulation binding scores: -8.85 E2 and -6.86 BPS for Esr1, -8.04 E2 and -6.33 BPS for Esr2a, and -8.41 E2 and -6.88 BPS for Esr2b.
Kulsange et al. 2024 *In vitro*: 3T3-L1 cells (mouse embryonic fibroblasts, pre-adipocyte cell line), n=3 biological replicates. Treatment: BPS (≥99.9% purity) in 0.02% DMSO at concentrations of 0 or 200 nM for up to 10 days.	Lipid accumulation (Oil Red O staining). Proteomics analysis. Bioinformatics: key DEPs, pathway enrichment for DEPs, hub gene analysis via STRING Protein-Protein Interaction network.	Lipid accumulation: Increased following 10-day exposure. Proteomics analysis: 1132 proteins identified with minimum two unique peptides, 69 proteins upregulated, and 248 downregulated with BPS.

Study Design	Outcomes assessed	Major Findings
		Differentially expressed proteins: ACOX1 (peroxisomal fatty acid β-oxidation system), ACOT2 and FABP4 (fatty acid metabolism and PPAR signaling), and ACADS (mitochondrial fatty acid oxidation) were upregulated, HIBCH (propanoate metabolism) and HACD2 (fatty acid metabolism) were downregulated. Pathway fold enrichment of differentially expressed proteins: Propanoate metabolism (17-fold), biosynthesis of unsaturated fatty acids (20-fold), fatty acid metabolism (17-fold), and PPAR signaling pathway (14-fold). Hub gene analysis: Fatty acid metabolism: ACOX1, SOD1, LAMP1, SCP2. Mitochondrial function and dynamics: FIS1, IMMT. Obesity and insulin resistance: VDAC1. Adipocyte cell biology and differentiation: CALR, RPN1. PPAR stabilizer: UBC.
Le Fol et al. 2017 *in vivo* BPS estrogenic activity. Zebrafish, embryo/larvae (transgenic, *cyp19a1b*-GFP, derived from AB strain). Treatment: BPS (purity not stated) in 0.01% v/v DMSO (vehicle control) at 0, 0.25, 0.5, 1, 2.5, 5, 10, 20, 30, and 60 µM (equivalent to 62.57, 125.14, and 250.03 µg/L and 1.25, 5.01, 7.51, and 15.02 mg/L, calculated by OEHHA) from 0 to 4 dpf. Solutions were completely renewed every 24 hours. Zebrafish co-exposed with either ER antagonist, ICI, at 1 µM, or anti-androgenic drug, flutamide (FLU), at 1 µM. 0.05 nM ethinyl estradiol (EE) utilized as positive control. No effect of BPS treatment on mortality.	*In vivo* BPS estrogenic activity: *cyp19a1b*-GFP induction (Esr mediated gene). Co-treatment with ICI. Co-treatment with FLU.	*In vivo* BPS estrogenic activity: *cyp19a1b*-GFP induction: Increased fluorescence in 30 (+3.0-fold) and 60 (+4.5-fold) µM groups. Co-treatment with ICI or FLU: No effect on BPS-mediated increase in fluorescence. Support for differential estrogenic response.
Lehle et al. 2024 *In vitro*: Mouse induced pluripotent stem cells (iPSCs) reprogrammed from mouse embryonic fibroblasts from a single male (XY) E13.5 fetus.	**Experiments 1, 2, and 3:** DNA methylation. Differentially methylated CpGs (DMCs) and differentially methylated regions (DMRs) (via Methylation BeadChip for Experiments 1 and 2 and	**Experiment 1:** DNA methylation: 12,173, 30,841, and 25,560 combined hypo- and hyper-methylated DMCs at 1, 50, and 100 µM, respectively.

Study Design	Outcomes assessed	Major Findings
Primordial germ cell-like cells (PGCLCs) culture derived from epiblast-like cells differentiated from mouse iPSCs. **Experiment 1: iPSCs.** Treatment: BPS (purity not reported), dissolved in absolute ethanol at 0, 1, 50, or 100 µM (equivalent to 0.25, 12.51, and 25.03 mg/L, calculated by OEHHA) for 24 hours in triplicate. **Experiment 2: iPSCs and PGCLCs.** Based on findings from Experiment 1, subsequent experiments treated with 0 or 1 µM BPS for 24 hours in triplicate for iPSCs and PGCLCs followed by a washing and recovery period in untreated media for 24 or 8 hours, respectively. Sertoli and granulosa cells isolated and cultured from juvenile mice were also evaluated but are nominally discussed and will be referred to as somatic cells here. **Experiment 3: Pluripotent to germline transition**. iPSCs were treated with 0 or 1µM BPS, differentiated into epiblast-like cells which were then differentiated into PGCLCs.	enzymatic methyl sequencing [EM-seq] for Experiment 3). Gene expression. Differentially expressed genes (DEGs) identification (via RNA-seq). **Experiment 2:** Hormone and other nuclear receptor expression: Erα (ESR1), Erβ (ESR2), AR, PPARγ (PPARG), and RXRα (RXRA) (immunofluorescence) and associations with BPS-induced alterations in DNA methylation. Proximity of genomic estrogen response elements [EREs] to alterations in DNA methylation. Pathway enrichment analysis: Identification of non-canonical endocrine signaling pathways. **Experiment 3:** Persistence of alterations in DNA methylation during pluripotent to germline transition in cell fate: comparison of DMCs and DEGs identified in treated iPSCs versus in the subsequently derived PGCLCs.	Concentration-dependent increase in total number of hypo- and hyper-methylated DMRs. Gene expression: Concentration-dependent increase in number of DEGs: 1 µM: 868 upregulated and 464 downregulated. 50 µM: 2,139 upregulated and 1,926 downregulated. 100 µM: 2,524 upregulated and 2,554 downregulated. Number of overlapping DEGs across all concentrations: 1,211. **Experiment 2:** DNA methylation: DMCs associated with enhancer regions for iPSCs and somatic cells; and promoter regions for PGCLCs. Number of DMCs: iPSCs: 13,959. PGCLCs: 7100. Sertoli cells: 10,407. Granulosa cells: 10,587. Gene expression: PGCLCs had the highest number (1890) of DEGs followed by iPSCs (1037) and somatic cells (Sertoli cells; 35 DEGs and granulosa cells; 2 DEGs). Hormone and other nuclear receptor expression and genomic EREs: Somatic cells – positive for ESR1 and ESR2; negative for AR, PPARG, and RXRA. iPSCs – positive for ESR2; negative for ESR1, AR, PPARG, and RXRA. PGCLCs – negative for assessed receptors. Higher frequency of estrogen responsive element half-sites within 500 base pairs of DMCs genome-wide in somatic cells and iPSCs when focusing on enhancer regions. Pathway enrichment analysis. Ubiquitin-like protease pathways, including pathways regulating protein degradation and 1-phosphatidylinositol-3 kinase (PI3K) identified as non-canonical endocrine signaling pathways in all cell types.

Study Design	Outcomes assessed	Major Findings
		For PGCLCs, four DEGs of seven genes associated with phosphatidylinositol-4 phosphatase signaling. **Experiment 3:** Persistence of alterations in DNA methylation during pluripotent to germline transition in cell fate: Lower numbers of BPS-associated DMCs and DEGs in PGCLCs (28,169 DMCs and 1437 DEGs) compared to directly exposed iPSCs (38,105 DMCs and 1637 DEGs). Overlap between directly exposed iPSCs and derived PGCLCs was 3.7% (DMCs) and 8.4% (DEGs). KEGG pathway analysis in the 138 overlapping DEGs included FoxO signaling pathway, Cell cycle, Lysosome, and p53 signaling pathway.
Z Li et al. 2023 *In vitro*: JEG-3; human choriocarcinoma cell line. Treatment: BPS (purity not reported) in DMSO at 0, 12.5, 25, 50, 100, or 200 µM (equivalent to 3.13, 6.26, 12.51, 25.03, and 50.06 mg/L, calculated by OEHHA) for up to 24 hours. Note: JEG-3 cells cannot synthesize E2 directly, therefore dehydroepiandrosterone (DHEA) at 500 ng/mL added to cells. Co-treatments with ROS inhibitor NAC at 0, 1, 2, 4, or 8 mM (cell viability) and 200 µM (oxidative stress) or GSK, a PERK inhibitor at 62.5, 125, 250, or 500 nM (cell viability). NAC and GSK concentrations not reported for other assays. Cell viability measured at all concentrations at 2, 4, 6, 12, and 24 hours for BPS or 12 hours for NAC and GSK: Decreased at 6 hours with 100 and 200 µM, 12 hours with 50 and 200 µM, and 24 hours with ≥50 µM BPS. Slightly decreased with 4 and 8 mM NAC and no effects with GSK.	E2 levels at 2, 4, 6, 12, and 24 hours with 50 µM BPS alone or co-treatments with NAC or GSK at 12 hours. Oxidative stress: ROS production at 4, 6, and 12 hours with 50 µM BPS alone or co-treatments with NAC or GSK at 12 hours. MDA (lipid peroxidation) and SOD concentrations at 4, 6, and 12 hours with 50 µM BPS. mRNA expression of *CYP19A1* at 12 hours with 25, 50, and 100 µM BPS alone 2, 4, 6, 12, and 24 hours with 50 µM BPS alone; or co-treatments of NAC or GSK and 50 µM BPS for 12 hours. Protein levels of CYP19A1 and endoplasmic reticulum stress-associated pathway proteins: ATF4, p-eIF2α/eIF2α (p-EIF2A/EIF2A), p-PERK/PERK at 12 hours with 50 µM BPS alone or co-treatments of NAC or GSK.	E2 levels (50 µM): Decreased at 2, 4, 6, and 12 hours with BPS alone. Attenuation of effects with NAC and GSK co-treatments. Oxidative stress (50 µM BPS) : Increased ROS at 4, 6, and 12 hours with BPS alone. Attenuation of effects with NAC co-treatment. Increased MDA content at 12 hours. Decreased SOD content at 4, 6 (NS), and 12 hours. *CYP19A1* gene expression: Decreased at 25 and 50 µM and increased at 100 µM BPS alone at 12 hours. Decreased at 4, 6, and 12 hours, and increased at 24 hours at 50 µM BPS alone. Attenuation of effects with NAC or GSK co-treatments. Endoplasmic reticulum stress protein levels (50 µM BPS): Increased ATF4, p-EIF2A/EIF2A, and p-PERK/PERK with BPS alone. Decreased CYP19A1 with BPS alone. Attenuation of effects with NAC or GSK co-treatments.
X Liang et al. 2021 *In vitro*: Human embryonic stem cell (hESC)-derived 3D embryoid bodies and hepatocyte-like cells.	All results are from 100nM BPS treatment groups. Embryoid bodies: Germ layer marker-related gene expression: Endoderm (*GATA6, CXCR4, FOXQ1*, and *HNF1B*),	Embryoid bodies: Germ layer marker-related gene expression: Decreased *KRT14* and *OTX2* expression. No effects on endoderm or mesoderm-related gene expression.

Study Design	Outcomes assessed	Major Findings
Treatment: BPS (purity > 98%) in 0.01% DMSO and cell culture media at concentrations 0 (control), 0.1, 1, 10, and 100 nM (equivalent to 25.03 and 250.27 ng/L and 2.50 and 25.03 µg/L, calculated by OEHHA) from differentiation day 0 to 21 to assess global differentiation and for the 18-day differentiation period to assess hepatic differentiation. Total RNA for RNA-seq was collected from undifferentiated hESCs and day 21 embryoid body cells from 0 (control) and 100 nM BPS-treated groups. RT-qPCR was performed on day 18 hepatocyte-like cells and day 21 embryoid bodies n = 3, repeated in triplicate.	Mesoderm (*EOMES, PDGFRA, TBX5,* and *GSC*), and Ectoderm (*NGN1, KRT14, TFAP2A,* and *OTX2*). Lipid metabolism-related gene expression (RNA-seq and RT-qPCR). RNA-seq analysis: Differentially expressed genes. KEGG pathways analysis. Hepatocyte-like cells: Hepatic marker gene expression (RT-qPCR). Lipid metabolism-related gene expression (RT-qPCR). HNF4α (HNFA) protein levels.	Lipid metabolism-related gene expression: Increased *APOA4, AFP, APOC3, APOA2, FGG, FGA, AHSG, APOB,* and *APOA1* via RNA-seq, and Increased *APOA4* and *FGB* via RT-qPCR in embryoid bodies. Differentially expressed genes: 159 upregulated and 26 downregulated genes in the 100nM BPS embryoid body group. KEGG pathway analysis: Cholesterol metabolism, Complement and coagulation cascades, Vitamin digestion and absorption, Fat digestion and absorption, PPAR signaling pathway, Hedgehog signaling pathway. Hepatocyte-like cells: Hepatic marker gene expression: Increased *HNF4A* in hepatocyte-like cells. No effect on lipid metabolism-related gene expression. No effect on HNF4A protein levels.
Lu et al. 2018 **Experiment 1:** Thyroid hormone receptor β (THRB) and ligand antagonism (yeast two-hybrid). Treatment: BPS (purity ≥ 98%) in DMSO (final volume unspecified) at 0 to 50 µM (equivalent to 12.51 mg/L, calculated by OEHHA) with 100 µM T3 for 2.5 hours. **Experiment 2:** Competitive binding assay using recombinant THRB ligand binding domain (LBD) and T3 as a fluorescent probe. Treatment: BPS (purity ≥ 98%) in DMSO (final volume unspecified) at 1.5 µM (equivalent to 375.41 µg/L, calculated by OEHHA) added to THRB with and without 1.5 µM T3. **Experiment 3:** Conformational changes on recombinant THRB LBD using fluorescence spectroscopy (cell-free system).	THRB/ligand antagonism (recombinant yeast two-hybrid assay). THRB/T3 competitive binding assay. Zebrafish *thrb* mRNA expression (qPCR) at 72 hpf. THRB LBD molecular dynamics simulations.	**Experiment 1:** THRB/ligand antagonism: Decreased β-galactosidase activity at 5 and 50 µM. Calculated IC10 = 312 nM. **Experiment 2:** THRB/T3 competitive binding assay: Decreased association constant with addition of T3, indicative of BPS binding at the same site as T3. **Experiment 3:** THRB LBD fluorescence spectroscopy: Decreased fluorescence at 15 and 20 µM. **Experiment 4:** Zebrafish *thrb* mRNA expression: Increased *thrb* expression at 1 µM. **Experiment 5:** THRB LBD molecular dynamics simulations: Changes in conformation following BPS binding with

Study Design	Outcomes assessed	Major Findings
Treatment: BPS (purity ≥ 98%) in DMSO (final volume unspecified) added to amplified THRB ligand binding domain (LBD) at 0, 1, 5, 10, 15, and 20 µM (equivalent to 250.27 µg/L and 1.25, 2.50, 3.75, and 5.01 mg/L, calculated by OEHHA). **Experiment 4:** *In vivo:* Zebrafish embryo/larvae (strain not specified). Treatment: BPS (purity ≥ 98%) in 0.02% DMSO (vehicle control) at 0, 0.01, 0.1, or 1 µM (equivalent to 2.50, 25.03, and 250.27 µg/L, calculated by OEHHA) from 0 to 72 hpf. **Experiment 5:** *In silico:* Tertiary THRB LBD in complex with BPS modeled based on X-ray crystal structure using MVD 4.2 software.		Increased average root-mean-squared deviation of α carbon atoms from 1.78 (ligand free) to 1.96 Å. Increased average distance between nitrogen NE2 of HIS435 at helix 11 and nitrogen N of Phe459 at helix 12 in from 4.41 (ligand free) to 10.5 3 Å. BPS formed hydrogen bonds with Thr273 and His435 with a corresponding occupancy of 83% and 93%, respectively.
Luo et al. 2023 H9c2 cells (rat myoblast cell line, derived from embryonic rat heart tissue) and HUVECs (human umbilical vein endothelial cells). Treatment: BPS (purity not reported) in 0.9% normal saline and cell culture media at concentrations 0 (control), 0.01, 0.1, 1, 10, 100, and 1000 µM (equivalent to 2.50, 25.03, and 250.27 µg/L and 2.50, 25.03, and 250.27 mg/L, calculated by OEHHA) for up to 26 hours. Oxidative stress assays: Cells were incubated with BPS for 2 hours followed with and without co-treatments of N-acetyl-L-cysteine (NAC, an oxidative stress inhibitor) or pyrrolidine dithiocarbamate (PDTC, an NF-κB [NFKB] inhibitor) for another 24 hours. Cell viability: Decreased in both cell lines with 100 and 1000 µM BPS. At 1000 µM, survival rates were 26% and 19% in H9c2 cells and HUVECs, respectively; therefore, 100 µM was selected as the high dose of the study.	Oxidative stress: ROS levels. NFKB phosphorylation assessed at 100 µM BPS with NAC co-treatment Apoptosis: Annexin V and propidium iodide (PI) double staining assessed at 10 µM BPS and at 100 µM BPS with NAC, NAC + PDTC, and PDTC co-treatments. Apoptosis-related protein expression: pro-apoptotic [BAX, CASP3], and anti-apoptotic [BCL2] assessed at 100 µM BPS with NAC, NAC + PDTC, and PDTC co-treatments.	Oxidative stress: H9c2 cells and HUVECs: Increased ROS production at 10 and 100 µM BPS. Attenuation of effects with NAC co-treatment at both concentrations and with PDTC at 100 µM BPS (only concentration assessed). NFKB phosphorylation: H9c2 cells and HUVECs: Increased phosphorylation with 100 µM BPS and attenuation of effects with NAC co-treatment. Apoptosis: H9c2 and HUVECs: Increased numbers of apoptotic cells at 100 µM BPS and attenuation of effects with 1 µM NAC, 1 µM NAC + 1 µM PDTC, or 1 µM PDTC co-treatments. No effects with 10 µM BPS. Apoptosis-related protein expression: H9c2 and HUVECs: Increased BAX and CASP3 and decreased BCL2 at 100 µM BPS; attenuation of effects with 1 µM NAC, 1 µM NAC + 1 µM PDTC, or 1 µM PDTC co-treatments.

Study Design	Outcomes assessed	Major Findings
(Ma et al. 2015) *In vitro*: Primary embryonic white leghorn chicken (*Gallus gallus domesticus*) hepatocytes. Treatment: BPS (98% purity) in 0.5% DMSO v/v (vehicle control) at 0, 0.01, 0.1, 1, 10, 100, or 300 µM (equivalent to 2.50, 25.03, and 250.27 µg/L and 2.50, 25.03, and 75.08 mg/L, calculated by OEHHA) for 36 hours. No effect of BPS treatment on cell viability	Assessed at 1, 10, or 300 µM. Estrogen-sensitive mRNA expression: Apolipoprotein II (*APOB*) and vitellogenin (*VTG*). mRNA expression screen: Avian ToxChip PCR array.	Estrogen-sensitive mRNA expression: Increased *APOB* and *VTG* at 300 µM. mRNA expression screen: Increased thyroid hormone pathway gene, *IGF1* (2.4-fold) at 10 µM, Increased xenobiotic metabolism genes, *CYP3A37* (4.3-fold), *CYP1A4* (40.6-fold), and *ALAS1* (4.2-fold); lipid homeostasis genes, *ACSL5* (2.3-fold), *SLCO1A2* (2.3-fold), and *LBFABP* (4.0-fold), apoptosis gene, *LOC100859733* (2.7-fold); and oxidative stress gene, *MT4* (9.8-fold) at 300 µM, and Decreased thyroid hormone pathway genes, *THRSP* (-2.1-fold), *IGF1* (-3.6-fold), hormone regulation and metabolism gene, *HSD3B1* (-2.1-fold), and lymphocyte chemoattractant factor, *IL16* (-5.4-fold) at 300 µM.
Ning et al. 2023 Embryos obtained via IVF from CD-1 (ICR) wild-type female (6-9 weeks old) and male mice (10-13 weeks old); cultured to 2-cell (24 hours), 4-cell (48 hours), morula (72 hours), and blastocyst (96 hours) stages. **Experiment 1: Dose- and time-response studies.** Treatment regimen 1 (dose-response study): zygotes treated with BPS (purity not reported) in 0.1 M DMSO at concentrations of 0 (media), 0 (vehicle; 1 mM DMSO), 0.001, 0.01, 0.1, 1, 10, or 100 µM (equivalent to 0.25, 2.50, 25.03, and 250.27 µg/L and 2.50 and 25.03 mg/L, calculated by OEHHA) for 96 hours. 100 µM BPS induced 2-cell block in preimplantation embryos, thus, subsequent experiments assessed 100 µM in their mechanistic evaluations. Treatment regimen 2 (time-response study): zygotes treated with BPS (purity not reported) in 0.1 M DMSO at concentrations of 0 or 100 µM for 0, 3, 6, 9, 12, 24, and 48 hours. **Experiment 2: Oxidative stress.**	**Experiment 1** (treatment regimens 1, 2, and 4): Developmental potency of pre-implantation embryos. **Experiment 2** (treatment regimens 3 and 4 [1200 units/mL SOD only]): Mitochondrial distribution. Expression of oxidative stress-related genes (RT-qPCR): mitochondrial DNA encoded subunit *Nd1* and antioxidant enzyme genes *Sod1*, *Gpx1*, *Gpx6*, and *Prdx2*. Total reactive oxygen species (ROS) levels (DCFH-DA). Mitochondrial membrane potential. Apoptosis (TUNEL assay; treatment regimen 3 only). Embryonic genome activation (EGA)-specific gene expression: *Hsc70* and *Hsp70.1*.	**Experiment 1:** Developmental potency: Dose-dependent decrease in developmental potency: Decreased blastocyst formation at 1 (-43%), 10 (-53%), and 100 (-100%) µM compared to control (NS; -17%). Decreased morula formation at 1 (-26%), 10 (-33%), and 100 (-100%) µM compared to control (NS; -9%). Decreased 4-cell embryo formation at 10 (-19%) and 100 (-97%) µM compared to control (NS; -2%). Decreased 2-cell embryos formation at 100 (-33%) µM compared to control (NS; -1%). Treatment regimen 2 Time-dependent decreases in developmental potency: Decreased blastocyst formation starting at 3 hours through 48 hours (-34-100%) compared to control (NS; -21%). Decreased morula formation starting at 6 hours through 48 hours (-28-100%) compared to control (NS; -14%). Decreased 4-cell embryo formation starting at 9 hours through 48 hours (%) compared to control (-23-94%) compared to 0 hour control (NS; -9%). Decreased 2-cell embryos formation starting at 12 hours through 48 hours (-16-43%) compared to control (NS; -2%). Treatment regimen 4: SOD at 1200 units/mL antagonized 2-cell block (4-cell embryos developed with SOD co-treatment (20%) compared to 3% with

Study Design	Outcomes assessed	Major Findings
Treatment regimen 3: BPS (purity not reported) in 0.1 M DMSO at concentrations of 0, 0.001, 1, or 100 µM in 2-cell (24 hours) and 4-cell embryos (48 hours). Treatment regimen 4: BPS (purity not reported) in 0.1 M DMSO at concentrations of 0 or 100 µM zygotes co-treated with 0, 300, 600, 900, or 1200 units/mL superoxide dismutase (SOD); 0, 0.01, 0.1, or 1 µM coenzyme Q10 (CoQ10); or 0, 4, 20, or 40 mg/L folic acid. Data are reported at 2-cell and 4-cell embryo stages for SOD, CoQ10, and folic acid, and morula and blastocyst stages for SOD.		100 µM BPS only; CoQ10 and folic acid did not alleviate the 2-cell block induced by 100 µM BPS. **Experiment 2:** Mitochondrial distribution: Treatment regimen 3: Increased mitochondria around the nucleus at 100 µM in the 2- and 4-cell embryos, indicating mitochondrial stress. Treatment regimen 4: Attenuation of mitochondrial effect with SOD cotreatment. Oxidative stress-related gene expression: Treatment regimen 3: Decreased *Nd1* at 1 and 100 µM, and Increased *Sod1*, *Gpx1*, and *Gpx6* at 100 µM and *Prdx2* at 0.001, 1, and 100 µM. Treatment 4: Decreased *Nd1* at100 µM with and without SOD cotreatment, and Increased *Sod1* and *Prdx2* with SOD cotreatment compared to control but decreased compared to BPS alone, while increases of *Gpx1* and *Gpx6* with BPS alone were attenuated with SOD co-treatment. Total ROS: Treatment regimen 3: Increased at 100 µM at the 2- and 4-cell stages. Treatment regimen 4: Effect attenuated with SOD co-treatment. Mitochondrial membrane potential: Treatment regimen 3: No effect. Apoptosis: Treatment regimen 3: No effect. EGA-specific gene expression: Decreased *Hsc70* at 100 µM and *Hsp70.1* at 1 and 100 µM, indicating inhibition of EGA. Treatment regimen 4: Effects attenuated with SOD cotreatment.

Study Design	Outcomes assessed	Major Findings
Peshdary et al. 2021 *In vitro*: H9 human embryonic stem cells. Treatment: BPS (> 97% purity) in 0.1% DMSO (vehicle control) at 0, 1, 10, 300, 400, or 500 µM (equivalent to 0.25, 2.50, 75.08, 100.11, and 125.14 mg/L, calculated by OEHHA) for 3 days. Media was replaced every 24 hours. RNA isolated 24 hours after the last exposure for RNA-seq. Study authors designated "overt cytotoxicity" as ≤ 50% viability. At 500 µM BPS, % viability was 30 ± 2, thus, this concentration was omitted from the analyses. At 400 µM BPS, % viability was 58 ± 4.	RNA-seq analysis: DEGs. Biological processes analyses using Ingenuity Pathway Analysis at 300 µM. Benchmark concentration (BMC) analysis using BMDExpress in the BioCarta embryogenesis pathway (containing 82 genes).	RNA-seq analysis: Number of DEGs: 1 µM: 0. 10 µM: 1. 300 µM: 3,420. 400 µM: 5,004. Pathway analysis: 99 significantly affected pathways with Superpathway of Cholesterol Biosynthesis and Role of NFAT in Cardiac Hypertrophy as the top z-scores for activation and inhibition of canonical pathways, respectively. 658 upstream regulators significantly affected, with microRNAs being the top upstream regulators affected. BMC analysis: BMC modeling fit 25 genes in the embryogenesis pathway, with 30.86% of the pathway perturbed. Median BMC of 81.25 µM.
Sabry et al. 2021a Bovine cumulus oocyte complexes (COCs), denuded oocytes, and cumulus cells. Treatment: BPS (purity not stated) in 0.1% ethanol at concentrations of 0 (media only), 0 (media + vehicle), or 0.05 mg/ml for 24 hours. Cells were used for IVF with untreated bovine sperm; sperm and oocytes were incubated for 18 hours, presumed zygotes were separated from cumulus cells and incubated until the 8-cell blastocyst stage.	COC and embryo morphology (n=10-12).	COC morphology: No effect. Embryo morphology: Accelerated embryo development with hatched blastocysts by Day 8.
Sabry et al. 2021b Bovine COCs, denuded oocytes, and cumulus cells; n=40. Treatment: BPS (purity not stated) in 0.1% ethanol at concentrations of 0 (media only), 0 (media + vehicle), or 0.05 mg/ml for 24 hours; COCs were then frozen, denuded and frozen separately, or fertilized.	Embryonic development (cleavage rate and blastocyst rate). Primary miRNA (pri-miR-21 and pri-miR-155) and mature miRNA (miR-21, miR-34C, miR-146a, and miR-155) expression in embryos.	Embryonic development rate: No effects. miRNA expression: No effects at any stage.

Study Design	Outcomes assessed	Major Findings
Cells were used for IVF with untreated bovine sperm; sperm and oocytes were incubated for 18 hours, presumed zygotes were separated from cumulus cells and incubated until 3 stages: 2-4-cell stage (n=40; 45 hours post-fertilization), 8-16 cell stage (n=20; 80 hours post-fertilization), and Day 8 post-fertilization (n=5).		
Saleh et al. 2021 Bovine COCs, denuded oocytes, and cumulus cells; n=60. Treatment: BPS (purity not stated) in 0.1% ethanol at concentrations of 0 (media only), 0 (media + vehicle), or 0.05 mg/ml for 24 hours; half of the COC were then frozen and half separated into cumulus cells and oocytes. Cells were used for IVF with untreated bovine sperm; sperm and oocytes were incubated for 18 hours, presumed zygotes were separated from cumulus cells and incubated until day 8 post-fertilization.	Embryonic development (cleavage rate at Hour 40-45; blastocyst rate at Day 8; % of total cleaved zygotes or total oocytes at 2-4 cell stage by hours 45-50; % of total cleaved zygotes or total oocytes at 8-16 cell stage by hour 75-80; % of total cleaved embryos or total embryos at 2-4 cells, 8-16 cells, and morula stage at day 8). Apoptosis (TUNEL; 2-4 cells, 8-16 cells, and blastocysts). Sex ratio of blastocysts. AMH and AMHRII protein expression in blastocysts (immunofluorescence).	Embryonic development: No effects. Apoptosis: Increased DNA fragmentation with treatment at 2-4 cell, 8-16 cell, and blastocyst stages compared to control. Sex ratio: No effect. AMH and AMHRII protein expression in blastocysts: Increased AMH and AMHRII expression with treatment.
(Ticiani et al. 2021) **Experiment 1:** BPS/Epidermal Growth Factor Receptor (EGFR) competitive binding assay, n=5. Treatment: BPS (purity not reported) 0.0001, 0.001, 0.01, 0.1, 1, or 10 µg/mL (equivalent to 0.0004, 0.0039, 0.039, 0.399, 3.99, and 39.95 µM, calculated by OEHHA). **Experiment 2:** Human primary term cytotrophoblast cells, n=6. Treatment: BPS (purity not reported) in 0.1% DMSO in the following exposure conditions: (1) 0 or 200 ng/mL BPS with and without 5 ng/mL EGF for 96 hours with exposure medium replaced every 48 hours (to evaluate syncytialization) or (2) 0, 1, or 10 µg/mL BPS for 5 minutes without and with 100 ng/mL fluorescently-labeled human EGF for five minutes	**Experiment 1:** BPS/EGFR competitive binding assay. **Experiment 2:** Syncytialization (immunocytochemistry). EGF internalization.	**Experiment 1:** EGFR competitive binding assay: Dose-dependent decrease of EGF-EGFR binding signal at concentrations ≥ 0.001 µg/mL. NS decrease at 0.001, 0.01, and 0.1 µg/mL. **Experiment 2:** Syncytialization: Decreased syncytialization with BPS+EGF compared to EGF alone. No effect compared to vehicle control. EGF internalization: Decreased at 1 (-21%) and 10 (-43%) µg/mL.

Study Design	Outcomes assessed	Major Findings
and incubated in media for 1 hour prior to imaging (to evaluate EGF internalization).		
Ticiani et al. 2022 *In vitro*: HTR-8/SVneo human extravillous trophoblast cell line. Treatment: BPS (purity not reported) in 0.1% DMSO in the following exposure conditions: (1) 0 or 1000 ng/mL BPS with and without 30 ng/mL EGF for 15 minutes (EGF-mediated phosphorylation), 2-6 days (cell proliferation), 72 hours (cell invasion with microfluidic chip), or 18 hours (trophoblast endovascular differentiation); (2) 0, 1, or 10 µg/mL BPS for 5 minutes without EGF followed by 5 minutes with 100 ng/mL fluorescently labeled EGF and incubated in media for 1 hour prior to imaging (EGF internalization); and (3) 0, 10, 100, 1000 ng/mL BPS with and without 30 ng/mL EGF for 16 hours (cell invasion, Transwell cell migration assay).	EGF-mediated phosphorylation: EGFR, AKT and MAPK. EGF internalization. EGF-mediated cell proliferation EGF-mediated cell invasion: Matrigel pre-coated Transwell cell culture inserts and 3D PDMS microfluidic chip. Trophoblast endovascular differentiation via tube-forming assay: total network length, total segment length, mesh size, nodes, junctions, and segments (1000 ng/mL BPS with and without EGF, 18 hours).	EGF-mediated phosphorylation: Decreased p-EGFR (~ -50%) with BPS+EGF co-exposure compared to EGF exposure alone. No effect on p-AKT or p-MAPK. EGF internalization: Decreased at 1 (NS; -26%) and 10 (-41%) µg/mL BPS. EGF-mediated cell proliferation: Decreased with BPS+EGF co-exposure compared to EGF alone from Days 4-6. No difference in proliferation between vehicle control, BPS alone, or EGF alone. EGF-mediated cell invasion: Decreased at 100 (~ -22%) and 1000 (~-41%) ng/mL BPS in the BPS+EGF co-exposure groups compared to EGF alone, using the Transwell assay. Decreased at 1000 (-33%) ng/mL BPS in the BPS+EGF co-exposure group compared to EGF alone, using the 3-D PDMS microfluidic chip system. Trophoblast endovascular differentiation: Decreased (~ -49%) mesh size with BPS alone compared to control. Decreased total network length (~ -36%), total segment length (~ -60%), mesh size (~ -89%), nodes (~ -37%), junctions (~ -39%), and segments (~ -78%) with BPS+EGF co-exposure compared to EGF exposure alone.
Vidal et al. 2024 *In vitro:* Second-trimester placenta organ-on-a-chip model: Incorporating the maternal blood chamber, maternal decidua vessels and lacunar blood interface, invading and columnar extravillous trophoblasts, placental villi, placental stroma, stromal-umbilical cord interface, and fetal circulation. Human primary placenta cells and the human THP-1 monocyte cell line: Primary decidual, trophoblast and stromal cells isolated from de-identified placentae and cultured.	Antioxidant capacity (glutathione [GSH] levels). Hormone levels (progesterone, prolactin, and beta human chorionic gonadotropin [β-hCG]). Apoptosis and/or necrosis (annexin V and propidium iodide fluorescent staining). Cytokine levels (granulocyte-macrophage colony-stimulating factor [GMCSF], interleukin [IL]1B, IL6, IL8, and IL10, and tumor necrosis factor-alpha [TNFA]). Glucose transport.	Antioxidant capacity (significance not reported): GSH levels were decreased (≥ 2-fold depletion) in STB and decidual cells and increased (~2-fold) in HUVECs. No effects in the other cell types. Hormone levels (significance not reported): Progesterone was decreased in PVEC, STB, decidual cells, CTBs, and stromal cells (-13 to -61%) and increased slightly in HUVECs (+8%). β-hCG was decreased in PVECs (-86%) and increased in STB, decidual cells, CTBs, and HUVECs (+17-159%). Prolactin was decreased in STB (-43%) and

Study Design	Outcomes assessed	Major Findings
Isolated trophoblasts were immortalized with SV40T lentivirus for modeling cytotrophoblasts and the syncytiotrophoblast. Seven cell-types seeded and cultured in cell chambers interconnected by microchannels. 1. Placental vascular endothelial cells [PVECs]. 2. Syncytiotrophoblast-like cells [STB] derived from forskolin-mediated syncytialization of trophoblasts. 3. Decidual cells [DEC]. 4. Cytotrophoblasts [CTBs]. 5. Stromal cells and, 6. THP-1 monocytes differentiated into macrophages, representing Hofbauer cells. 7. HUVECs. Treatment: 150 ng/mL BPS (purity not reported) in PVEC media (endothelial cell medium with 5x endothelial cell growth supplement and 5% fetal bovine serum) for 72 hours. Cigarette smoke extract (1:50) was used as a positive control. Chips and assays were run with replicates. This was a model development and validation study. In addition to evaluation of the organ-on-a-chip system, specific cell-type responses within the system were assessed.		increased in decidual cells, CTBs, and stromal cells (+32-39%). Data on estrogen and VEGF not reported. Apoptosis and/or necrosis (significance not reported, ≥ 2-fold changes): Increased percentages of late apoptotic STB (+2.72-fold) and necrotic decidual cells (+2.99-fold). Decreased percentages of late apoptotic (-2.49-fold) and necrotic (-12.99-fold) CTBs. Decreased percentage of late apoptotic (-2.63-fold) HUVECs. Note – It was difficult to analyze the <2-fold data quantitatively. Cytokine levels (significance not reported, ≥ 2-fold changes): Overall trend towards an anti-inflammatory state across the system. GMCSF was decreased in STB and HUVECs and increased in decidual cells. Decreased IL1B in STBs. IL6 was decreased in STBs and increased in CTBs and decidual cells. Decreased TNFA in stromal cells. Note – It was difficult to analyze the <2-fold data quantitatively. Glucose transport: No effects.

Table 4.3.14 Developmental toxicity effects of BPS: Molecular Epidemiology Studies not included in Table 4.1.1.

Study Design	Outcomes assessed	Major Findings	Notes
Blaauwendraad et al. 2021 **Setting:** Generation R Study, Rotterdam, The Netherlands, 2004-2006. **Study n:** 225 mother-child dyads. **Mean (SD) maternal age:** 31.9 (3.7) years **Inclusion criteria:** ≤18 weeks gestation, living in Rotterdam, Netherlands, singleton pregnancy. **BPS exposure measurement:** Three spot urine samples at median of 12.6 weeks (first trimester [TM1]), 20.4 weeks (TM2), and 30.2 weeks (TM3). Limit of detection (LOD): 0.05 ng/mL, % samples >LOD: 70.7% in TM1, 31.1% in TM2, and 20.0% in TM3, Values < LOD were imputed with LOD÷√2; Creatinine-adjusted median (25^{th}, 75^{th}): 0.81 (0.23, 3.88) nanomoles per liter (nmol/L) in TM1, < LOD (< LOD, 0.45) nmol/L in TM2, and < LOD (< LOD, 0.13) nmol/L in TM3. **Covariates included in statistical models**: Maternal age, educational level, pre-pregnancy BMI, parity, smoking, alcohol use and total energy intake.	Outcomes were measured by targeted metabolomics analyses in umbilical vein cord blood. Neonatal metabolite profiles: Amino acids: branched-chain, aromatic, essential, non-essential. Non-esterified fatty acids (NEFA): saturated, mono-unsaturated, poly-unsaturated. Phospholipids: Diacyl-phosphatidyl-cholines: mono-unsaturated and poly-unsaturated. Acyl-alkyl-phosphatidylcholines: saturated, mono-unsaturated, and poly-unsaturated. Acyl-lysophosphatidylcholines: saturated, mono-unsaturated, and poly-unsaturated. Alkyl-lysophosphatidylcholines: saturated and mono-unsaturated. Sphingomyelines: mono-unsaturated and poly-unsaturated. Carnitines: Free carnitine. Acyl-carnitines: small-, medium-, and large-chains.	Average BPS levels (per interquartile range (IQR) increase) were associated with: Lower overall concentrations of alkyl-lysophosphatidylcholines (-0.20 standard deviation score [SDS]; 95% CI: -0.39 to -0.01) and saturated alkyl-lysophosphatidylcholines (-0.21 SDS; 95% CI: −0.40 to −0.02) concentrations. First trimester BPS levels (per IQR increase) were associated with: Higher overall concentrations of acyl-carnitines (0.22 SDS; 95% CI: 0.02 to 0.41) and higher concentrations for the following chain lengths: small- (0.19 SDS; 95% CI: 0.00, 0.39), medium- (0.20 SDS; 95% CI: 0.00, 0.29), and large-chain (0.28 SDS; 95% CI: 0.08, 0.47). Third trimester BPS levels (per IQR increase) were associated with: Lower overall concentrations of acyl-carnitines (-0.12 SDS; 95% CI: -0.22 to -0.01); and lower concentrations for the following chain lengths: small-chain (-0.11 SDS; 95% CI: -0.22, 0.00). large-chain (-0.13 SDS; 95% CI: -0.24, -0.03). Lower overall concentrations of NEFA (-0.11 SDS; 95% CI: -0.22, 0.00); and saturated NEFA (-0.11 SDS; 95% CI: -0.22, -0.01). Lower concentrations of mono-unsaturated acyl-lysophosphatidyl-cholines (-0.13 SDS; 95% CI: -0.24, -0.02). Overall associations present after false discovery rate correction but not after Bonferroni correction. No associations between overall or trimester-specific BPS and amino acid, diacyl-phosphatidyl-choline, acyl-alkyl-phosphatidylcholine, and sphingomyeline concentrations.	Associations with individual neonatal metabolites are published in the paper's supplementary materials. BPA and BPF were also associated with neonatal metabolomic profiles.

Study Design	Outcomes assessed	Major Findings	Notes
J Chen et al. 2024 **Setting:** Shanghai-Minhang Birth Cohort Study, China, 2012. **Study sample size (n):** 345 mother-child dyads. **Mean (standard deviation [SD]) maternal age:** 28.2 (3.5) years. **Inclusion criteria:** pregnant women at first prenatal care visit (12-16 weeks of gestation) at study hospital, singleton pregnancy. **BPS exposure measurement:** Spot urine samples at median of 32 weeks gestation (range 29-37 weeks); LOD: 0.004 µg/L, Percent samples (%) > LOD: 20.98%, Values < LOD were imputed with LOD÷√2; Creatinine-adjusted geometric mean (SD): 0.01 (0.00) and median (25^{th}, 75^{th}): 0.01 (0.00, 0.02) µg/g. **Covariates included in statistical models**: household income, maternal age at delivery (years), gestational age at delivery (weeks), parity, maternal pre-pregnancy body mass index (BMI), maternal passive smoking before conception, and sex.	Placental DNA methylation of CpG sites in four reproduction-related genes: *FGF13* (13 sites), *PCDH8* and *RBMXL2* (32 sites each), and *SPACA1* (22 sites). Outcomes were measured in placental samples collected at delivery. Tissues were obtained from the maternal side of the placenta, 2 centimeters from the umbilical cord, for CpG methylation, analyzed as a continuous variable.	BPS, analyzed as detected versus not detected, was not significantly associated with placental DNA methylation at the CpG sites assessed.	BPA and BPF were associated with higher methylation levels.
Ferguson et al. 2019 **Setting:** LIFECODES cohort, Boston, US, 2006−2008. **Study sample size (n):** 482 pregnant women. **Maternal age:** 12%: < 25 years, 20%: 25 to < 30 years, 39%: 30 to < 35 years, 24%: 35 to < 40 years, 5%: ≥ 40 years. **Inclusion criteria:** Women were recruited as part of a nested case-control study which selected all 130 women that delivered preterm and 352 randomly selected term births. **BPS exposure measurement:** Urine samples at up to 4 points in pregnancy (median 10, 18, 26, and 35 weeks);	Oxidative biomarkers measured in maternal urine samples: 8-isoprostane and 8-hydroxydeoxyguanosine (8-OHdG).	BPS (analyzed as detect versus non-detect) was associated with an increase in 8-isoprostane (18.5% change, 95% CI: 7.68 to 30.05, p = < 0.01). There was NS association with increased 8-OHdG (6.18% change, 95% CI: -0.27 to 13.1, p = 0.06). Associations did not differ significantly by timing of sample collection or race/ethnicity. Findings were robust to sensitivity analyses examining data from term births only.	

Study Design	Outcomes assessed	Major Findings	Notes
LOD: 0.4 ng/mL, Percent (%) > LOD: 20.6%, Values < LOD were imputed with LOD÷√2; Specific gravity-adjusted median (25th, 75th): < LOD (<LOD, 0.70) ng/mL. **Covariates included in statistical models**: urinary specific gravity, gestational age at sample collection, maternal age, race, education level, pre-pregnancy body mass index, and smoking during pregnancy. Models were weighted to consider unequal selection of preterm and term births.			
Kelley et al. 2019 **Setting:** Michigan Mother-Infant Pairs pregnancy cohort, Michigan, USA, 2012 -2015. **Study n:** 56 mother-child dyads. **Mean (SD) maternal age:** 31.9 (3.7) years. **Inclusion criteria:** enrolled in first prenatal visit at study hospital, ≥ 18 years of age, no prior infertility treatment, singleton pregnancy, 8-14 weeks gestation. **BPS exposure measurement:** Spot urine samples at 8 and 14 weeks; LOD: not reported % > LOD: not reported Values < LOD were imputed with LOD÷√2; Percentiles not reported (assumed to be similar to those reported by (McCabe et al. 2020), tabulated below). **Covariates included in statistical models**: pre-pregnancy BMI, maternal age, history of smoking, mode of delivery (vaginal versus cesarean), infant sex, and gestational age at delivery.	Maternal and newborn cytokine levels. Plasma levels of 12 inflammatory cytokines from maternal venous blood from TM1 (presume same timeframe as urine collection) and just prior to delivery, and umbilical cord blood (of mixed arterial and venous origin). Cytokines: Granulocyte macrophage colony-stimulating factor (GM-CSF), interferon (IFN)-γ, monocyte chemotactic protein (MCP)-1, MCP-3, macrophage inflammatory protein (MIP)-1α, MIP-1β, tumor necrosis factor (TNF)-α, vascular endothelial growth factor (VEGF), interleukin (IL)-1β, IL-6, IL-8, and IL-17α. Cytokines with levels below the LOD were imputed with LOD/√2	BPS levels were positively associated with maternal VEGF measured at delivery (specific estimate not reported) in unadjusted models. BPS levels were not correlated with maternal or newborn cytokine levels in adjusted models.	In same sample, higher BPS levels were associated with lower birthweight (Goodrich et al. 2019).
McCabe et al. 2020 **Setting:** Michigan Mother-Infant Pairs pregnancy cohort, Michigan, USA, 2011-2017. **Study n:** 69 mother-infant dyads. **Median (25th, 75th) maternal age:** 32 (30, 34) years.	Differentially methylated CpG sites. Differentially methylated regions. Gene-set enrichment analyses. Outcomes were measured in DNA isolated from umbilical cord blood leukocytes of newborns for epigenome-wide DNA methylation analysis.	BPS, analyzed as detected versus not detected, was associated with one differentially methylated site in *VPS53*: cg06871344 ($p \leq 0.0001$, $\lambda = 0.674$). No effects on differentially methylated regions.	BPA was associated with DNA methylation at 38 CpG sites.

Study Design	Outcomes assessed	Major Findings	Notes
Inclusion criteria: enrolled in first prenatal visit at study hospital, ≥ 18 years of age, no prior infertility treatment, singleton pregnancy, 8-14 weeks gestation. **BPS exposure measurement:** Spot urine samples at 8-14 weeks gestation; LOD: 0.2 ng/mL, % > LOD: 57.9%, Values < LOD were imputed with LOD÷√2; Specific gravity adjusted mean (range): 0.37 (< LOD, 4.50) ng/mL and median (25^{th}, 75^{th}): 0.226 (0.145, 0.0365) ng/mL. **Covariates included in statistical models**: infant sex, B cells, nucleated red blood cells, and sample plate (batch).			
L Wang et al. 2021 **Setting:** Birth cohort, Wuhan, China, 2013-2015. **Study n:** 745 mother-child dyads. **Mean (SD) maternal age:** 28.6 (3.3) years **Inclusion criteria:** ≤16 weeks gestation, singleton pregnancy, receiving prenatal care and gave birth at study hospital. **BPS exposure measurement:** Three spot urine samples at mean (SD) of 13 (1.1) weeks (TM1), 23.6 (3.2) weeks (TM2), and 36.0 (3.3) weeks (TM3); LOD: 0.04 ng/mL, % > LOD: 84.7% in TM1, 86.6% in TM2, and 89.6% in TM3, Values < LOD were imputed with LOD÷√2; Specific gravity adjusted median (25^{th}, 75^{th}): 0.32 (0.12, 0.94) µg/L in TM1, 0.43 (0.16, 1.31) µg/L in TM2, and 0.47 (0.20, 1.33) µg/L in TM3. **Covariates included in statistical models**: maternal age, pre-pregnancy BMI, educational level, parity, passive smoking during pregnancy, gestational age at birth, and gestational age at urine sample collection. **Analyses stratified by:** sex	Mitochondrial DNA copy number (mtDNAcn) measured in DNA isolated from umbilical cord blood leukocytes.	No statistically significant associations between maternal BPS concentrations and newborn mtDNAcn. Sex-stratified analyses: Males: First trimester BPS associated with lower mtDNAcn. Percent change (95% CI) compared to quartile (Q)1: Q2: -58.00 (-76.58, -24.66). Q3: -64.65 (-79.40, -39.33). Q4: -59.07 (-75.16, -32.58). Females: no statistically significant associations.	While not statistically significant, the mothers of male newborns were exposed to higher BPS than mothers of female newborns during all three trimesters.

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APPENDIX A. LITERATURE SEARCH APPROACH ON THE DEVELOPMENTAL TOXICITY OF BPS

- Searches of the published scientific literature on the developmental and reproductive toxicity (DART) of bisphenol S (BPS) were conducted in January 2022 and updates to the original search were conducted in February 2023, July 2023, January 2024, and October 2024. Additional studies that came to OEHHA's attention after the last comprehensive search (e.g., via updated focused searches in PubMed) are also included in this document. Nine relevant publications were identified in this updated search.
- The goal was to identify peer reviewed- open source and proprietary journal articles, print and digital books, reports, and gray literature that potentially reported toxicological and epidemiological information on the DART of this chemical.

The searches were conducted using the following three approaches:

- Primary searches in major biomedical databases, conducted by OEHHA librarian Nancy Firchow, MLS
- Searches in other data sources, including authoritative reviews and reports, and databases or web resources, conducted by OEHHA scientists
- Additional focused searches, conducted by OEHHA scientists

In addition to information identified from these searches, OEHHA also considered the following:

- One submission received during the data call-in period (March 4 – April 18, 2022) (https://oehha.ca.gov/proposition-65/comments/comment-submissions-request-relevant-information-reproductive-toxicity)

Primary Search Process

1. *Data Sources*

The biomedical literature databases used as data sources that were searched to find information on BPS are listed below.

PubMed (National Library of Medicine) (https://www.ncbi.nlm.nih.gov/pmc/)
Embase (https://www.embase.com/)
Scopus (https://www.scopus.com/)
SciFinder-n (https://scifinder-n.cas.org/)

Google Scholar (https://scholar.google.com)

2. Search term identification

- The US EPA's CompTox Chemicals Dashboard (https://comptox.epa.gov/dashboard) was used to identify synonyms for BPS. The PubMed MeSH database (https://www.ncbi.nlm.nih.gov/mesh/) was used to find additional synonyms, subject headings and other index terms related to the chemical.
- The PubMed DART filter (https://www.nlm.nih.gov/bsd/pubmed_subsets/dart_strategy.html) was used for developmental and reproductive toxicity-related terminology.
- National Toxicology Program's Standard Search Strings for Literature Database Searches: Appendix to the Draft Handbook for Preparing Report on Carcinogens Monographs (NTP 2015) (https://ntp.niehs.nih.gov/ntp/roc/handbook/rochandbookappendix_508.pdf) was used to identify search strategies for Experimental Animals and ADME concepts.
- Additional strategies for DART and Key Characteristics of Female Reproductive Toxicity and Key Characteristics of Male Reproductive Toxicity were developed by OEHHA.

3. Primary search execution

Searches were executed in PubMed, Embase, Scopus, SciFinder^{n}, and Google Scholar in January 2022, February 2023, July 2023, January 2024, and October 2024.

Three separate searches were done in PubMed, Embase and Scopus. Searches in these databases were divided into evidence streams as:

- Human DART Studies
- Animal DART Studies
- ADME Studies

Mechanistic data were identified in the animal search, that included studies of mammals and non-mammalian species as well as studies with *in vitro* experimental design. In addition, searches using the Key Characteristics of female and male reproductive toxicants (see Tables A.1 and A.2 below) were used to identify studies with relevant mechanistic data. The basic structure used for each search and the search dates are shown in Tables A.1 through A.3.

Table A.1 Human DART studies search structure (PubMed, Embase, Scopus)

Search Dates	Search step	Search Concepts
1/2022 1/2023 7/2023 1/2024 10/2024	#1	BPS terms
	#2	DART terms (PubMed DART Filter)
	#3	Additional DART terms (OEHHA strategy)
	#4	Key Characteristics of Male Reproductive Toxicants (OEHHA Strategy)
	#5	Key Characteristics of Female Reproductive Toxicants (OEHHA Strategy)
	#6	#2 OR #3 OR #4 OR #5
	#7	#1 AND #6
	#8	Remove animals from #7

Table A.2 Animal DART studies search structure (PubMed, Embase, Scopus)

Search Dates	Search step	Search Concepts
1/2022 1/2023 7/2023 1/2024	#1	BPS terms
	#2	DART terms (PubMed DART Filter)
	#3	Additional DART terms (OEHHA strategy)
	#4	Key Characteristics of Male Reproductive Toxicants terms (OEHHA Strategy)

Search Dates	Search step	Search Concepts
10/2024	#5	Key Characteristics of Female Reproductive Toxicants terms (OEHHA Strategy)
	#6	#2 OR #3 OR #4 OR #5
	#7	#1 AND #6
	#8	Experimental Animals terms (RoC strategy)
	#9	#7 AND #8

Table A.3 ADME studies search structure (PubMed, Embase, Scopus)

Search Date	Search step	Search Concepts
8/2022	#1	BPS terms
	#2	ADME terms (RoC Strategy)
	#3	#1 AND #2

The searches were run first in PubMed. The search terms and syntax were then tailored according to the search features unique to the other databases. For example, Embase uses different subject headings than PubMed, so the Emtree subject heading list was searched to identify equivalent terms to replace the MeSH terms used in the PubMed searches.

Two separate searches were run in SciFinder^{n}. Searches in this database were divided into Human and Animal evidence streams. The basic structure used in each search is shown in Tables A.4 and A.5.

Table A.4 Human DART studies search structure (SciFinder-n)

Search Dates	Search step	Search Concepts
1/2022	#1	BPS terms
	#2	Limit to Journal Article
	#3	Limit to human concept
	#4	Limit to Database "CA Plus"
	#5	Search within results: DART terms

CAplus (chemical abstract plus) is a database of chemical information that can be accessed via SciFinder-n

Table A.5 Animal studies search structure (SciFinder-n)

Search Dates	Search step	Search Concepts
1/2022	#1	BPS terms
	#2	Limit to Journal Article
	#3	Limit to animals concept
	#4	Limit to Database "CA Plus"
	#5	Search within results: DART terms

CAplus, chemical abstract plus.

One search was run in Google Scholar. The basic structure used in the search is shown in Table A.6.

Table A.6 DART studies search structure (Google Scholar)

Search Dates	Search step	Search Concepts
1/2022 7/2023 1/2024 10/2024	#1	(BPS terms) AND (DART terms)

Results from all databases were uploaded to EndNote, maintaining separate libraries for each of the three concepts searched (human DART studies, animal DART studies, and ADME studies). Duplicates were removed. The results of the primary searches for BPS are shown in Table A.7.

Table A.7 BPS DART studies search results (totals from all search dates)

Search	PubMed Results	Embase Results	Scopus Results	SciFinder-n Results	Google Scholar Results	Unique Results After Deduplication
Human DART	867	758	793	131	29	984
Animal DART	553	632	511	102	22	699
ADME	236	489	505	*	*	759
*SciFinder-n and Google Scholar were not searched for ADME evidence stream.						

4. Other data sources

Additional databases and websites of governmental and other authoritative entities (e.g., US EPA, European Chemicals Agency) were searched for data and reports that may have been missed in the primary literature search. Other relevant studies were identified from citations in individual articles, and through alert services (e.g., ScienceDirect, Google Scholar, etc.) and updated PubMed searches.

Literature Screening Process

Use of Health Assessment Workspace Collaborative

The EndNote libraries containing the literature search results (citations) for BPS were uploaded to HAWC (Health Assessment Workspace Collaborative, (https://hawcproject.org). HAWC is a tool used for multi-level screening of literature search results. Using HAWC, the references were screened and tagged.

In Level 1 screening, each citation was first screened by at least one OEHHA scientist, based solely on titles and abstracts, using specific inclusion and exclusion criteria to eliminate studies or articles that did not contain information on BPS and studies of its DART or other key related topics (e.g., pharmacokinetics, mechanisms of action). This initial screen of title and abstracts (Level 1) was intended to identify all studies deemed to have a reasonable possibility of containing information relevant to DART that could be useful for the review process, and to further identify (i.e., tag in HAWC) studies

relevant to specific aspects of DART (e.g., male reproductive toxicity, female reproductive toxicity, developmental toxicity).

Screening the literature relevant to developmental toxicity

For purposes of identifying the available evidence on the developmental toxicity of BPS, citations identified as having a reasonable possibility of containing information relevant to either endpoint underwent Level 2 screening. In the Level 2 screening of this subset of citations, the full texts were obtained. These full papers were screened independently by one OEHHA scientist, using similar inclusion/exclusion criteria as was used in the Level 1 screening. However, Level 2 reviewers could make more accurate judgements about the relevance of the articles because they were reviewing the full text in addition to the title and abstract. Following Level 2 screening, the tagging of articles according to key topics was updated in HAWC. Level 1 and 2 screenings were repeated as search results were updated, and with additional relevant studies identified from citations in individual articles and alert services (e.g., ScienceDirect, Google Scholar).

Detailed PubMed Literature Search Strategies – Primary Searches

Table A.8 PubMed search strategy for human DART studies

SET #	STRATEGY	CONCEPT GROUP
1	(80-09-1[rn] OR "Bisphenol S"[tiab] OR "bis(4-hydroxyphenyl)sulfone"[nm] OR "bis(4-hydroxyphenyl)sulfone"[tiab] OR "4,4'-Sulfonyldiphenol"[tiab] OR "Phenol, 4,4'-sulfonylbis-"[tiab] OR "BPS-monoglucuronide"[tiab] OR "BPS-1G"[tiab] OR "bisphenol S dicyanate ester"[tiab] OR (bps[tiab] NOT ("bps"[tiab] NOT "bisphenol"[tiab]))	Chemical Terms
2	(abnormalities, drug-induced [mh] AND (fetus [mh] or pregnancy [mh])) OR ((abnormalities, multiple/chemically induced [mh] OR abnormalities, multiple/epidemiology [mh] OR abnormalities, multiple/etiology[mh] OR abnormalities, multiple/genetics [mh] OR abnormalities, multiple/pathology [mh]) AND (pregnancy [mh] OR fetus [mh]))OR (abnormalities, radiation-induced [mh] AND (fetus [mh] or pregnancy [mh])) OR abortion, habitual/chemically induced [mh] OR abortion, habitual/etiology [mh] OR abortion, spontaneous/chemically induced [mh] OR abortion, spontaneous/etiology [mh] OR (alcoholic intoxication[mh] AND (fetus [mh] or pregnancy [mh])) OR (alcohol drinking [mh:noexp] AND (fetus [mh] or pregnancy [mh])) OR Birth Defects Res B Dev Reprod Toxicol [TA] OR birth weight/drug effects [mh] OR birth weight/radiation effects [mh] OR breast feeding/drug effects [mh] OR (carcinogens, environmental [mh] AND (fetus [mh] or pregnancy [mh])) OR (carcinogens [mh] AND (fetus [mh] OR pregnancy [mh])) OR (cardiovascular abnormalities/ci [mh] AND fetus [mh]) OR (cardiovascular abnormalities/et [mh] AND fetus [mh]) OR (cocaine[mh] AND (fetus [mh] or pregnancy [mh])) OR (congenital abnormalities [mh] AND (fetus [mh] or pregnancy [mh])) OR (dna damage [mh] AND (pregnancy [mh] OR fetus [mh])) OR embryo/de [mh] OR embryo/re [mh] OR embryo loss/ci [mh] OR embryonic and fetal development/drug effects [mh] OR embryonic and fetal development/radiation effects [mh] OR embryonic structures/drug effects [mh] OR embryonic structures/pathology [mh] OR embryonic structures/radiation effects [mh] OR (environmental exposure[mh] AND (pregnancy [mh] OR fetus [mh])) OR fertility/drug effects [mh] OR fertility/radiation effects [mh] OR fetal alcohol syndrome[mh:noexp] OR fetal death/chemically induced [mh] OR fetal death/etiology [mh] OR fetal death/genetics [mh] OR fetal death/pathology [mh] OR fetal diseases/chemically induced [mh] OR fetal diseases/etiology [mh] OR fetal diseases/genetics [mh] OR fetal growth retardation/et [mh] OR fetal growth retardation/ci [mh] OR fetal resorption/chemically induced [mh] OR fetal resorption/etiology [mh] OR fetal resorption/genetics [mh] OR fetus/abnormalities [mh] OR fetus/drug effects [mh] OR fetus/radiation effects [mh] OR (fetus*[tw] AND expos*[tw]) OR (genetic diseases, inborn/CI [mh] AND (fetus [mh] OR pregnancy [mh])) OR germ cells/drug effects [mh] OR germ cells/radiation effects [mh] OR (hazardous substances [mh] AND (fetus [mh] or pregnancy [mh])) OR heavy metal poisoning[mh] OR lactation/drug effects [mh] OR lactation/radiation effects [mh] OR (lead [mh:noexp] AND (fetus [mh] or pregnancy [mh])) OR (lead poisoning[mh] AND (fetus [mh] or pregnancy [mh]))OR maternal exposure [mh] OR maternal-fetal exchange/genetics [mh] OR maternal-fetal exchange/drug effects [mh] OR maternal-fetal exchange/radiation effects[mh] OR (mutagens [mh] AND (pregnancy [mh] OR fetus [mh])) OR neonatal abstinence syndrome[mh] OR "neonatal abstinence syndrome"[ti] OR neonatal sepsis [mh] OR ovary/drug effects [mh] OR ovary/radiation effects [mh] OR paternal exposure [mh] OR placenta diseases/chemically induced [mh] OR placenta diseases/etiology [mh] OR placenta/abnormalities [mh] OR placenta/drug effects [mh] OR placenta/radiation effects [mh] OR pregnancy Complications, Infectious/epidemiology [mh] OR pregnancy Complications/ci [mh] OR pregnancy outcome/ge [mh] OR (prenatal*[tw] AND expos*[tw]) OR prenatal exposure delayed effects [mh] OR (protein deficiency[mh:noexp] AND (fetus [mh] or pregnancy [mh])) OR reproduction/drug effects [mh:noexp] OR reproduction/radiation effects [mh] OR rubella/congenital[mh:noexp] OR rubella syndrome, congenital/etiology[mh:noexp] OR (teratogens [mh] AND (pregnancy [mh] OR fetus [mh]))OR Teratology [Journal] OR teratology [mh] OR testis/drug effects [mh] OR testis/radiation effects [mh]	PubMed Dart strategy

SET #	STRATEGY	CONCEPT GROUP
3	"abortion, spontaneous"[mh] OR "abortion*"[tiab] OR "Acrosome"[mh] OR "Acrosome"[tiab] OR "Adrenarche"[tiab] OR "androgen antagonists"[mh] OR "androgen*"[tiab] OR "androgens"[mh] OR "Androstenedione"[tiab] OR "anogenital distance"[tiab] OR "ano genital distance"[tiab] OR "anovulat*"[tiab] OR "Aspermia"[tiab] OR "atretic follicle*"[tiab] OR "Azoospermia"[tiab] OR "birth defect*"[tiab] OR "birth weight"[mh] OR "birth weight"[tiab] OR "breast feed*"[tiab] OR "breast feeding"[mh] OR "breastfeed*"[tiab] OR "chorionic villi"[tiab] OR "conception*"[tiab] OR "congenital abnormalities"[mh] OR "Congenital"[tiab] OR "corpus luteum"[tiab] OR "cumulus cell*"[tiab] OR "cytotrophoblast*"[tiab] OR "decidua"[tiab] OR "deciduum"[tiab] OR "dna damage"[mh] OR "ductus deferens"[tiab] OR "efferent duct*"[tiab] OR "ejaculat*"[tiab] OR "Embryo"[tiab] OR "Embryoes"[tiab] OR "embryonic and fetal development"[mh] OR "embryonic structures"[mh] OR "Embryonic"[tiab] OR "embryotoxic*"[tiab] OR "endometri*"[tiab] OR "Epididymis"[mh] OR "Epididymis"[tiab] OR "erecti*"[tiab] OR "Estradiol"[tiab] OR "estrogen antagonists"[mh] OR "estrogen receptor modulators"[mh] OR "estrogen*"[tiab] OR "estrogens"[mh] OR "Estrus"[tiab] OR "fallopian tube*"[tiab] OR "fallopian tubes"[mh] OR "fecund*"[tiab] OR "Fertility"[mh] OR "Fertility"[tiab] OR "Fertilization"[tiab] OR "Fetal"[tiab] OR "Fetus"[mh] OR "Fetus"[tiab] OR "foetal"[tiab] OR "foetus"[tiab] OR "follicle stimulating hormone"[tiab] OR "FSH"[tiab] OR "genetic diseases, inborn"[mh] OR "genital diseases, female"[mh] OR "genital diseases, male"[mh] OR "genital*"[tiab] OR "genitalia"[mh] OR "germ cell*"[tiab] OR "germ cells"[mh] OR "gestat*"[tiab] OR "gonad*"[tiab] OR "gonadal disorders"[mh] OR "gonadal hormones"[mh] OR "gonadotropins"[mh] OR "gonads"[mh] OR "graafian follicle*"[tiab] OR "granulosa cell*"[tiab] OR "human development"[mh] OR "Implantation"[tiab] OR "in utero"[tiab] OR "infant*"[tiab] OR "infant, newborn"[mh] OR "infertil*"[tiab] OR "Inhibin"[tiab] OR "Intrauterine"[tiab] OR "Lactation"[tiab] OR "lactation disorders"[mh] OR "leydig cell*"[tiab] OR "leydig cells"[mh] OR "LH"[tiab] OR "luteal cell*"[tiab] OR "luteinizing hormone"[tiab] OR "maternal exposure"[mh] OR "Maternal"[tiab] OR "Menses"[tiab] OR "menstrua*"[tiab] OR "miscarriage*"[tiab] OR "neonat*"[tiab] OR "Oligospermia"[tiab] OR "oocyte*"[tiab] OR "Oogonia"[tiab] OR "Ova"[tiab] OR "ovarian follicle*"[tiab] OR "Ovarian"[tiab] OR "Ovaries"[tiab] OR "Ovary"[mh] OR "Ovary"[tiab] OR "oviduct*"[tiab] OR "oviducts"[mh] OR "ovulat*"[tiab] OR "Ovum"[mh] OR "Ovum"[tiab] OR "paternal exposure"[mh] OR "Paternal"[tiab] OR "peripubert*"[tiab] OR "pituitary hormones"[mh] OR "placenta*"[tiab] OR "placenta"[mh] OR "placental hormones"[mh] OR "preconception*"[tiab] OR "pre conception*"[tiab] OR "pregnan*"[tiab] OR "pregnancy complications"[mh] OR "pregnancy"[mh] OR "prenatal exposure delayed effects"[mh] OR "prenatal"[tiab] OR "Pre-natal"[tiab] OR "Preterm"[tiab] OR "Pre-term"[tiab] OR "primary follicle*"[tiab] OR "Progesterone"[tiab] OR "progestin*"[tiab] OR "progestins"[mh] OR "Prostate"[mh] OR "Prostate"[tiab] OR "reproduct*"[tiab] OR "reproductive physiological phenomena"[mh] OR "secondary follicle*"[tiab] OR "Semen"[mh] OR "Semen"[tiab] OR "seminal vesicle*"[tiab] OR "seminal vesicles"[mh] OR "Seminal"[tiab] OR "seminiferous epithelium"[tiab] OR "seminiferous tubule*"[tiab] OR "seminiferous tubules"[mh] OR "Seminiferous"[tiab] OR "sertoli cells"[mh] OR "sertoli cell*"[tiab] OR "sexual development"[mh] OR "Sperm"[tiab] OR "spermatid*"[tiab] OR "spermatocyte*"[tiab] OR "spermatogenesis"[tiab] OR "Spermatogonia"[tiab] OR "Spermatozoa"[mh] OR "Spermatozoa"[tiab] OR "Sterile"[tiab] OR "Sterility"[tiab] OR "stillbirth*"[tiab] OR "Stillborn"[tiab] OR "syncytiotrophoblast*"[tiab] OR "teratogen*"[tiab] OR "teratogens"[mh] OR "tertiary follicle*"[tiab] OR "Testes"[tiab] OR "testic*"[tiab] OR "Testis"[mh] OR "Testis"[tiab] OR "Testosterone"[tiab] OR "theca cell*"[tiab] OR "thyroid hormones"[mh] OR "trophoblast*"[tiab] OR "urogenital abnormalities"[mh] OR "urogenital*"[tiab] OR "Uterine"[tiab] OR "Uterus"[mh] OR "Uterus"[tiab] OR "vagina*"[tiab] OR "vas deferens"[mh] OR "vas deferens"[tiab] OR "zygote*"[tiab]	Additional DART terms (OEHHA Strategy)
4	"spermatozoa"[mh] OR "acrosome reaction"[mh] OR "Sperm Capacitation"[mh] OR "sperm transport"[mh] OR "sperm-ovum interactions"[mh] OR "acrosome"[tiab] OR "spermatozoa"[tiab] OR	

SET #	STRATEGY	CONCEPT GROUP
	"sperm"[tiab] OR "spermatogonia"[tiab] OR "spermatophore*"[tiab] OR "spermatocyte*"[tiab] OR "spermatid*"[tiab] OR "spermatogenesis"[tiab] OR "capacitation"[tiab] OR (("Germ cells"[mh] OR "germ cell*"[tiab]) AND ("male"[mh] OR "male"[tiab])) OR "Leydig cells"[mh] OR "leydig cell*"[tiab] OR "sertoli cells"[mh] OR "sertoli cell*"[tiab] OR "cytoskeleton"[tiab] OR "gonadal somatic cells"[tiab] OR "follicle-stimulating hormone"[mh] OR "testosterone congeners"[mh] OR "luteinizing hormone"[mh] OR "androgens"[mh] OR "follicle stimulating hormone*"[tiab] OR "FSH"[tiab] OR "luteinizing hormone"[tiab] OR "LH"[tiab] OR "Inhibin"[tiab] OR "testosterone"[tiab] OR "prolactin"[tiab] OR "androgen*"[tiab] OR "gonadotropin releasing hormone"[tiab] OR "GnRH"[tiab] OR "steroidogenic"[tiab] OR "reproductive hormone*"[tiab] OR "reproductive steroid hormone*"[tiab] OR "sex steroid*"[tiab] OR "hypothalamic pituitary gonadal axis"[tiab] OR "hpg axis"[tiab] OR "hypothalamic pituitary adrenal axis"[tiab] OR "hypothalamic pituitary thyroid axis"[tiab] OR "CYP3A4"[tiab] OR "CYP17A1"[tiab] OR "aromatase"[tiab] OR "receptors, gonadotropin"[mh] OR "receptors, pituitary hormone"[mh] OR "receptors, estrogen"[mh] OR "receptors, oxytocin"[mh] OR "receptors, androgen"[mh] OR "hormone receptor*"[tiab] OR "lh receptor*"[tiab] OR "gonadotropin receptor*"[tiab] OR "estrogen receptor*"[tiab] OR "oestrogen receptor*"[tiab] OR "fsh receptor*"[tiab] OR "androgen receptor*"[tiab] OR "testosterone receptor*"[tiab] OR "prolactin receptor*"[tiab] OR "DNA Adducts"[mh] OR "comet assay"[mh] OR "Germ-line mutation"[mh] OR "Mutagenesis"[mh] OR "Mutagenicity tests"[mh] OR "sister chromatid exchange"[mh] OR "Mutation"[mh] OR "DNA Repair"[mh] OR "genomic instability"[mh] OR "Aneuploidy"[mh] OR "ames assay"[tiab] OR "ames test"[tiab] OR "bacterial reverse mutation assay"[tiab] OR "clastogen*"[tiab] OR "genetic toxicology"[tiab] OR "hyperploid"[tiab] OR "micronucleus test"[tiab] OR "tetraploid"[tiab] OR "chromosome aberrations"[tiab] OR "mutation*"[tiab] OR "chromosome translocation*"[tiab] OR "dna protein crosslink*"[tiab] OR "dna damag*"[tiab] OR "dna inhibit*"[tiab] OR "Micronuclei"[tiab] OR "Micronucleus"[tiab] OR "Mutagens"[tiab] OR "strand break*"[tiab] OR "unscheduled dna synthes*"[tiab] OR "chromosomal aberration*"[tiab] OR "chromosome aberration"[tiab] OR "chromosomal abnormalit*"[tiab] OR "chromosome abnormalit*"[tiab] OR "chromosome damage*"[tiab] OR "genotoxic*"[tiab] OR "adduct formation"[tiab] OR "dna adduct*"[tiab] OR "dna break*"[tiab] OR "dsdna break*"[tiab] OR ("DNA"[tiab]AND "Crosslink"[tiab]) OR "microsatellite-instability"[tiab] OR "chromosomal-instability"[tiab] OR "binucleation"[tiab] OR "binucleated"[tiab] OR (("comet assay"[tiab] OR "Mutagenic"[tiab] OR "Mutagenicity"[tiab] OR "mutations"[tiab] OR "chromosomal-aberration-test"[tiab] OR "sister chromatid exchange"[tiab] OR "SOS-response"[tiab] OR "polyploid*"[tiab] OR "genomic instability"[tiab] OR "dna repair*"[tiab] OR "aneuploid*"[tiab]) NOT "Medline"[Filter]) OR "epigenesis, genetic"[mh] OR "epigenomics"[mh] OR "DNA methylation"[mh] OR "gene silencing"[mh] OR "histone deacetylases"[mh] OR "RNA Interference"[mh] OR "microRNAs"[mh] OR "rna, small interfering"[mh] OR "cpg islands/genetics"[mh] OR "cpg island methylator"[tiab] OR "cpg island methylation"[tiab] OR "epigenotype"[tiab] OR "epimutation*"[tiab] OR "methylation associated silencing"[tiab] OR "histone tail modifications"[tiab] OR "histone tail modification"[tiab] OR "chromatin organization"[tiab] OR "chromatin packag*"[tiab] OR "histone modification"[tiab] OR "histone retention"[tiab] OR "epigenetic*"[tiab] OR "epigenomic*"[tiab] OR "RNA Interference"[tiab] OR "noncoding rna"[tiab] OR "ncRNA"[tiab] OR "gene activation"[tiab] OR "proteasome"[tiab] OR "DNA methylation"[tiab] OR "Methylation"[Title] OR "CIMP"[tiab] OR "Free Radicals"[mh] OR "Reactive Oxygen Species"[mh] OR "Oxidative stress"[mh] OR "Electron Transport"[mh] OR "free radical*"[tiab] OR "oxygen radical*"[tiab] OR "Oxidative stress"[tiab] OR "redox balance"[tiab] OR "oxidative damage*"[tiab] OR "Reactive Oxygen Species"[tiab] OR "reactive nitrogen species"[tiab] OR "superoxide radical*"[tiab] OR "hydroxyl radical"[tiab] OR "glutathione deplet*"[tiab] OR "oxidative protein damage"[tiab] OR "C-reactive protein"[mh] OR "eosinophils"[mh] OR ("fibrinogen"[tiab]AND "Inflammation"[tiab]) OR "chronicinflammation"[tiab] OR "chronically inflamed"[tiab] OR "acute inflammat*"[tiab] OR "infiltrating leukocyt*"[tiab] OR "inflammatory-leukocyte"[tiab] OR "inflammatory-leukocytes"[tiab] OR "leukocyte infiltrat*"[tiab] OR "pro-inflammatory"[tiab] OR "proinflammatory"[tiab] OR "macrophage-recruitment"[tiab] OR "macrophage inflammatory proteins"[tiab] OR "macrophage colony stimulating factor*"[tiab] OR "urethritis"[tiab] OR "prostatitis"[tiab] OR "seminal vesiculitis"[tiab] OR "epididymitis"[tiab] OR "orchitis"[tiab]	Key Characteristics of Male Reproductive Toxicants
5	("hypothalamic pituitary ovarian axis"[tiab] OR "hpo axis"[tiab] OR "gonadal hormones"[mh] OR "pituitary hormones"[mh] OR "gonadotropin releasing hormone"[mh] OR "follicle stimulating hormone"[mh] OR "testosterone"[mh] OR "receptors, gonadotropin"[mh] OR "receptors, pituitary hormone"[mh] OR "receptors, estrogen"[mh] OR "receptors, oxytocin"[mh] OR "estrogens"[mh] OR "estradiol"[mh] OR "estriol"[mh] OR "estrone"[mh] OR "luteinizing hormone"[mh] OR "androgens"[mh] OR "hydroxyprogesterones"[mh] OR "Dehydroepiandrosterone"[mh] OR "Androstenedione"[mh] OR "Androstenediol"[mh] OR "Dihydrotestosterone"[mh] OR "androgen receptor*"[tiab] OR "estradiol receptor*"[tiab] OR "estrogen receptor*"[tiab] OR "follicle stimulating hormone"[tiab] OR "fsh	Key Characteristics of Female Reproductive Toxicants

SET #	STRATEGY	CONCEPT GROUP
	receptor*"[tiab] OR "gonadotropin releasing hormone"[tiab] OR "hormone receptor*"[tiab] OR "lh receptor*"[tiab] OR "luteinizing hormone"[tiab] OR "oestrogen receptor*"[tiab] OR "ovarian hormone*"[tiab] OR "ovarian steroid*"[tiab] OR "oxytocin receptor*"[tiab] OR "plasma membrane receptor*"[tiab] OR "prolactin receptor*"[tiab] OR "reproductive hormone*"[tiab] OR "sex hormone*"[tiab] OR "testosterone receptor*"[tiab] OR "activin"[tiab] OR "estradiol"[tiab] OR "estriol"[tiab] OR "estrogen"[tiab] OR "estrone"[tiab] OR "FSH"[tiab] OR "gnrh"[tiab] OR "gonadotropin*"[tiab] OR "gonadotropin receptor*"[tiab] OR "hcg"[tiab] OR "inhibin"[tiab] OR "LH"[tiab] OR "LHRH"[tiab] OR "oestriol"[tiab] OR "oestradiol"[tiab] OR "oestrogen"[tiab] OR "oestrone"[tiab] OR "Oxytocin"[tiab] OR "progesterone"[tiab] OR "prolactin"[tiab] OR "Steroidogenic"[tiab] OR "testosterone"[tiab] OR "Pregnenolone"[tiab] OR "17alpha hydroxy 6 methylene progesterone"[Supplementary Concept] OR "Dehydroepiandrosterone"[tiab] OR "DHEA"[tiab] OR "DHEAS"[tiab] OR "Androstenedione"[tiab] OR "Androstenediol"[tiab] OR "Dihydrotestosterone"[tiab] OR "steroidogenic acute regulatory protein"[Supplementary Concept] OR "steroidogenic acute regulatory protein"[tiab] OR "star protein"[tiab] OR "cholesterol side chain cleavage enzyme"[mh] OR "cholesterol side chain cleavage enzyme"[tiab] OR "cholesterol desmolase"[tiab] OR "cytochrome p 450 scc"[tiab] OR "P450scc"[tiab] OR "CYP11A"[tiab] OR "CYP11A1"[tiab] OR "17alpha hydroxylase"[tiab] OR "17,20 lyase"[tiab] OR "P450c17"[tiab] OR "CYP17"[tiab] OR "aromatase"[mh] OR "aromatase"[tiab] OR "cytochrome p450 family 19"[mh] OR "cytochrome p450 family 19"[tiab] OR "P450arom"[tiab] OR "CYP19"[tiab] OR "3 or 17 beta hydroxysteroid dehydrogenase"[Supplementary Concept] OR "3beta hydroxysteroid dehydrogenase"[tiab] OR "3beta hsd"[tiab] OR "17beta hydroxysteroid dehydrogenase"[tiab] OR "17beta hsd*"[tiab] OR "5alpha-reductase"[tiab] OR ("DNA Adducts"[mh] OR "Comet Assay"[mh] OR "Germ-line mutation"[mh] OR "Mutagenesis"[mh] OR "Mutagenicity tests"[mh] OR "Sister-chromatid exchange"[mh] OR "Mutation"[mh] OR "Ames-Assay"[tiab] OR "Ames-test"[tiab] OR "Bacterial-Reverse-Mutation-Assay"[tiab] OR "clastogen*"[tiab] OR "dna repair*"[tiab] OR "Genetic-toxicology"[tiab] OR "hyperploid"[tiab] OR "micronucleus-test"[tiab] OR "tetraploid"[tiab] OR "Chromosome-aberrations"[tiab] OR "DNA-damage"[tiab] OR "mutation*"[tiab] OR "chromosome-translocations"[tiab] OR "dna protein crosslink*"[tiab] OR "dna damag*"[tiab] OR "dna inhibit*"[tiab] OR "Micronuclei"[tiab] OR "Micronucleus"[tiab] OR "Mutagens"[tiab] OR "strand break*"[tiab] OR "unscheduled dna synthes*"[tiab] OR "chromosomal aberration*"[tiab] OR "chromosome aberration*"[tiab] OR "chromosomal abnormalit*"[tiab] OR "chromosome abnormalit*"[tiab] OR "genotoxic*"[tiab] OR "adduct-formation"[tiab] OR "dna adduct*"[tiab] OR "dna break*"[tiab] OR "dsdna break*"[tiab]) OR ("epigenesis, genetic"[mh] OR "epigenomics"[mh] OR "DNA methylation"[mh] OR "gene silencing"[mh] OR "histone deacetylases"[mh] OR "RNA Interference"[mh] OR "microRNAs"[mh] OR "rna, small interfering"[mh] OR "cpg islands/genetics"[mh] OR "cpg island methylator"[tiab] OR "cpg island methylation"[tiab] OR "epigenotype"[tiab] OR "epimutation*"[tiab] OR "methylation associated silencing"[tiab] OR "histone tail modifications"[tiab] OR "histone tail modification"[tiab] OR "chromatin organization"[tiab] OR "chromatin packag*"[tiab] OR "histone modification"[tiab] OR "histone retention"[tiab] OR "epigenetic*"[tiab] OR "epigenomic*"[tiab] OR "RNA Interference"[tiab] OR "noncoding rna"[tiab] OR "ncRNA"[tiab] OR "gene activation"[tiab] OR "proteasome"[tiab] OR "DNA methylation"[tiab] OR "Methylation"[Title] OR "CIMP"[tiab]) OR ("mitochondria"[mh] OR "oxidative phosphorylation"[mh] OR "mitochrondria*"[tiab] OR "oxidative phosphorylation"[tiab] OR "oxidative damage"[tiab] OR "fatty acid beta oxidation"[tiab] OR "calcium buffering"[tiab] OR "ca2 buffering"[tiab] OR "mitochondrial dna mutation*"[tiab] OR "mtdna mutation*"[tiab] OR "mtDNA"[tiab]) OR ("Free Radicals"[mh] OR "Reactive Oxygen Species"[mh] OR "Oxidative stress"[mh] OR "Electron Transport"[mh] OR "free radical*"[tiab] OR "oxygen radical*"[tiab] OR "Oxidative stress"[tiab] OR "redox balance"[tiab] OR "oxidative damage*"[tiab] OR "Reactive Oxygen Species"[tiab] OR "reactive nitrogen species"[tiab] OR "superoxide radical*"[tiab] OR "hydroxyl radical"[tiab] OR "glutathione deplet*"[tiab] OR "oxidative protein damage"[tiab]) OR ("cytotoxicity, immunologic"[mh] OR "Immunologic Factors"[mh] OR "Immunomodulation"[mh] OR "B-Cell Activation Factor Receptor"[mh] OR "Antigenic Modulation"[mh] OR "B-Cell Activating Factor"[mh] OR "Immunologic Factors"[Pharmacological Action] OR "b-cell-activation"[tiab] OR "immune surveillance"[tiab] OR "immune suppress*"[tiab] OR "immunostimulant"[tiab] OR "immune-activation"[tiab] OR "immunodeficien*"[tiab] OR "somatic-hypermutation"[tiab] OR "immune-activation"[tiab] OR "immune-system-activation"[tiab] OR "Chronic-antigenic-stimulation"[tiab] OR "immunosuppress*"[tiab] OR "immune dysregulation"[tiab]) OR ("signal transduction"[mh] OR "signal transduction"[tiab] OR "signal pathway*"[tiab] OR "signaling pathway*"[tiab] OR "ion channel"[tiab] OR "signaling system*"[tiab] OR "cell signal*"[tiab] OR "cellular signal*"[tiab] OR "intracellular signal*"[tiab] OR "signal cascade*"[tiab] OR "signaling cascade*"[tiab] OR "second messenger*"[tiab] OR "calcium signal*"[tiab]) OR ("cell communication"[mh] OR "gap junctions"[mh] OR "connexins"[mh] OR "connexins"[Supplementary Concept] OR "cell	

SET #	STRATEGY	CONCEPT GROUP
	communication*"[tiab] OR "cellular communication*"[tiab] OR "intracellular communication*"[tiab] OR "cell interaction*"[tiab] OR "gap junction*"[tiab] OR "connexin*"[tiab]) OR ("Apoptosis"[mh] OR "cytotoxicity, immunologic"[mh] OR "Caspases"[mh] OR "autophagy"[mh] OR "necrosis"[mh] OR "Autolysis"[mh] OR "Angiogenesis Modulating Agents"[mh] OR "Angiogenesis Inducing Agents"[Pharmacological Action] OR "Angiogenesis Inducing Agents"[mh] OR "neovascularization, pathologic"[mh] OR "Cell Proliferation"[mh] OR "homeostasis"[mh] OR "Cyclin-Dependent Kinases"[mh] OR "Cyclin-Dependent Kinase Inhibitor Proteins"[mh] OR "Mitogens"[mh] OR "Mitogens"[Pharmacological Action] OR "cell hypoxia"[mh] OR "angiogenic"[tiab] OR "Apoptosis"[tiab] OR "autophagy"[tiab] OR "Caspases"[tiab] OR "cell cycle control*"[tiab] OR "cell cycle arrest"[tiab] OR "cell hypoxia"[tiab] OR "Cell Proliferation"[tiab] OR "cellular-energetics"[tiab] OR "cellular-hypoxia"[tiab] OR "cellular proliferation"[tiab] OR "cellular replication*"[tiab] OR "Cytogenesis"[tiab] OR "Cytogenic"[tiab] OR "Cytotoxin"[tiab] OR "hepatocellular-proliferation"[tiab] OR "hyperplasia"[tiab] OR "hypoxic cell*"[tiab] OR "mitogenesis"[tiab] OR "mitotic checkpoint*"[tiab] OR "Neoplasia"[tiab] OR "p53 delet*"[tiab] OR "p53 inactivat*"[tiab] OR "p53 inhibit*"[tiab] OR "prb delet*"[tiab] OR "prb inactivat*"[tiab] OR "prb inhibit*"[tiab] OR "programmed cell death"[tiab] OR ("Rb"[All Fields] AND "p16ink4a inactiv*"[tiab]) OR "retinoblastoma-protein"[tiab] OR "senescence"[tiab] OR "senescent"[tiab] OR "survivin"[tiab]) OR "microtubules"[mh] OR "spindle apparatus"[mh] OR "microtubule organizing center"[mh] OR "microtubule*"[tiab] OR "spindle formation"[tiab] OR "spindle apparatus"[tiab] OR "meiotic spindle*"[tiab] OR "mitotic spindle*"[tiab])	
6	#2 OR #3 OR #4 OR #5	Combine DART concept groups
7	#1 AND #6	Combine Chemical + DART
8	#7 NOT (animals[mh] NOT humans[mh])	Remove animal studies **FINAL**

Table A.9 PubMed search strategy for animal DART studies

SET #	STRATEGY	CONCEPT GROUP
1	(80-09-1[rn] OR "Bisphenol S"[tiab] OR "bis(4-hydroxyphenyl)sulfone"[nm] OR "bis(4-hydroxyphenyl)sulfone"[tiab] OR "4,4'-Sulfonyldiphenol"[tiab] OR "Phenol, 4,4'-sulfonylbis-"[tiab] OR "BPS-monoglucuronide"[tiab] OR "BPS-1G"[tiab] OR "bisphenol S dicyanate ester"[tiab] OR (bps[tiab] NOT ("bps"[tiab] NOT "bisphenol"[tiab])))	Chemical Terms
2	(abnormalities, drug-induced [mh] AND (fetus [mh] or pregnancy [mh])) OR ((abnormalities, multiple/chemically induced [mh] OR abnormalities, multiple/epidemiology [mh] OR abnormalities, multiple/etiology[mh] OR abnormalities, multiple/genetics [mh] OR abnormalities, multiple/pathology [mh]) AND (pregnancy [mh] OR fetus [mh]))OR (abnormalities, radiation-induced [mh] AND (fetus [mh] or pregnancy [mh])) OR abortion, habitual/chemically induced [mh] OR abortion, habitual/etiology [mh] OR abortion, spontaneous/chemically induced [mh] OR abortion, spontaneous/etiology [mh] OR (alcoholic intoxication[mh] AND (fetus [mh] or pregnancy [mh])) OR (alcohol drinking [mh:noexp] AND (fetus [mh] or pregnancy [mh])) OR Birth Defects Res B Dev Reprod Toxicol [TA] OR birth weight/drug effects [mh] OR birth weight/radiation effects [mh] OR breast feeding/drug effects [mh] OR (carcinogens, environmental [mh] AND (fetus [mh] or pregnancy [mh])) OR (carcinogens [mh] AND (fetus [mh] OR pregnancy [mh])) OR (cardiovascular abnormalities/ci [mh] AND fetus [mh]) OR (cardiovascular abnormalities/et [mh] AND fetus [mh]) OR (cocaine[mh] AND (fetus [mh] or pregnancy [mh])) OR (congenital abnormalities [mh] AND (fetus [mh] or pregnancy [mh])) OR (dna damage [mh] AND (pregnancy [mh] OR fetus [mh])) OR embryo/de [mh] OR embryo/re [mh] OR embryo loss/ci [mh] OR embryonic and fetal development/drug effects [mh] OR embryonic and fetal development/radiation effects [mh] OR embryonic structures/drug effects [mh] OR embryonic structures/pathology [mh] OR embryonic structures/radiation effects [mh] OR (environmental exposure[mh] AND (pregnancy [mh] OR fetus [mh])) OR fertility/drug effects [mh] OR fertility/radiation effects [mh] OR fetal alcohol syndrome[mh:noexp] OR fetal death/chemically induced [mh] OR fetal death/etiology [mh] OR fetal death/genetics [mh] OR fetal death/pathology [mh] OR fetal diseases/chemically induced [mh] OR fetal diseases/etiology [mh] OR fetal diseases/genetics [mh] OR fetal growth retardation/et [mh] OR fetal growth retardation/ci [mh] OR fetal resorption/chemically induced [mh] OR fetal resorption/etiology [mh] OR fetal resorption/genetics [mh] OR fetus/abnormalities [mh] OR fetus/drug effects [mh] OR fetus/radiation effects [mh] OR (fetus*[tw] AND expos*[tw]) OR (genetic diseases, inborn/CI [mh] AND (fetus [mh] OR pregnancy [mh])) OR germ cells/drug effects [mh] OR germ cells/radiation effects [mh] OR (hazardous substances [mh] AND (fetus [mh] or pregnancy [mh])) OR heavy metal poisoning[mh] OR lactation/drug effects [mh] OR lactation/radiation effects [mh] OR (lead [mh:noexp] AND (fetus [mh] or pregnancy [mh])) OR (lead poisoning[mh] AND (fetus [mh] or pregnancy [mh]))OR maternal exposure [mh] OR maternal-fetal exchange/genetics [mh] OR maternal-fetal exchange/drug effects [mh] OR maternal-fetal exchange/radiation effects[mh] OR (mutagens [mh] AND (pregnancy [mh] OR fetus [mh])) OR neonatal abstinence syndrome[mh] OR "neonatal abstinence syndrome"[ti] OR neonatal sepsis [mh] OR ovary/drug effects [mh] OR ovary/radiation effects [mh] OR paternal exposure [mh] OR placenta diseases/chemically induced [mh] OR placenta diseases/etiology [mh] OR placenta/abnormalities [mh] OR placenta/drug effects [mh] OR placenta/radiation effects [mh] OR pregnancy Complications, Infectious/epidemiology [mh] OR pregnancy Complications/ci [mh] OR pregnancy outcome/ge [mh] OR (prenatal*[tw] AND expos*[tw]) OR prenatal exposure delayed effects [mh] OR (protein deficiency[mh:noexp] AND (fetus [mh] or pregnancy [mh])) OR reproduction/drug effects [mh:noexp] OR reproduction/radiation effects [mh] OR rubella/congenital[mh:noexp] OR rubella syndrome, congenital/etiology[mh:noexp] OR (teratogens [mh] AND (pregnancy [mh] OR fetus [mh]))OR Teratology [Journal] OR teratology [mh] OR testis/drug effects [mh] OR testis/radiation effects [mh]	PubMed DART strategy

SET #	STRATEGY	CONCEPT GROUP
3	"abortion, spontaneous"[mh] OR "abortion*"[tiab] OR "Acrosome"[mh] OR "Acrosome"[tiab] OR "Adrenarche"[tiab] OR "androgen antagonists"[mh] OR "androgen*"[tiab] OR "androgens"[mh] OR "Androstenedione"[tiab] OR "anogenital distance"[tiab] OR "ano genital distance"[tiab] OR "anovulat*"[tiab] OR "Aspermia"[tiab] OR "atretic follicle*"[tiab] OR "Azoospermia"[tiab] OR "birth defect*"[tiab] OR "birth weight"[mh] OR "birth weight"[tiab] OR "breast feed*"[tiab] OR "breast feeding"[mh] OR "breastfeed*"[tiab] OR "chorionic villi"[tiab] OR "conception*"[tiab] OR "congenital abnormalities"[mh] OR "Congenital"[tiab] OR "corpus luteum"[tiab] OR "cumulus cell*"[tiab] OR "cytotrophoblast*"[tiab] OR "decidua"[tiab] OR "deciduum"[tiab] OR "dna damage"[mh] OR "ductus deferens"[tiab] OR "efferent duct*"[tiab] OR "ejaculat*"[tiab] OR "Embryo"[tiab] OR "Embryoes"[tiab] OR "embryonic and fetal development"[mh] OR "embryonic structures"[mh] OR "Embryonic"[tiab] OR "embryotoxic*"[tiab] OR "endometri*"[tiab] OR "Epididymis"[mh] OR "Epididymis"[tiab] OR "erecti*"[tiab] OR "Estradiol"[tiab] OR "estrogen antagonists"[mh] OR "estrogen receptor modulators"[mh] OR "estrogen*"[tiab] OR "estrogens"[mh] OR "Estrus"[tiab] OR "fallopian tube*"[tiab] OR "fallopian tubes"[mh] OR "fecund*"[tiab] OR "Fertility"[mh] OR "Fertility"[tiab] OR "Fertilization"[tiab] OR "Fetal"[tiab] OR "Fetus"[mh] OR "Fetus"[tiab] OR "foetal"[tiab] OR "foetus"[tiab] OR "follicle stimulating hormone"[tiab] OR "FSH"[tiab] OR "genetic diseases, inborn"[mh] OR "genital diseases, female"[mh] OR "genital diseases, male"[mh] OR "genital*"[tiab] OR "genitalia"[mh] OR "germ cell*"[tiab] OR "germ cells"[mh] OR "gestat*"[tiab] OR "gonad*"[tiab] OR "gonadal disorders"[mh] OR "gonadal hormones"[mh] OR "gonadotropins"[mh] OR "gonads"[mh] OR "graafian follicle*"[tiab] OR "granulosa cell*"[tiab] OR "human development"[mh] OR "Implantation"[tiab] OR "in utero"[tiab] OR "infant*"[tiab] OR "infant, newborn"[mh] OR "infertil*"[tiab] OR "Inhibin"[tiab] OR "Intrauterine"[tiab] OR "Lactation"[tiab] OR "lactation disorders"[mh] OR "leydig cell*"[tiab] OR "leydig cells"[mh] OR "LH"[tiab] OR "luteal cell*"[tiab] OR "luteinizing hormone"[tiab] OR "maternal exposure"[mh] OR "Maternal"[tiab] OR "Menses"[tiab] OR "menstrua*"[tiab] OR "miscarriage*"[tiab] OR "neonat*"[tiab] OR "Oligospermia"[tiab] OR "oocyte*"[tiab] OR "Oogonia"[tiab] OR "Ova"[tiab] OR "ovarian follicle*"[tiab] OR "Ovarian"[tiab] OR "Ovaries"[tiab] OR "Ovary"[mh] OR "Ovary"[tiab] OR "oviduct*"[tiab] OR "oviducts"[mh] OR "ovulat*"[tiab] OR "Ovum"[mh] OR "Ovum"[tiab] OR "paternal exposure"[mh] OR "Paternal"[tiab] OR "peripubert*"[tiab] OR "pituitary hormones"[mh] OR "placenta*"[tiab] OR "placenta"[mh] OR "placental hormones"[mh] OR "preconception*"[tiab] OR "pre conception*"[tiab] OR "pregnan*"[tiab] OR "pregnancy complications"[mh] OR "pregnancy"[mh] OR "prenatal exposure delayed effects"[mh] OR "prenatal"[tiab] OR "Pre-natal"[tiab] OR "Preterm"[tiab] OR "Pre-term"[tiab] OR "primary follicle*"[tiab] OR "Progesterone"[tiab] OR "progestin*"[tiab] OR "progestins"[mh] OR "Prostate"[mh] OR "Prostate"[tiab] OR "reproduct*"[tiab] OR "reproductive physiological phenomena"[mh] OR "secondary follicle*"[tiab] OR "Semen"[mh] OR "Semen"[tiab] OR "seminal vesicle*"[tiab] OR "seminal vesicles"[mh] OR "Seminal"[tiab] OR "seminiferous epithelium"[tiab] OR "seminiferous tubule*"[tiab] OR "seminiferous tubules"[mh] OR "Seminiferous"[tiab] OR "sertoli cells"[mh] OR "sertoli cell*"[tiab] OR "sexual development"[mh] OR "Sperm"[tiab] OR "spermatid*"[tiab] OR "spermatocyte*"[tiab] OR "spermatogenesis"[tiab] OR "Spermatogonia"[tiab] OR "Spermatozoa"[mh] OR "Spermatozoa"[tiab] OR "Sterile"[tiab] OR "Sterility"[tiab] OR "stillbirth*"[tiab] OR "Stillborn"[tiab] OR "syncytiotrophoblast*"[tiab] OR "teratogen*"[tiab] OR "teratogens"[mh] OR "tertiary follicle*"[tiab] OR "Testes"[tiab] OR "testic*"[tiab] OR "Testis"[mh] OR "Testis"[tiab] OR "Testosterone"[tiab] OR "theca cell*"[tiab] OR "thyroid hormones"[mh] OR "trophoblast*"[tiab] OR "urogenital abnormalities"[mh] OR "urogenital*"[tiab] OR "Uterine"[tiab] OR "Uterus"[mh] OR "Uterus"[tiab] OR "vagina*"[tiab] OR "vas deferens"[mh] OR "vas deferens"[tiab] OR "zygote*"[tiab]	Additional DART terms (OEHHA Strategy)

SET #	STRATEGY	CONCEPT GROUP
4	"spermatozoa"[mh] OR "acrosome reaction"[mh] OR "Sperm Capacitation"[mh] OR "sperm transport"[mh] OR "sperm-ovum interactions"[mh] OR "acrosome"[tiab] OR "spermatozoa"[tiab] OR "sperm"[tiab] OR "spermatogonia"[tiab] OR "spermatophore*"[tiab] OR "spermatocyte*"[tiab] OR "spermatid*"[tiab] OR "spermatogenesis"[tiab] OR "capacitation"[tiab] OR (("Germ cells"[mh] OR "germ cell*"[tiab]) AND ("male"[mh] OR "male"[tiab])) OR "Leydig cells"[mh] OR "leydig cell*"[tiab] OR "sertoli cells"[mh] OR "sertoli cell*"[tiab] OR "cytoskeleton"[tiab] OR "gonadal somatic cells"[tiab] OR "follicle-stimulating hormone"[mh] OR "testosterone congeners"[mh] OR "luteinizing hormone"[mh] OR "androgens"[mh] OR "follicle stimulating hormone*"[tiab] OR "FSH"[tiab] OR "luteinizing hormone"[tiab] OR "LH"[tiab] OR "Inhibin"[tiab] OR "testosterone"[tiab] OR "prolactin"[tiab] OR "androgen*"[tiab] OR "gonadotropin releasing hormone"[tiab] OR "GnRH"[tiab] OR "steroidogenic"[tiab] OR "reproductive hormone*"[tiab] OR "reproductive steroid hormone*"[tiab] OR "sex steroid*"[tiab] OR "hypothalamic pituitary gonadal axis"[tiab] OR "hpg axis"[tiab] OR "hypothalamic pituitary adrenal axis"[tiab] OR "hypothalamic pituitary thyroid axis"[tiab] OR "CYP3A4"[tiab] OR "CYP17A1"[tiab] OR "aromatase"[tiab] OR "receptors, gonadotropin"[mh] OR "receptors, pituitary hormone"[mh] OR "receptors, estrogen"[mh] OR "receptors, oxytocin"[mh] OR "receptors, androgen"[mh] OR "hormone receptor*"[tiab] OR "lh receptor*"[tiab] OR "gonadotropin receptor*"[tiab] OR "estrogen receptor*"[tiab] OR "oestrogen receptor*"[tiab] OR "fsh receptor*"[tiab] OR "androgen receptor*"[tiab] OR "testosterone receptor*"[tiab] OR "prolactin receptor*"[tiab] OR "DNA Adducts"[mh] OR "comet assay"[mh] OR "Germ-line mutation"[mh] OR "Mutagenesis"[mh] OR "Mutagenicity tests"[mh] OR "sister chromatid exchange"[mh] OR "Mutation"[mh] OR "DNA Repair"[mh] OR "genomic instability"[mh] OR "Aneuploidy"[mh] OR "ames assay"[tiab] OR "ames test"[tiab] OR "bacterial reverse mutation assay"[tiab] OR "clastogen*"[tiab] OR "genetic toxicology"[tiab] OR "hyperploid"[tiab] OR "micronucleus test"[tiab] OR "tetraploid"[tiab] OR "chromosome aberrations"[tiab] OR "mutation*"[tiab] OR "chromosome translocation*"[tiab] OR "dna protein crosslink*"[tiab] OR "dna damag*"[tiab] OR "dna inhibit*"[tiab] OR "Micronuclei"[tiab] OR "Micronucleus"[tiab] OR "Mutagens"[tiab] OR "strand break*"[tiab] OR "unscheduled dna synthes*"[tiab] OR "chromosomal aberration*"[tiab] OR "chromosome aberration"[tiab] OR	Key Characteristics of Male Reproductive Toxicants

SET #	STRATEGY	CONCEPT GROUP
	"chromosomal abnormalit*"[tiab] OR "chromosome abnormalit*"[tiab] OR "chromosome damage*"[tiab] OR "genotoxic*"[tiab] OR "adduct formation"[tiab] OR "dna adduct*"[tiab] OR "dna break*"[tiab] OR "dsdna break*"[tiab] OR ("DNA"[tiab]AND "Crosslink"[tiab]) OR "microsatellite-instability"[tiab] OR "chromosomal-instability"[tiab] OR "binucleation"[tiab] OR "binucleated"[tiab] OR (("comet assay"[tiab] OR "Mutagenic"[tiab] OR "Mutagenicity"[tiab] OR "mutations"[tiab] OR "chromosomal-aberration-test"[tiab] OR "sister chromatid exchange"[tiab] OR "SOS-response"[tiab] OR "polyploid*"[tiab] OR "genomic instability"[tiab] OR "dna repair*"[tiab] OR "aneuploid*"[tiab]) NOT "Medline"[Filter]) OR "epigenesis, genetic"[mh] OR "epigenomics"[mh] OR "DNA methylation"[mh] OR "gene silencing"[mh] OR "histone deacetylases"[mh] OR "RNA Interference"[mh] OR "microRNAs"[mh] OR "rna, small interfering"[mh] OR "cpg islands/genetics"[mh] OR "cpg island methylator"[tiab] OR "cpg island methylation"[tiab] OR "epigenotype"[tiab] OR "epimutation*"[tiab] OR "methylation associated silencing"[tiab] OR "histone tail modifications"[tiab] OR "histone tail modification"[tiab] OR "chromatin organization"[tiab] OR "chromatin packag*"[tiab] OR "histone modification"[tiab] OR "histone retention"[tiab] OR "epigenetic*"[tiab] OR "epigenomic*"[tiab] OR "RNA Interference"[tiab] OR "noncoding rna"[tiab] OR "ncRNA"[tiab] OR "gene activation"[tiab] OR "proteasome"[tiab] OR "DNA methylation"[tiab] OR "Methylation"[Title] OR "CIMP"[tiab] OR "Free Radicals"[mh] OR "Reactive Oxygen Species"[mh] OR "Oxidative stress"[mh] OR "Electron Transport"[mh] OR "free radical*"[tiab] OR "oxygen radical*"[tiab] OR "Oxidative stress"[tiab] OR "redox balance"[tiab] OR "oxidative damage*"[tiab] OR "Reactive Oxygen Species"[tiab] OR "reactive nitrogen species"[tiab] OR "superoxide radical*"[tiab] OR "hydroxyl radical"[tiab] OR "glutathione deplet*"[tiab] OR "oxidative protein damage"[tiab] OR "C-reactive protein"[mh] OR "eosinophils"[mh] OR ("fibrinogen"[tiab]AND "Inflammation"[tiab]) OR "chronicinflammation"[tiab] OR "chronically inflamed"[tiab] OR "acute inflammat*"[tiab] OR "infiltrating leukocyt*"[tiab] OR "inflammatory-leukocyte"[tiab] OR "inflammatory-leukocytes"[tiab] OR "leukocyte infiltrat*"[tiab] OR "pro-inflammatory"[tiab] OR "proinflammatory"[tiab] OR "macrophage-recruitment"[tiab] OR "macrophage inflammatory proteins"[tiab] OR "macrophage colony stimulating factor*"[tiab] OR "urethritis"[tiab] OR "prostatitis"[tiab] OR "seminal vesiculitis"[tiab] OR "epididymitis"[tiab] OR "orchitis"[tiab]	
5	("hypothalamic pituitary ovarian axis"[tiab] OR "hpo axis"[tiab] OR "gonadal hormones"[mh] OR "pituitary hormones"[mh] OR "gonadotropin releasing hormone"[mh] OR "follicle stimulating hormone"[mh] OR "testosterone"[mh] OR "receptors, gonadotropin"[mh] OR "receptors, pituitary hormone"[mh] OR "receptors, estrogen"[mh] OR "receptors, oxytocin"[mh] OR "estrogens"[mh] OR "estradiol"[mh] OR "estriol"[mh] OR "estrone"[mh] OR "luteinizing hormone"[mh] OR "androgens"[mh] OR "hydroxyprogesterones"[mh] OR "Dehydroepiandrosterone"[mh] OR "Androstenedione"[mh] OR "Androstenediol"[mh] OR "Dihydrotestosterone"[mh] OR "androgen receptor*"[tiab] OR "estradiol receptor*"[tiab] OR "estrogen receptor*"[tiab] OR "follicle stimulating hormone"[tiab] OR "fsh receptor*"[tiab] OR "gonadotropin releasing hormone"[tiab] OR "hormone receptor*"[tiab] OR "lh receptor*"[tiab] OR "luteinizing hormone"[tiab] OR "oestrogen receptor*"[tiab] OR "ovarian hormone*"[tiab] OR "ovarian steroid*"[tiab] OR "oxytocin receptor*"[tiab] OR "plasma membrane receptor*"[tiab] OR "prolactin receptor*"[tiab] OR "reproductive hormone*"[tiab] OR "sex hormone*"[tiab] OR "testosterone receptor*"[tiab] OR "activin"[tiab] OR "estradiol"[tiab] OR "estriol"[tiab] OR "estrogen"[tiab] OR "estrone"[tiab] OR "FSH"[tiab] OR "gnrh"[tiab] OR "gonadotropin*"[tiab] OR "gonadotropin receptor*"[tiab] OR "hcg"[tiab] OR "inhibin"[tiab] OR "LH"[tiab] OR "LHRH"[tiab] OR "oestriol"[tiab] OR "oestradiol"[tiab] OR "oestrogen"[tiab] OR "oestrone"[tiab] OR "Oxytocin"[tiab] OR "progesterone"[tiab] OR "prolactin"[tiab] OR "Steroidogenic"[tiab] OR "testosterone"[tiab] OR "Pregnenolone"[tiab] OR "17alpha hydroxy 6 methylene progesterone"[Supplementary Concept] OR "Dehydroepiandrosterone"[tiab] OR "DHEA"[tiab] OR "DHEAS"[tiab] OR "Androstenedione"[tiab] OR "Androstenediol"[tiab] OR "Dihydrotestosterone"[tiab]	Key Characteristics of Female Reproductive Toxicants

SET #	STRATEGY	CONCEPT GROUP
	OR "steroidogenic acute regulatory protein"[Supplementary Concept] OR "steroidogenic acute regulatory protein"[tiab] OR "star protein"[tiab] OR "cholesterol side chain cleavage enzyme"[mh] OR "cholesterol side chain cleavage enzyme"[tiab] OR "cholesterol desmolase"[tiab] OR "cytochrome p 450 scc"[tiab] OR "P450scc"[tiab] OR "CYP11A"[tiab] OR "CYP11A1"[tiab] OR "17alpha hydroxylase"[tiab] OR "17,20 lyase"[tiab] OR "P450c17"[tiab] OR "CYP17"[tiab] OR "aromatase"[mh] OR "aromatase"[tiab] OR "cytochrome p450 family 19"[mh] OR "cytochrome p450 family 19"[tiab] OR "P450arom"[tiab] OR "CYP19"[tiab] OR "3 or 17 beta hydroxysteroid dehydrogenase"[Supplementary Concept] OR "3beta hydroxysteroid dehydrogenase"[tiab] OR "3beta hsd"[tiab] OR "17beta hydroxysteroid dehydrogenase"[tiab] OR "17beta hsd*"[tiab] OR "5alpha-reductase"[tiab] OR ("DNA Adducts"[mh] OR "Comet Assay"[mh] OR "Germ-line mutation"[mh] OR "Mutagenesis"[mh] OR "Mutagenicity tests"[mh] OR "Sister-chromatid exchange"[mh] OR "Mutation"[mh] OR "Ames-Assay"[tiab] OR "Ames-test"[tiab] OR "Bacterial-Reverse-Mutation-Assay"[tiab] OR "clastogen*"[tiab] OR "dna repair*"[tiab] OR "Genetic-toxicology"[tiab] OR "hyperploid"[tiab] OR "micronucleus-test"[tiab] OR "tetraploid"[tiab] OR "Chromosome-aberrations"[tiab] OR "DNA-damage"[tiab] OR "mutation*"[tiab] OR "chromosome-translocations"[tiab] OR "dna protein crosslink*"[tiab] OR "dna damag*"[tiab] OR "dna inhibit*"[tiab] OR "Micronuclei"[tiab] OR "Micronucleus"[tiab] OR "Mutagens"[tiab] OR "strand break*"[tiab] OR "unscheduled dna synthes*"[tiab] OR "chromosomal aberration*"[tiab] OR "chromosome aberration*"[tiab] OR "chromosomal abnormalit*"[tiab] OR "chromosome abnormalit*"[tiab] OR "genotoxic*"[tiab] OR "adduct-formation"[tiab] OR "dna adduct*"[tiab] OR "dna break*"[tiab] OR "dsdna break*"[tiab]) OR ("epigenesis, genetic"[mh] OR "epigenomics"[mh] OR "DNA methylation"[mh] OR "gene silencing"[mh] OR "histone deacetylases"[mh] OR "RNA Interference"[mh] OR "microRNAs"[mh] OR "rna, small interfering"[mh] OR "cpg islands/genetics"[mh] OR "cpg island methylator"[tiab] OR "cpg island methylation"[tiab] OR "epigenotype"[tiab] OR "epimutation*"[tiab] OR "methylation associated silencing"[tiab] OR "histone tail modifications"[tiab] OR "histone tail modification"[tiab] OR "chromatin organization"[tiab] OR "chromatin packag*"[tiab] OR "histone modification"[tiab] OR "histone retention"[tiab] OR "epigenetic*"[tiab] OR "epigenomic*"[tiab] OR "RNA Interference"[tiab] OR "noncoding rna"[tiab] OR "ncRNA"[tiab] OR "gene activation"[tiab] OR "proteasome"[tiab] OR "DNA methylation"[tiab] OR "Methylation"[Title] OR "CIMP"[tiab]) OR ("mitochondria"[mh] OR "oxidative phosphorylation"[mh] OR "mitochrondria*"[tiab] OR "oxidative phosphorylation"[tiab] OR "oxidative damage"[tiab] OR "fatty acid beta oxidation"[tiab] OR "calcium buffering"[tiab] OR "ca2 buffering"[tiab] OR "mitochondrial dna mutation*"[tiab] OR "mtdna mutation*"[tiab] OR "mtDNA"[tiab]) OR ("Free Radicals"[mh] OR "Reactive Oxygen Species"[mh] OR "Oxidative stress"[mh] OR "Electron Transport"[mh] OR "free radical*"[tiab] OR "oxygen radical*"[tiab] OR "Oxidative stress"[tiab] OR "redox balance"[tiab] OR "oxidative damage*"[tiab] OR "Reactive Oxygen Species"[tiab] OR "reactive nitrogen species"[tiab] OR "superoxide radical*"[tiab] OR "hydroxyl radical"[tiab] OR "glutathione deplet*"[tiab] OR "oxidative protein damage"[tiab]) OR ("cytotoxicity, immunologic"[mh] OR "Immunologic Factors"[mh] OR "Immunomodulation"[mh] OR "B-Cell Activation Factor Receptor"[mh] OR "Antigenic Modulation"[mh] OR "B-Cell Activating Factor"[mh] OR "Immunologic Factors"[Pharmacological Action] OR "b-cell-activation"[tiab] OR "immune surveillance"[tiab] OR "immune suppress*"[tiab] OR "immunostimulant"[tiab] OR "immune-activation"[tiab] OR "immunodeficien*"[tiab] OR "somatic-hypermutation"[tiab] OR "immune-activation"[tiab] OR "immune-system-activation"[tiab] OR "Chronic-antigenic-stimulation"[tiab] OR "immunosuppress*"[tiab] OR "immune dysregulation"[tiab]) OR ("signal transduction"[mh] OR "signal transduction"[tiab] OR "signal pathway*"[tiab] OR "signaling pathway*"[tiab] OR "ion channel"[tiab] OR "signaling system*"[tiab] OR "cell signal*"[tiab] OR "cellular signal*"[tiab] OR "intracellular signal*"[tiab] OR "signal cascade*"[tiab] OR "signaling cascade*"[tiab] OR "second messenger*"[tiab] OR "calcium signal*"[tiab]) OR ("cell communication"[mh] OR "gap junctions"[mh] OR "connexins"[mh] OR "connexins"[Supplementary Concept] OR "cell communication*"[tiab] OR "cellular communication*"[tiab] OR "intracellular communication*"[tiab] OR "cell interaction*"[tiab] OR "gap junction*"[tiab] OR "connexin*"[tiab]) OR ("Apoptosis"[mh] OR "cytotoxicity, immunologic"[mh] OR "Caspases"[mh] OR "autophagy"[mh] OR "necrosis"[mh] OR	

SET #	STRATEGY	CONCEPT GROUP
	"Autolysis"[mh] OR "Angiogenesis Modulating Agents"[mh] OR "Angiogenesis Inducing Agents"[Pharmacological Action] OR "Angiogenesis Inducing Agents"[mh] OR "neovascularization, pathologic"[mh] OR "Cell Proliferation"[mh] OR "homeostasis"[mh] OR "Cyclin-Dependent Kinases"[mh] OR "Cyclin-Dependent Kinase Inhibitor Proteins"[mh] OR "Mitogens"[mh] OR "Mitogens"[Pharmacological Action] OR "cell hypoxia"[mh] OR "angiogenic"[tiab] OR "Apoptosis"[tiab] OR "autophagy"[tiab] OR "Caspases"[tiab] OR "cell cycle control*"[tiab] OR "cell cycle arrest"[tiab] OR "cell hypoxia"[tiab] OR "Cell Proliferation"[tiab] OR "cellular-energetics"[tiab] OR "cellular-hypoxia"[tiab] OR "cellular proliferation"[tiab] OR "cellular replication*"[tiab] OR "Cytogenesis"[tiab] OR "Cytogenic"[tiab] OR "Cytotoxin"[tiab] OR "hepatocellular-proliferation"[tiab] OR "hyperplasia"[tiab] OR "hypoxic cell*"[tiab] OR "mitogenesis"[tiab] OR "mitotic checkpoint*"[tiab] OR "Neoplasia"[tiab] OR "p53 delet*"[tiab] OR "p53 inactivat*"[tiab] OR "p53 inhibit*"[tiab] OR "prb delet*"[tiab] OR "prb inactivat*"[tiab] OR "prb inhibit*"[tiab] OR "programmed cell death"[tiab] OR ("Rb"[All Fields] AND "p16ink4a inactiv*"[tiab]) OR "retinoblastoma-protein"[tiab] OR "senescence"[tiab] OR "senescent"[tiab] OR "survivin"[tiab]) OR "microtubules"[mh] OR "spindle apparatus"[mh] OR "microtubule organizing center"[mh] OR "microtubule*"[tiab] OR "spindle formation"[tiab] OR "spindle apparatus"[tiab] OR "meiotic spindle*"[tiab] OR "mitotic spindle*"[tiab])	
6	#2 OR #3 OR #4 OR #5	Combine DART concept groups
7	#1 AND #6	Combine Chemical + DART
8	("Animals, Genetically Modified"[mh] OR "Animals, Inbred Strains"[mh] OR "Chimera"[mh] OR "Animals, Laboratory"[mh] OR animals[mh:noexp]) OR (animal-stud*[tiab] OR wood-mouse[tiab] OR murinae[tiab] OR muridae[tiab] OR cricetinae[tiab] OR rodentia[tiab] OR rodent[tiab] OR rodents[tiab] OR ferrets[tiab] OR ferret[tiab] OR polecat*[tiab] OR mustela-putorius[tiab] OR cavia[tiab] OR callithrix[tiab] OR marmoset*[tiab] OR chinchilla*[tiab] OR jird[tiab] OR jirds[tiab] OR merione[tiab] OR meriones[tiab] OR cats[tiab] OR cat[tiab] OR felis[tiab] OR canis[tiab] OR sheep[tiab] OR sheeps[tiab] OR goats[tiab] OR goat[tiab] OR capra[tiab] OR saguinus[tiab] OR tamarin*[tiab] OR leontopithecus[tiab] OR ape[tiab] OR apes[tiab] OR pan-paniscus[tiab] OR bonobo*[tiab] OR pan-troglodytes[tiab] OR gibbon*[tiab] OR siamang*[tiab] OR nomascus[tiab] OR symphalangus[tiab] OR chimpanzee*[tiab] OR orangutan*[tiab] OR horse[tiab] OR horses[tiab] OR equus[tiab] OR cow[tiab] OR cows[tiab] OR chicken[tiab] OR chickens[tiab] OR wistar[tiab] OR balb[tiab] OR C57[tiab] OR C57bl[tiab] OR quail[tiab] OR long-evans[tiab] OR guppy[tiab] OR medaka[tiab] OR zebrafish[tiab] OR flying-fox[tiab] OR Fruit-bat[tiab] OR non-human-primate*[tiab] OR capuchin*[tiab] OR rhesus[tiab] OR macaque*[tiab] OR cattle[tiab] OR bovine[tiab] OR pigs[tiab] OR pig[tiab] OR swine[tiab] OR swines[tiab] OR piglet*[tiab] OR Sprague-Dawley[tiab] OR vervet*[tiab]) OR ((mice[tiab] OR mouse[tiab] OR murine[tiab] OR rats[tiab] OR rat[tiab] OR hamster[tiab] OR hamsters[tiab] OR guinea-pig*[tiab] OR gerbil*[tiab] OR rabbits[tiab] OR rabbit[tiab] OR dogs[tiab] OR dog[tiab] OR monkey[tiab] OR monkeys[tiab] OR pongo-pygmaeus[tiab] OR sow[tiab] OR sows[tiab] OR boar[tiab] OR boars[tiab]) NOT medline[sb]) OR ((in vitro[tiab] OR in vitro techniques[mh] OR cell line*[tiab]) AND animals[mh:noexp])	Experimental Animals (RoC modified)
9	#7 AND #8	Combine Chemical + DART + Animals

Table A.10 PubMed search strategy for ADME

SET #	STRATEGY	CONCEPT GROUP
1	(80-09-1[rn] OR "Bisphenol S"[tiab] OR "bis(4-hydroxyphenyl)sulfone"[nm] OR "bis(4-hydroxyphenyl)sulfone"[tiab] OR "4,4'-Sulfonyldiphenol"[tiab] OR "Phenol, 4,4'-sulfonylbis-"[tiab] OR "BPS-monoglucuronide"[tiab] OR "BPS-1G"[tiab] OR "bisphenol S dicyanate ester"[tiab] OR (bps[tiab] NOT ("bps"[tiab] NOT "bisphenol"[tiab])))	Chemical Terms
2	(("Volume of Distribution"[tiab] OR "Toxicokinetics"[mh] OR "tissue distribut*"[tiab] OR "Renal Elimination"[mh] OR "protein bound"[tiab] OR "protein bind*"[tiab] OR "plasma protein"[tiab] OR "Pharmacokinetics"[mh] OR "Metabolism"[mh] OR "kinetic"[tiab] OR "Intestinal Elimination"[mh] OR "Hepatobiliary Elimination"[mh] OR "Hepatobiliary"[tiab] OR "enterohepatic"[tiab] OR "entero-hepatic"[tiab] OR "Distribution volume"[tiab] OR "cellular clearance"[tiab] OR "cell clearance"[tiab] OR "Biotransformation"[tiab] OR "bioavailability"[tiab] OR "ADME"[tiab] OR "absorptive"[tiab] OR "PBPK"[tiab] OR "toxicodynamic*"[tiab] OR ("Skin"[tiab] AND "absorption"[tiab]) OR ("Oral"[tiab] AND "absorption"[tiab]) OR ("Injection"[tiab] AND "absorption"[tiab]) OR ("Gavage"[tiab] AND "absorption"[tiab]) OR ("Dietary"[tiab] AND "absorption"[tiab]) OR ("Dermal"[tiab] AND "absorption"[tiab])) OR (("urine"[tiab] OR "Urination"[tiab] OR "toxicokinetic*"[tiab] OR "Pharmacokinetic*"[tiab] OR "Metabolite*"[tiab] OR "metabolism"[tiab] OR "Metabolic*"[tiab] OR "feces"[tiab] OR "fecal"[tiab] OR "excretion"[tiab] OR "defecation"[tiab] OR "biliary"[tiab] OR "Bile"[tiab]) NOT Medline[sb]))	ADME Terms
3	#1 AND #2	Combine Chemical + ADME terms

APPENDIX B. SUMMARY OF EPIDEMIOLOGIC STUDIES OF DEVELOPMENTAL TOXICITY

Table B.1 BPS: Summary of epidemiologic studies of developmental toxicity*.

Study/ Design	Date of Collection/ Sample size	LOD (ng/mL)/ Adjustment for < LOD	% samples with BPS detected	Matrix, Median BPS (ng/mL)**	25th, 75th Percentile (ng/mL)***	Results****
Birth Outcomes						
Aker et al. 2019b Cohort	2011–2017 N = 922	0.1 LOD÷√2	Visit 1: 94.5 Visit 2: 93.1 Visit 3: 94.3	Urine, Visit 1: 0.40 Visit 2: 0.40 Visit 3: 0.40	Visit 1: 0.20, 0.99 Visit 2: 0.20, 0.90 Visit 3: 0.20, 0.90	Results varied by timing of exposure measurement: Higher odds of LGA with BPS exposure measured at 16–28 weeks (all visits averaged). Higher odds of SGA with BPS exposure measured at 24–28 weeks (visit 3).
Aker et al. 2020 Cohort	2011–2017 N = 540	0.1 LOD÷√2	Visit 1: 94.5 Visit 2: 93.1 Visit 3: 94.3	Urine, Visit 1: 0.40 Visit 2: 0.40 Visit 3: 0.40	Visit 1: 0.20, 0.99 Visit 2: 0.20, 0.90 Visit 3: 0.20, 0.90	Results varied by maternal report of negative life events: Average BPS (16–28 weeks) associated with shorter gestational length in pregnancies with maternal report of negative life events. Results varied by fetal sex: Associations were stronger among mothers with male fetuses.
Aung et al. 2019 Case-control	2006–2008 N = 480	0.4 LOD÷√2	20.6	Urine, < LOD	< LOD, < LOD	Results varied by timing of exposure measurement: Higher odds of preterm birth with exposure measured at 35 weeks.
Bommarito et al.2024) Case-cohort	2008–2018 N = 900	0.4–1.6 Multiple imputation	52	Urine, NR	NR, NR	BPS associated with shorter femur length.
Y Chen et al. 2024 Cohort	2012 N = 537	0.004 LOD÷2	24.6	Urine, 0.01	0.00, 0.03	BPS associated with larger abdominal skinfold thickness at birth.
Ferguson et al. 2018 Cohort	2006–2008 N = 476	0.4 LOD÷√2	26.7	Urine, < LOD	< LOD, 0.59	Results varied by offspring sex: BPS associated with lower fetal weight in males. BPS associated with longer femur length and larger head circumference in females.

Study/ Design	Date of Collection/ Sample size	LOD (ng/mL)/ Adjustment for < LOD	% samples with BPS detected	Matrix, Median BPS (ng/mL)**	25th, 75th Percentile (ng/mL)***	Results****
Goodrich et al. 2019 Cohort	2012–2015 N = 56	0.2 LOD÷√2	37.5	Urine, < LOD	< LOD, 0.26	BPS associated with lower birthweight and Fenton z-score.
Hu et al. 2019 Cohort	2013–2015 N = 845	0.04 LOD÷√2	All: 86.8 TM1: 84.3 TM2: 86.5 TM3: 89.6	Urine, All: 0.38 TM1: 0.30 TM2: 0.39 TM3: 0.43	All: 0.13, 1.11 TM1: 0.10, 0.95 TM2: 0.14, 1.17 TM3: 0.17, 1.21	Results varied by timing of exposure measurement: Lower birthweight with TM1 and TM2 BPS exposure. Shorter length at birth with TM2 exposure.
Huang et al. 2019 Cohort	2014–2015 N = 850	0.04 LOD÷√2	TM1: 62.4 TM2: 64.6 TM3: 68.1	Urine, TM1: 0.35 TM2: 0.47 TM3: 0.51	TM1: 0.13, 1.07 TM2: 0.16, 1.39 TM3: 0.20, 1.43	No significant associations with gestation length or preterm birth.
Jedynak et al. 2022 Cohort	2014–2017 N = 478	0.1 Random values below LOD	TM2: 15 TM3: 18	Urine, TM2: < LOD TM3: < LOD	TM2: < LOD, < LOD TM3: < LOD, < LOD	Results varied by timing of *in utero* growth measurement: BPS detected in both TM2 and TM3 was associated with longer femur length at 32 weeks.
S Kim et al. 2021 Cohort	2017–2020 N = 180	0.02 LOD÷√2	66.1	Urine, 0.05	0.03, 0.1	No significant associations with gestational age. Evidence of U-shaped association with birthweight in univariate exposure-response function.
Kim et al. 2024 Cohort	2022–2023 N = 107	0.01 LOD÷√2	NR	Urine, All: 0.37 TM1: 0.23 TM2: 0.25 Birth: 0.65	All: 0.13, 0.81 TM1: 0.12, 0.62 TM2: 0.08, 0.47 Birth: 0.41, 1.75	No significant associations with estimated fetal weight or birthweight.
X Li et al. 2024 Cohort	2019–2020 N = 113	LOD: NR LOQ: 0.1 LOQ÷√2	46.0	Urine, 0.31	0.07, 0.57	No significant associations with birthweight.
J Liang et al. 2020 Cohort	2015–2018 N = 2023	0.046 LOD÷2	86.9	Serum, 0.097	0.096, 0.107	No significant associations with birthweight, birth length, or ponderal index.

Study/ Design	Date of Collection/ Sample size	LOD (ng/mL)/ Adjustment for < LOD	% samples with BPS detected	Matrix, Median BPS (ng/mL)**	25th, 75th Percentile (ng/mL)***	Results****
Liang et al. 2021a Cohort	2015–2017 N = 801	0.046 LOD÷2	90.9	Serum, 0.098	0.096, 0.110	Results varied by maternal age: BPS associated with shorter telomere length among offspring of mothers ages 28 and older.
Liang et al. 2021b Cohort	2015–2018 N = 2023	0.046 LOD÷2	86.9	Serum, 0.097	0.096, 0.107	Higher odds of preterm birth. Evidence of U-shaped association for preterm birth. Associations were stronger for pregnancies with male fetuses.
Mustieles et al. 2018 Cohort	2005–2016 N = 73	0.1 LOD÷√2	Preconcep-tion: 53 Prenatal: 55	Urine, Preconception: 0.46 Prenatal: 0.31	Preconception: 0.29, 0.83 Prenatal: 0.19, 0.55	Preconception BPS associated with higher birthweight. No significant associations with prenatal BPS and birthweight or head circumference.
Mustieles et al. 2020 Cohort	2005–2018 N = 163	0.1 LOD÷√2	80.7	Urine, 0.47	0.32, 0.77	Preconception BPS associated with higher risk of preterm birth.
Sol et al. 2021† Cohort	2004–2005 N = 1379	0.05 LOD÷√2	TM1: 67.9 TM2: 29.4	Urine, TM1: 0.17 TM2: <0.03	TM1: 0.03, 0.61 TM2: 0.03, 0.10	TM1 BPS associated with larger fetal head circumference and fetal weight measured in TM2 and TM3 and at birth. TM1 BPS associated with lower odds of SGA.
Stevens et al. 2023 Cohort	2009–2014 N = 438	0.1 Imputed as instrument value when possible, all other values imputed as ½ the minimum reported value	87	Urine, 0.3	0.2, 0.6	No associations between TM2 BPS with infant size, fat mass, or fat mass percent.
Trasande et al. 2023 Cohort	1998–2023 N = 3619	LOD varied by cohort LOD÷√2	At least 50%	Urine, All: 0.3 TM1: 0.3 TM2: 0.4 TM3: 0.3	All IQR: 0.6 TM1 IQR: 0.6 TM2 IQR: 0.6 TM3 IQR: 0.6	Results varied by timing of exposure: TM2 BPS associated with higher birthweight z-score. TM3 BPS associated with higher odds of SGA and low birthweight. Some associations varied by race and ethnic group.

Study/ Design	Date of Collection/ Sample size	LOD (ng/mL)/ Adjustment for < LOD	% samples with BPS detected	Matrix, Median BPS (ng/mL)**	25th, 75th Percentile (ng/mL)***	Results****
Wan et al. 2018 Cross-sectional	2012–2014 N = 985	LOD: NR LOQ:0.02 LOQ÷√2	93.7	Urine, GM: 0.17	0.07, 0.42	BPS associated with longer gestation length.
J Wang et al. 2021 Cohort	2013–2016 N = 289 twin pairs	0.05 LOD÷√2	All: 78.5 TM1: 82.4 TM2: 78.2 TM3: 75.1	Urine, All: 0.29 TM1: 0.29 TM2: 0.24 TM3: 0.30	All: 0.09, 0.73 TM1: 0.09, 0.71 TM2: 0.09, 0.80 TM3: 0.09, 0.72	Results varied by timing of exposure measurement: Higher birthweight with TM2 and TM3 BPS.
Yang et al. 2021 Cross-sectional	2011–2013 N = 1197	0.03 LOD÷√2	47.9	Urine, < LOD	NR, NR	BPS associated with shorter gestation length.
Zhang et al. 2021 Cohort	2005–2018 N = 386	0.1 LOD÷√2	TM1: 72.4 TM2: 67.5 TM3: 78.6	Urine, TM1: 0.33 TM2: 0.28 TM3: 0.35	TM1: 0.19, 0.66 TM2: 0.16, 0.58 TM3: 0.20, 0.70	No significant associations with preterm birth.
Zhou et al. 2020 Cross-sectional	2011–2012 N = 322	0.03 LOD÷√2	52.5	Urine, 0.04 µg/g	0.02 µg/g, 0.22 µg/g	No significant associations with fetal growth parameters measured by ultrasound between 35 and 42 weeks.
Zhu et al. 2023 Case-control	2010–2016 N = 286	0.002 ng/g NR	NR	Placenta Cases: 1.18 ng/g Controls: 1.83 ng/g	Cases: 1.70, 3.36 ng/g Controls: 1.70, 3.40 ng/g	No significant associations with neural tube defects.

Study/ Design	Date of Collection/ Sample size	LOD (ng/mL)/ Adjustment for < LOD	% samples with BPS detected	Matrix, Median BPS (ng/mL)**	25th, 75th Percentile (ng/mL)***	Results****
Infant Growth						
Blaauwendraad et al. 2024 Cohort	2016–2019 N = 1091	NR LOD÷√2	TM1: 81.5 TM2: 79.7 TM3: 81.4	Urine, TM1: 0.59 TM2: 0.62 TM3: 0.60	TM1: 0.10, 6.49 TM2: 0.11, 6.33 TM3: 0.10, 5.71	TM3 BPS associated with lower subscapular skinfold measured from birth to 4 years.
Y Chen et al. 2024 Cohort	2012 N = 537	0.004 LOD÷2	24.6	Urine, 0.01 µg/g	0.00 µg/g, 0.03 µg/g	BPS associated with greater scapular skinfold thickness, abdominal skinfold thickness, and arm circumference at 6 months. In females, BPS associated with rapid growth from birth to 6 and 12 months and with overweight at 12 months.
Colombini et al. 2025 Cohort	2014–2017 N=341	0.1 Random values between 0–LOD and LOD–LOQ	TM2: 27 TM3: 27	Urine, TM2: 0.1 TM3: 0.1	5th and 95th TM2: 0.1, 3.68 TM3: 0.1, 2.76	TM2 BPS associated with greater child fat mass percent at 3 years of age.
X Li et al. 2024 Cohort	2019–2020 N = 113	LOD: NR LOQ: 0.1 LOQ÷√2	46.0	Urine, 0.31 µg/g	0.07 µg/g, 0.57 µg/g	No significant associations with weight at 6 and 12 months, or postnatal growth rate.
Lv et al. 2024 Cohort	2013–2016 N = 1978	LOD: 0.01–0.04 (exact LOD NR) LOD÷2	TM1: 84.91 TM2: 88.07 TM3: 89.82	Urine, TM1: 0.53 TM2: 0.53 TM3: 0.53	TM1: < LOD, 2.42 TM2: < LOD, 1.50 TM3: 0.23, 2.12	Average and TM1 BPS were associated with larger offspring BMI z-score at 2 years.
Ouidir et al. 2024 Cohort	2014–2017 N = 364	NR LOD: 0.10 LOQ: 0.40 LOD÷√2	TM2: 27.7 TM3: 28	Urine, TM2: 0.10 TM3: 0.10	5th, 95th TM2: 0.10, 2.86 TM3: 0.10, 2.76	BPS > LOQ in TM2 was associated with a higher offspring BMI at 3 and 36 months.

Study/ Design	Date of Collection/ Sample size	LOD (ng/mL)/ Adjustment for < LOD	% samples with BPS detected	Matrix, Median BPS (ng/mL)**	25th, 75th Percentile (ng/mL)***	Results****
Stevens et al. 2023 Cohort	2009–2014 N = 438	0.1 Imputed as instrument value when possible, all other values imputed as ½ the minimum reported value	87	Urine, 0.3	0.2, 0.6	No associations between TM2 BPS and body composition at birth or 5 months.
Xiong et al. 2023a Cohort	2013–2015 N = 826	0.04 LOD÷2	TM1: 84.7 TM2: 86.9 TM3: 88	Urine, TM1: 0.35 TM2: 0.41 TM3: 0.39	TM1: 0.12, 1.11 TM2: 0.15, 1.18 TM3: 0.15, 1.10	TM1 BPS associated with higher odds of having a 'low-increasing' growth trajectory in the first two years compared to a 'moderate-stable' trajectory. Average BPS associated with higher odds of a 'moderate increasing' trajectory.
Neurodevelopmental Outcomes						
Bornehag et al. 2021 Cohort	2007–2010 N = 803	0.03 Instrument readings under LOD	97.4	Urine, 0.07	0.04, 0.12	No significant associations with IQ.
Chen et al. 2023 Cohort	2012 N = 424	0.004 LOD÷2	23.6	Urine, 0.01 µg/g	0.00, 0.02 µg/g	No significant associations with IQ.
England-Mason et al. 2021 Cohort	2009–2012 N = 310	0.1 LOD÷√2	61	Urine, GM: 0.22	NR, NR	No significant associations with executive function.
Geiger et al. 2023 Cohort	2010–2012 N = 68	0.1 Instrument readings under LOD	99.3	Urine, 0.3	NR, NR	Results varied by offspring sex: BPS associated with more emotionally reactive behavioral problems and internalizing behavioral problems in girls.

Study/ Design	Date of Collection/ Sample size	LOD (ng/mL)/ Adjustment for < LOD	% samples with BPS detected	Matrix, Median BPS (ng/mL)**	25th, 75th Percentile (ng/mL)***	Results****
Jiang et al. 2020 Cohort	2014–2015 N = 456	0.2 LOD÷√2	All: NR TM1: 81.8 TM2: 85.3 TM3: 88.2	Urine, All: 0.37 TM1: 0.34 TM2: 0.42 TM3: 0.39	All: < LOD, 0.89 TM1: < LOD, 1.18 TM2: < LOD, 1.20 TM3: < LOD, 1.11	BPS associated with lower psychomotor developmental index scores. Results for mental development index scores varied by timing: TM1 BPS associated with higher mental development index.
Lei et al. 2024 Cohort	2013–2016 N = 600	0.003 LOD÷√2	76.5	Urine, 0.02	0.01, 0.08	TM1 BPS associated with higher odds of emotional problems.
J Li et al. 2024 Cohort	2015–2017 N = 744	0.046–0.507 LOD÷√2	85.9	Serum, 0.096	0.096, 0.104	No associations with vision acuity or visual impairment.
Liu et al. 2021 Cohort	2009–2012 N = 394	0.1 LOD÷√2	58	Urine, 0.20 µg/g	< LOD, 0.40 µg/g	No significant associations with Bayley Scales of Infant Development.
Mustieles et al. 2023 Cohort	2014–2017 N = 406	0.10 Random selection of values between 0 and LOD	TM2: 26 TM3: 28	Urine, TM2: < LOD TM3: < LOD	TM2: < LOD, 0.21 TM3: < LOD, 0.26	TM3 BPS associated with worse child behavior scores for social awareness, social cognition, and social communication.
Rolland et al. 2025 Cohort	2014–2017 N=151	0.1 Imputed using distribution-based methods.	TM2: 28 TM3: 30	Urine, TM2: < LOD TM3: < LOD	5th and 95th Percentiles TM2: < LOD, 1.0 TM3: < LOD, 1.0	TM2 BPS associated with reduced infant eye tracking time at 24 months.
van den Dries et al. 2020 Cohort	2004–2006 N = 1282	0.05 LOD÷√2	TM1: 67.8 TM2: 29.8 TM3:19	Urine, TM1: 0.2 TM2: < LOD TM3, < LOD	TM1: < LOD, 0.6 TM2: < LOD, 0.1 TM3: < LOD, < LOD	No significant associations with nonverbal IQ.

Study/ Design	Date of Collection/ Sample size	LOD (ng/mL)/ Adjustment for < LOD	% samples with BPS detected	Matrix, Median BPS (ng/mL)**	25th, 75th Percentile (ng/mL)***	Results****
Woodbury et al. 2025 Cohort two cohorts combined)	2017–2019 N = 217	0.1 Assigned machine-read values or LOD÷√2	≥ 75	Urine ECHO-PROTECT: 0.53 IKIDS: 0.40	ECHO-PROTECT: 0.21, 0.86 IKIDS: 0.19, 0.62	No significant associations with non-nutritive sucking in infants.
Zhou et al. 2025 Cohort	2012–2015 N = 545	0.5 LOD÷√2	38.9	Urine, 0.32	0.14, 0.94	Findings varied by socioeconomic status: TM2 BPS associated with worse cognitive development at 2 years among the high socioeconomic status group only.
Immune function and Related Outcomes						
Abellan et al. 2022 Meta-analysis of 4 cohorts	1999–2010 N = 3007	0.05 – 0.33 No imputation.	10-71	Urine, NR	NR, NR	BPS associated with lower odds of late and persistent wheeze.
Coiffier et al. 2023 Cohort	2014–2017 N = 457	0.1 No imputation.	44	Urine, 1.28	0.51, 2.35	BPS associated with higher functional residual capacity, higher tidal volume at 2 months, and higher odds of asthma and bronchiolitis at 3 years.
Gaylord et al. 2023 Cohort	2010–NR N = 501	0.08 LOD÷√2	TM1: 52 TM2: 57 TM3: 51	Urine, TM1: 0.11 TM2: 0.13 TM3: 0.09	TM1: < LOD, 0.52 TM2: < LOD, 0.58 TM3: < LOD, 0.48	Results varied by offspring sex. BPS associated with higher odds of asthma for males.
Karramass et al. 2023† Cohort	2004–2005 N = 1020	0.01 LOD÷√2	TM1: 68.9, TM2: 29.0 TM3: 19.5	Urine, TM1: 0.2 TM2: 0.03 TM3: < LOD	TM1: 0.03, 0.6 TM2: 0.03, 0.1 TM3: < LOD, < LOD	BPS associated with lower force vital capacity, forced expiratory volume. Results for asthma varied by offspring sex: Higher odds of asthma in girls. Lower odds of asthma in boys.
Kuraoka et al. 2024 Cohort	2013–2014 N = 3513	0.18 NR	14.3	Urine, 0.39	NR, NR	No significant association with asthma.

Study/ Design	Date of Collection/ Sample size	LOD (ng/mL)/ Adjustment for < LOD	% samples with BPS detected	Matrix, Median BPS (ng/mL)**	25th, 75th Percentile (ng/mL)***	Results****
Li et al. 2021 Cohort	2019–2020 N = 111	LOD: NR LOQ: 0.1 LOQ÷2	46.8	Urine, < LOD	< LOD, 0.35	No significant associations with eczema or cord blood cytokine concentrations.
Miller et al. 2025 Cohort (9 combined cohorts)	1998–2017 N = 3038	Varied by cohort LOD÷√2	69.9	Urine, 0.29	0.10, 0.69	BPS was associated with reduced odds of atopic dermatitis in girls only.
Endocrine and Cardiometabolic Effects						
Bigambo et al. 2024 Cross-sectional	NR N = 378	LOD: NR LOQ = 0.05 LOQ÷2	57.4	Cord blood, 0.093	0.035, 0.367	Results varied by pre-pregnancy BMI and delivery mode: BPS associated with lower cord blood follicle-stimulating hormone in people with normal BMI and in people with cesarean delivery.
Blaauwendraad et al. 2022a Cohort	2004–2005 N = 935	0.05 LOD÷√2	TM1: 67.8 TM2: 29.2 TM3: 19.8	Urine, TM1: 0.7 TM2: < LOD TM3: < LOD	TM1: < LOD, 2.3 TM2: < LOD, 0.4 TM3: < LOD, < LOD	No associations with carotid intima-media thickness or carotid distensibility.
Derakhshan et al. 2021 Cohort	2002–2006 N = 882	0.05 LOD÷√2	TM1: 66.6 TM2: 29.8 TM3: 18.9	Urine, TM1: 0.34 TM2: 0.24 TM3: < LOD	TM1: < LOD, 8.83 TM2: < LOD, 1.69 TM3: < LOD, < LOD	No associations with cord blood or childhood serum thyroid stimulating hormone or free thyroxine.
Sol et al. 2020† Cohort	2004–2005 N = 757	0.06 LOD÷√2	TM1: 69.7 TM2: 29.9	Urine, Boys: TM1: 0.20 TM2: < LOD Girls: TM1: 0.15 TM2: < LOD	Boys: TM1: < LOD, 0.75 TM2: < LOD, 0.13 Girls: TM1: < LOD, 0.58 TM2: < LOD, 0.10	Results varied by offspring sex: TM1 BPS associated with lower insulin and glucose in boys. TM2 BPS associated with lower odds of high low density lipoprotein cholesterol in boys.
Svensson et al. 2023 Cohort	2007–2010 N = 1105	0.04 LOD÷√2	97.5	Urine, GM: 0.07	0.03, 0.12	No associations between TM1 BPS and offspring BMI or overweight at 5.5 years.

Study/ Design	Date of Collection/ Sample size	LOD (ng/mL)/ Adjustment for < LOD	% samples with BPS detected	Matrix, Median BPS (ng/mL)**	25th, 75th Percentile (ng/mL)***	Results****
Wang et al. 2022 Cohort	2012 N = 528	0.004 LOD÷2	24.2	Urine, 0.01 ug/g	< LOD, 0.03 µg/g	BPS associated with higher kisspeptin levels. Associations were stronger in boys.
Xi et al. 2023Cohort	2012 N = 258	0.004 LOD÷√2	21.32	Urine, 0.007 µg/g	0.004, 0.019 µg/g	Results varied by offspring sex: BPS associated with lower thyroid stimulating hormone in male newborns.
Xiong et al. 2023b Cohort	2013–2015 N = 904	0.04 LOD÷√2	TM1: 84.51 TM2: 86.95 TM3: 88.72	Urine, TM1: 0.39 TM2: 0.37 TM3: 0.40	TM1: 0.18, 1.14 TM2: 0.18, 1.11 TM3: 0.20, 1.06	BPS associated with higher neonatal thyroid stimulating hormone levels.
Z Wang et al. 2021 Cohort	2012 N = 545	0.004 LOD÷2	24.8	Urine, 0.01 µg/g	< LOD, 0.03 µg/g	No significant results with digit ratio (ratio of lengths of finger 2 and 4) at 6 years.
Bone Mass and Mineral Density						
Liang et al. 2023 Cohort	2015–2018 N = 230	0.046 LOD÷2	86.1	Serum, 0.097	0.096, 0.106	Results varied by offspring sex: TM1 BPS associated with lower bone mass density z-score and higher odds of low bone mineral density in boys.
van Zwol-Janssens et al. 2020† Cohort	2004–2005 N = 1362	0.05 LOD÷√2	TM1: 67.8 TM2: 29.5 TM3: 19.3	Urine, TM1: 0.17 TM2: 0.03 TM3: 0.03	TM1: 0.03, 0.61 TM2: 0.03, 0.10 TM3: 0.03, < LOD	BPS associated with lower bone mineral density at age 10 but not age 6.

Study/ Design	Date of Collection/ Sample size	LOD (ng/mL)/ Adjustment for < LOD	% samples with BPS detected	Matrix, Median BPS (ng/mL)**	25th, 75th Percentile (ng/mL)***	Results****
Offspring Reproductive Development						
Blaauwendraad et al. 2022b† Cohort	2004–2005 N = 1197	0.15 LOD÷√2	TM1: 68.5 TM2: 29.7 TM3: 20	Urine, Males: TM1: 0.2 TM2: < LOD TM3: < LOD Females: TM1: 0.2 TM2: < LOD TM3: < LOD	Males: TM1: 0.03, 0.7 TM2: < LOD, < LOD TM3: < LOD, < LOD Females: TM1: < LOD, 0.6 TM2: < LOD, 0.08 TM3:< LOD, < LOD	Results varied by offspring sex: BPS associated with delayed age at first menstruation for girls.
Chen et al. 2025 Cohort	2012 N=545	0.004 LOD÷√2	24.8	Urine, 0.01 µg/g	0.00 µg/g, 0.03 µg/g	Results varied by offspring sex: BPS associated with longer anus-fourchette distance and longer anus-clitoris distance at 48 months, and rapid anogenital distance growth in girls only.

*Studies ordered by outcome, then by author; Abbreviations: BPS = bisphenol S, BMI = body mass index, ECHO-PROTECT = ECHO Program Puerto Rico Study, GM = geometric mean, IKIDS = Illinois Kids Development Study, IQ = intelligence quotient, IQR = interquartile range (75th minus 25th percentile), LGA= large for gestational age, LOD = limit of detection, LOQ = limit of quantification, NR = not reported, ng/mL = nanograms per milliliter, ng/g = nanograms per gram, SGA= small for gestational age, TM1 = trimester 1, TM2 = trimester 2, TM3 = trimester 3, µg/g = micrograms per gram.

** Mean is reported only when median wasn't available. A range of medians or means was given if multiple samples (e.g., trimester specific samples) were analyzed.

*** A range of 25th percentiles and 75th percentiles was given if multiple samples (e.g. trimester specific samples) were analyzed.

**** Brief overview of summary results focused on statistically significant findings. See Table 4.1.1 for complete reporting of methodology and results for each study.

† Studies with concentrations converted from nmol/L to ng/mL.